

GLP intravenous toxicity studies of APOSEC™ in mice, rats, and Cynomolgus monkeys: ICH compliance is mandatory

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Additional file 5: File name: “Additional file 5_Overview of Toxicology Studies for APOSEC.pdf”, Title of Data: “Overview of Toxicology Studies for APOSEC™ conducted by MC Toxicology Consulting GmbH”, Description of data: “Overview over the toxicology studies for APOSEC™ issued by MC Toxicology Consulting GmbH, 1070 Wien, Austria, Siebensterngasse 31/8.”

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99 Abstract

100 **Background:** APOSEC™ is a cell-free biological therapeutic derived from the
101 secretome of irradiated peripheral blood mononuclear cells (PBMCs). This
102 investigational medicinal product has shown regenerative potential in preclinical
103 models of acute myocardial infarction, cardiomyopathy, myocarditis, stroke, and
104 spinal cord injury after intravenous administration.

105 **Methods:** To assess systemic safety, Good Laboratory Practice (GLP) compliant
106 toxicology studies were conducted in mice, rats, and Cynomolgus monkeys, with
107 the latter selected as the species most relevant to human translation. Cynomolgus
108 monkeys received twice-weekly intravenous infusions at 35, 110, and 350/225/200
109 U/kg body weight, followed by a two-week treatment-free recovery period.
110 Monitoring included clinical observations, clinical pathology, urinalysis,
111 electrocardiography, and histopathology.

112 **Results:** Acute and repeated-dose toxicology studies in rats and mice at doses up
113 to 500 U/kg body weight did not identify a no observed adverse effect level (NOAEL).
114 In Cynomolgus monkeys, high-dose APOSEC™ caused transient, reversible
115 vasodilation with associated systemic neurovascular signs, requiring interim dose
116 reductions. Two male animals were sacrificed prematurely after the initial 350 U/kg
117 infusion because of severe, life-threatening exaggerated vasodilatory responses,
118 corresponding to 10 times the anticipated human intended dose. No test item-
119 related effects were observed on body weight, food or water consumption, clinical

pathology, urinalysis, or recovery-phase parameters. Minor lymphoid organ findings were considered incidental, and the NOAEL was established at 200 U/kg.

Conclusion: These findings support a favourable systemic safety profile for intravenous APOSEC™ at therapeutic and moderately supratherapeutic doses. They also show that mouse and rat models failed to predict the mortality observed in 2 of 5 Cynomolgus monkeys treated with 350 U/kg body weight in this GLP safety study. The results underscore the importance of non-human primate studies in ICH-compliant preclinical development. Accordingly, secretome-based investigational medicinal products should undergo non-clinical safety assessment in accordance with ICH S6(R1) before first-in-human studies.

Introduction

The secretome of stressed peripheral blood mononuclear cells (PBMCs; APOSEC™, derived from APO=**a**poptotic and SEC=**s**ecretome) has emerged as a potent mediator of tissue regeneration. Its effects are mediated mainly by paracrine bioactive factors that reactivate stalled wound-healing cascades and attenuate inflammation. Preclinical and clinical evidence shows that APOSEC™, comprising APO-1 for intravenous and APO-2 for topical application, both manufactured by the same process – contains angiogenic factors, matrix metalloproteinases, cytokines, lipids, and exosomes (1–5).

In vitro, APOSEC™ acts through several mechanisms, including angiogenesis (6–8), re-epithelialisation (6–9), cytoprotection, and up-regulation of anti-apoptotic gene

products in primary cultured cells (10,11). At the immune-cell level, we showed that APOSEC™ prevents platelet aggregation (12), stabilizes granulocytes (13), inhibits dendritic-cell maturation (14), stabilizes basophils and mast cells (15), prevents monocyte activation (16), promotes M1/M2 differentiation (17), and attenuates T-cell activation *in vitro* (18). APOSEC™ also activates proangiogenic and anti-proteolytic processes in naïve PBMCs, protects the endothelial barrier (19), and contains antimicrobial peptides (3). We further showed that APOSEC™ induces nitric oxide (NO) production in human endothelial cells *in vitro* and *in vivo* and causes dose-dependent vasodilation in coronary arteries *ex vivo* (12). Moreover, APOSEC™ attenuated hypoxia- and inflammation-induced damage in several preclinical disease models, including acute and latent myocardial infarction (11,12,20,21), myocarditis (18), stroke and spinal cord injury (10,17), and acute wound healing and burn injury (5–9). Based on these signals, APOSCIENCE™ selected chronic diabetic foot ulcers (DFU) as the first indication for a GMP/GCP-compliant clinical trial (22,23).

The development of allogeneic APOSEC™ was guided by two scientific-advice procedures with BASG (Austria) and the Paul Ehrlich Institute (Germany) (Additional files 1 and 2). Regulatory authorities classified APOSEC™ as a biological medicinal product under Directive 2001/83/EC; therefore, its non-clinical safety assessment falls within the scope of ICH S6. During development, autologous APOSEC™ was evaluated in the randomized phase I MARSYAS I safety and tolerability study (ClinicalTrials.gov identifier: NCT02284360), which demonstrated the safety and tolerability of topically applied autologous GMP-grade APOSEC™ (22). Between

2019 and 2023, GMP-grade allogeneic APOSEC™ was evaluated in a DFU trial (Additional file 3). In both trials, APOSEC™ was blended with alginate gel (NUGEL©, Systagenix, Gargrave, North Yorkshire, England). MARSYAS II was a multinational, randomized, double-blind, placebo-controlled, GCP-compliant DFU trial (MARSYAS I/II; ClinicalTrials.gov identifier: NCT04277598) (23,24).

Before initiating the GCP trial in chronic wounds, we completed an ICH-compliant development pathway for allogeneic APOSEC™. This included: a) identifying and contracting an Austrian CMO with clean-room capacity and an existing GMP manufacturing authorization (24); b) equipping the CMO in Linz with a GMP-compliant lyophilizer, with institutional support from Dr Christian Gabriel and Mag. Werner Watzinger†; c) validating two viral reduction steps by an independent CRO (Charles River Laboratories, Cologne, Germany), as allogeneic APOSEC™ is generated from multiple PBMC donors (25); d) developing two cell-based potency assays reflecting the experimentally established main mode of action (MOA) *in vitro* and *in vivo*, standardized against an *in-house* APOSEC™ reference batch; e) demonstrating, through a GMP/ICH-compliant stability programme, that APOSEC™ remains stable and biologically potent at -80°C, at -20°C for 6 years, and at +4°C for 2 years; and f) conducting an extensive GLP toxicology programme to demonstrate to regulators the safety and tolerability of human allogeneic GMP-grade APOSEC™ for topical and intravenous application (26). Together, these GMP and GLP documents enabled APOSCIENCE™ to initiate the first GCP-compliant clinical trial in patients with diabetic foot ulcers (22,23).

186 Recently, the scientific community noted that the French regulatory authority had
187 permitted systemic infusion of an extracellular vesicle-enriched secretome (ECVES)
188 in patients on the basis of a GLP toxicology programme that may not have fully met
189 ICH requirements (27,28). According to Humbert et al., only Sprague Dawley rats
190 and BALB/c mice were exposed intravenously to the final ECVES product. No clear
191 preclinical rationale for the IMP dose or robust preclinical efficacy data had been
192 published beforehand (29). Notably, although clinically relevant AMI models were
193 available (30), none had been reported before initiation of the SECRET-HF trial
194 (NCT05774509). From a regulatory perspective, it is also relevant that the ECVES
195 potency assay was used without validation against an ECVES reference batch.

196 Stressed PBMC secretome therapy originated at the Medical University of Vienna
197 in 2005. In 2008, APOSCIENCE™ and the Medical University of Vienna filed the
198 intellectual property application for the APOSEC™ platform technology (AMI patent
199 as Additional file 4). In the following years, regenerative medicine shifted from cell-
200 and ATMP-centred concepts towards extracellular MSC-secretome approaches.
201 The International Society for Extracellular Vesicles (ISEV), founded in 2012, has
202 contributed substantially to the development of this field. Seminal work by Gnecchi,
203 Lai, and Wollert helped establish that the secretome, rather than the stem cell or
204 ATMP itself, likely mediates the reported clinical benefits (31–33). Between 2010
205 and 2011, we showed that a single infusion of APOSEC™, containing the stressed,
206 unmodified secretome without concentration steps, prevented AMI (11). More
207 importantly for clinical translation, APOSEC™ retained its curative potency after
208 double viral clearance (4). Further preclinical work showed that one intravenous

APOSEC™ infusion attenuated systemic inflammatory signatures in the heart, liver, and spleen in a porcine AMI model (34). APOSCIENCE™ has consistently pursued the translation of APOSEC™ into patient care. Accordingly, we complied with ICH S6(R1) safety requirements and conducted an extensive repeated-dose toxicology programme in Cynomolgus monkeys (Additional file 5).

This publication aims to: a) summarize the human relevance of GLP toxicology programmes for secretome therapy; b) make the complete intravenous GLP toxicology study reports publicly available; c) provide a cost analysis of these ICH-compliant GLP safety studies in mice, rats, and macaques; and d) explain why ICH compliance is essential for developing new secretome-based investigational medicinal products.

Methods

Quality Statement

All APOSCIENCE-associated analytical and experimental work was performed under validated quality-management systems at APOSCIENCE AG (Vienna, Austria), the Austrian Red Cross Blood Transfusion Service of Upper Austria (Linz, Austria), SYNLAB Analytics and Services Switzerland AG (Birsfelden, Switzerland), Symbiosis GmbH (Eppelheim, Germany), and the contract research organisation LPT. External testing was performed and documented according to validated standard operating procedures. Experimental work at the Medical University of Vienna followed GMP-compliant planning, execution, and documentation. Detailed

manufacturing, assay, animal-model, and statistical procedures are provided in the Supplementary Methods. APOSCIENCE™ owns all GLP, GCP, and GMP documents, as well as the APOSEC platform technology.

Legal requirements for IMP development

Regulatory authorities classify APOSEC™ as a biological medicinal product under Directive 2001/83/EC (Additional files 1 and 2). Accordingly, its non-clinical safety assessment falls within the scope of ICH S6. The non-clinical development strategy must support planned phase I–III clinical trials for both topical and intravenous administration. Relevant guidance includes ICH S6 on the preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998) and, where applicable, ICH M3(R2) on non-clinical safety studies supporting human clinical trials and marketing authorisation for pharmaceuticals (EMA/CHMP/ICH/286/1995).

ICH-compliant toxicology studies

APOSEC™ was manufactured at the Red Cross Blood Transfusion Service of Upper Austria in Linz, Austria. Toxicology studies were conducted at LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG, Hamburg, Germany. All animal studies reported here were approved by the competent German authorities: the Behörde für Gesundheit und Verbraucherschutz, Amt für Verbraucherschutz, Lebensmittelsicherheit und Veterinärwesen, Hamburg, Germany (reference numbers V1/591-00.33, V1305-591-00.33, V1307-591-00.33, and V1305-591-00.33), and/or the Ministerium für Energiewende, Landwirtschaft, Umwelt und

ländliche Räume, Kiel, Germany (reference number V244-27284/2015-722.04). All studies were performed in accordance with the Guide for the Care and Use of Laboratory Animals.

GMP-compliant preparation of APOSEC™

Blood donor selection and donation procedures comply with European and national regulations, including eligibility criteria, procedural requirements, and documentation standards. Written informed consent was obtained from all donors.

APOSEC™ is manufactured from donations of selected donors who meet predefined quality criteria, including age below 45 years, CRP below 2 mg/dL, and erythrocyte values within specified limits. PBMCs are isolated from buffy coats by density centrifugation using lymphocyte separation medium, washed twice with Dulbecco's phosphate-buffered saline, and resuspended in CellGenix GMP DC Medium. Apoptosis is induced by 60 Gy irradiation (2×30 Gy), followed by culture for $24 \text{ h} \pm 2 \text{ h}$ at a standardized density of 25×10^6 cells/mL. After centrifugation, PBMCs are removed and the PBMC secretome-containing supernatant is sterile filtered. In-process controls ensure product quality, standardize manufacturing, and minimize batch-to-batch variation. Donations processed individually up to this stage are then pooled and subjected to methylene blue/light treatment as the first viral reduction step. The product is stored at -80°C before lyophilisation and a second, orthogonal viral reduction step by irradiation with 25–35 kGy, which also provides terminal sterilization. Final vials are stored again at -80°C . APOSEC™ is cell-free (Additional file 3).

274 **General compliance and test article preparation**

275 The non-clinical safety evaluation was performed in accordance with the OECD
276 Principles of Good Laboratory Practice (GLP), ICH S6(R1) guidance on the
277 preclinical safety evaluation of biotechnology-derived pharmaceuticals, and ICH
278 M3(R2) recommendations for non-clinical safety studies supporting clinical trials.
279 The study protocol, conduct, and reporting were audited by the Quality Assurance
280 Unit of Global Pathology Support B.V. Pre-study, histopathology-phase, and
281 reporting-phase inspections were conducted on 19 September 2019 and 17–18
282 October 2019, respectively. All findings were formally documented and reported to
283 the Principal Investigator, Test Site Management, Study Director, and Leading QA.

284 **Acute toxicity of APOSEC™ after single intravenous administration in**
285 **Crl:CD(SD) rats**

286 This study assessed the toxicity of APOSEC™ after a single intravenous
287 administration in CD rats. It was conducted in accordance with the Note for
288 Guidance on single-dose toxicity (3BS1a), issued in August 1987 and published in
289 April 2001 (26).

290 **Four-week toxicity of APOSECTM after intravenous slow-bolus administration**
291 **three times weekly in mice**

292 This study assessed the toxicity and local tolerance of APOSEC™ after repeated
293 intravenous slow-bolus administration to C57BL/6N mice three times weekly for four
294 weeks and evaluated reversibility after a two-week recovery period (26).

Two-week toxicity of APOSEC™ after twice-weekly intravenous slow-bolus administration in Cynomolgus monkeys

This study assessed the toxicity of APOSEC™ after repeated intravenous administration in Cynomolgus monkeys (*Macaca fascicularis*). Following a 4- to 5-week acclimatization period, 34 treatment-naïve healthy adult monkeys (18 males, 16 females) were enrolled based on clinical health screening and body weight within $\pm 10\%$ of sex-specific means. Animals were individually housed under controlled environmental conditions ($22\text{ }^{\circ}\text{C} \pm 3\text{ }^{\circ}\text{C}$; $55\% \pm 10\%$ relative humidity; 12 h light/dark cycle) and provided a commercial primate diet once daily and tap water ad libitum. The study protocol was approved by the competent veterinary authority, and all procedures were conducted in strict compliance with the Guide for the Care and Use of Laboratory Animals, OECD GLP principles, and ICH S6(R1) and ICH M3(R2) guidelines.

Animals were randomized into four groups: Group 1 (vehicle control, 0.9% NaCl), Group 2 (35 U/kg), Group 3 (110 U/kg), and Group 4 (initially 350 U/kg, subsequently reduced to 225/200 U/kg due to dose-dependent adverse responses). Recovery subgroups (2 males, 2 females per group) were included in Groups 1 and 4 (see Table 1).

314 Table 1: Groups, dose levels and group size

Group	Allogeneic APOSEC™ dose, i.v. [Units/kg b.w.]	No. and sex of animals MS (+RP)
1	0 (saline control)	3 (+2) m 3 (+2) f
2	35	3 (+0) m 3 (+0) f
3	110	3 (+0) m 3 (+0) f
4	350/225/200	5 (+2) m 3 (+2) f

315 b.w. = body weight, i.v. = intravenous, m = male, f = female, MS = main study, RP
 316 = recovery period

317 APOSEC™ was administered via intravenous infusion into the vena cephalica twice
 318 weekly over two weeks (days 1, 4, 8, and 11). Administration volumes were adjusted
 319 per dose and sex (5 mL/kg for the initial male dose; 15 mL/kg for all subsequent
 320 doses), with infusion rates modulated accordingly (see Table 2). Control animals
 321 received equivalent volumes of sterile 0.9% NaCl on the same schedule.

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325

326 Table 2: Concentration of APOSEC™ in the i.v. study with respective dose
327 reductions

Group	Dose level [Units/kg]	Content per test item vial [Units]	Volume of 0.9% NaCl to be added per Vial [mL/vial]	Resulting concentration of the administration solution [Units/mL]	Administration volume [mL/kg b.w.]
1 st dose of male animals					
2	35	500	71.43	7	5
3	110	500	22.73	22	5
4	350	500	7.14	70	5
2 nd to 3 rd dose of male animals					
1 st dose of female animals and male recovery animals of group 4					
2	35	500	214.59	2.33	15
3	110	500	68.49	7.30	15
4	350	500	21.45	23.31	15
4	225 [#]	500	33.33	15.00	15
4 th dose of male animals					
2 nd to 4 th dose of female animals and male recovery animals of group 4					
2	35	500	214.59	2.33	15
3	110	500	68.49	7.30	15
4	200	500	37.50	13.33	15

328 [#] = all female animals in group 4 (high dose group) started with a dose of 225 U/kg;
329 b.w. = body weight, i.v. = intravenous

330 Clinical observations, behavioural monitoring, and local tolerance assessments
331 were performed individually prior to and after each infusion. Body weight, food
332 consumption, and water intake were recorded twice weekly. Electrocardiography
333 (ECG) and peripheral arterial blood pressure were measured at baseline (predose)
334 and 5 minutes post-infusion on days 1 and 11. Ophthalmological and auditory
335 examinations were conducted at baseline, end of treatment, and end of recovery.

336 Blood samples for haematology (EDTA-anticoagulated whole blood), coagulation
337 (citrate plasma), and clinical chemistry (serum) were collected from the vena
338 cephalica or saphena magna in fasted animals at baseline, end of treatment, and

end of recovery (recovery animals). Urinalysis was performed at corresponding time points. Following terminal sacrifice (pentobarbital 150 mg/kg i.v.) and carotid exsanguination, a comprehensive gross necropsy was performed by a board-certified veterinary pathologist. All major organs and tissues were weighed, fixed in 10% neutral buffered formalin, and processed for histopathological examination (H&E staining). Frozen sections of heart, liver, and kidney were stained with Oil Red-O for lipid accumulation. Infusion site tissues were evaluated for local tolerance, including inflammatory infiltrates and architectural changes. Bone marrow smears from the 7th rib (Pappenheim stain) were assessed for myeloid:erythroid ratios. Recovery animals underwent identical gross and histopathological evaluations to assess reversibility.

Statistical comparisons between treated groups (groups 2–4) and the control group (group 1) were performed using parametric methods. Homogeneity of variances and normality were assessed via Bartlett's and Shapiro–Wilks tests, respectively. Data exhibiting heterogeneity or non-normality were log-transformed or rank-transformed prior to analysis. Body weight, food/water consumption, ECG, hemodynamic, haematology, coagulation, clinical chemistry, and organ weights were analysed using Dunnett's multiple t-tests ($p \leq 0.05$ and $p \leq 0.01$). Histopathological and incidence data were analysed using Fisher's exact test ($p \leq 0.05$). All statistical evaluations were performed using Provantis® Integrated preclinical software (v10.2.1). Biological relevance of statistically significant findings was independently assessed by the study pathologist and toxicologist, with emphasis on dose-dependence, temporal relationship, and historical control ranges.

362 Results

363 **Acute toxicity of APOSEC™ after single intravenous administration in** 364 **Crl:CD(SD) rats**

365 Consistent with prior reporting (Wuschko et al.), a single intravenous administration
366 of APOSEC™ in CD rats across a dose range of 50 to 500 U/kg was well tolerated.
367 No mortality, systemic toxicity, or test-item-related macroscopic abnormalities were
368 observed during the 14-day observation period. All animals maintained normal body
369 weight gain, and terminal gross pathology revealed no treatment-related findings.
370 Consequently, the no-observed-effect level (NOEL) was established at or above the
371 highest tested dose of 500 U/kg (26).

372 **Four-week toxicity of APOSEC™ after intravenous slow-bolus administration** 373 **three times weekly in mice**

374 In a four-week repeated-dose intravenous study in mice, APOSEC™ administered
375 at 50, 250, and 500 U/kg three times weekly was well tolerated. Throughout the
376 treatment and recovery periods, no mortality, systemic or local intolerance, or
377 treatment-related alterations in clinical pathology, telemetry, or special sensory
378 exams were observed. Body weight, food and water consumption, and terminal
379 gross pathology remained unaffected, with complete reversibility confirmed in the
380 recovery cohort. Consequently, the no-observed-adverse-effect level (NOAEL) was
381 established at the highest tested dose of 500 U/kg (26).

Two-week toxicity of APOSEC™ after twice-weekly intravenous slow-bolus administration in Cynomolgus monkeys

In contrast to the single- and repeated-dose rodent data, the primate study revealed a markedly different systemic safety profile. No test item-related signs of local intolerance were observed at infusion sites during clinical monitoring or necropsy. Microscopic examination of infusion sites revealed acute inflammatory infiltrates, granulation tissue, and subcutaneous haemorrhage across all groups, including controls, which were attributed to the technical infusion procedure rather than the test item.

Regarding systemic tolerance, no mortality or premature sacrifice occurred in Groups 1 (0.9% NaCl), 2 (35 U/kg), or 3 (110 U/kg). In Group 4 (initially 350 U/kg), two male animals were sacrificed prematurely on day 1 following the first infusion due to severe, exaggerated vasodilatory responses. Within 20 minutes post-administration, both animals exhibited hyperthermia followed by rapid hypothermia, markedly reduced motility, lateral recumbency, diminished reflexes, and clonic convulsions. Macroscopic findings included enlarged axillary lymph nodes, emphysematous lungs, and haemorrhagic/edematous subcutaneous tissue in the lower extremities, correlating microscopically with diffuse phlegmonous inflammation and interstitial edema. These pronounced pharmacodynamic effects prompted an interim dose reduction to 225 U/kg. At the adjusted high dose, systemic signs included asthenia, somnolence, mydriasis, lateral recumbency, increased respiratory rate, laboured breathing, reduced reflexes, convulsions, salivation, and emesis, primarily on administration days and up to one day post-infusion. Most signs

emerged within 20–60 minutes and resolved within 6 hours. Due to these effects, the dose was further reduced to 200 U/kg on day 11 for male animals and on day 4 for female animals and recovery males. In Group 3, mild systemic signs (reduced motility, asthenia, mydriasis, lateral recumbency, and convulsions) were observed in one male following the third administration (see Table 3). Body weight trajectories, food and water consumption, ECG parameters, peripheral arterial blood pressure, and ophthalmological/auditory findings showed no test item-related influence at any dose level.

Table 3: Occurrence of systemic signs of toxicity

Dose level of Allogeneic APOSEC™	Finding	Sex	Number of animals	Test day of first occurrence	Total no. of days
Group 1: Vehicle control	none	m: f:	0/5 0/5	N/A N/A	N/A N/A
Group 2: 35 U/kg	none	m: f:	0/3 0/3	N/A N/A	N/A N/A
Group 3: 110 U/kg	reduced motility	m: f:	2/3 0/3	8 N/A	1 N/A
	asthenia	m: f:	1/3 0/3	8 N/A	1 N/A
	mydriasis	m: f:	1/3 0/3	8 N/A	1 N/A
	lateral position	m: f:	1/3 0/3	8 N/A	1 N/A
	clonic convulsions	m: f:	1/3 0/3	8 N/A	1 N/A
Group 4: 350/225/200 U/kg	reduced motility	m: f:	7/7 5/5	1 1	1-4 1-4
	asthenia	m: f:	5/7 5/5	1 1	1-4 2-4
	mydriasis	m: f:	3/7 2/5	4 1	1-2 1-2

	lateral position	m: f:	6/7 5/5	1 1	1-2 1-3
	(clonic) convulsions	m: f:	5/7 4/5	1 1	1 1-3
	somnolent	m: f:	5/7 4/5	1 1	1-3 1-4
	increased respiratory rate	m: f:	3/7 0/5	4 N/A	1 N/A
	laboured breathing	m: f:	3/7 0/5	4 N/A	1 N/A
	reduced reflexes	m: f:	4/7 0/5	1 N/A	1 N/A
	salivation	m: f:	1/7 0/5	4 N/A	1 N/A
	increased body temperature	m: f:	2/7 0/5	1 N/A	1 N/A
	decreased body temperature	m: f:	2/7 0/5	1 N/A	1 N/A
	Emesis	m: f:	1/7 0/5	4 N/A	1 N/A

414 m = male, f = female; N/A = not applicable

415 No test item-related alterations were observed in haematology, coagulation, or
416 clinical chemistry parameters. Coagulation indices (PT, aPTT) and leukocyte
417 profiles remained within normal limits. Clinical chemistry parameters, including
418 hepatic enzymes (ALAT, ASAT, LDH, γ -GT, ALP), electrolytes, calcium,
419 triglycerides, and globulin fractions, remained within normal biological variability with
420 no dose- or time-dependent trends. Urinalysis at baseline, end of treatment, and
421 end of recovery showed no test item-related changes in pH, specific gravity, or
422 qualitative analytes.

423 At terminal sacrifice, spleen enlargement was noted in two high-dose males, with
424 follicular hyperplasia confirmed microscopically in one. Enlarged axillary lymph

nodes were observed in one control male and one high-dose male, both showing medullary hyperplasia histologically. These lymphoid changes were considered incidental or related to the administration route. No test item-related alterations were observed in organ weights, bone marrow cellularity, or myeloid:erythroid ratios.

Animals in the recovery groups were observed for 14 days post-final administration. No test item-related local intolerance, premature deaths, or systemic toxicity signs were noted. Body weight gain, food/water consumption, and clinical pathology parameters remained unaffected. Gross and histopathological examinations revealed no toxicologically relevant changes; all microscopic findings were attributed to coincidental, mode-of-administration, or spontaneous background origins. No test item-related changes were observed in any organ or physiological parameter during the recovery phase.

In addition to the primary toxicological findings, a categorical cost analysis and resource allocation breakdown for the ICH-compliant GLP toxicity programs (acute rodent study in 2016 and repeated-dose primate study in 2019) are provided as additional files (see Additional files 6–8). Together with the supplementary Certificates of Analysis, these documents ensure full transparency regarding the study's operational scale, quality control framework, and regulatory compliance pathway, supporting reproducibility and future development planning.

Discussion

A two-week repeated-dose intravenous GLP toxicology study in Cynomolgus monkeys (NHPs) was conducted to assess the systemic safety of APOSEC™. The no-observed-adverse-effect level (NOAEL) was established at 200 U/kg body weight after twice-weekly intravenous administration. In the high-dose group, two male NHPs initially treated with 350 U/kg—corresponding to 10 times the anticipated human intended dose—required premature sacrifice after the first infusion because of exaggerated vasodilation. Clinical signs included rapid hyperthermia followed by hypothermia, markedly reduced motility, lateral recumbency, diminished reflexes, and clonic convulsions. This suspected unexpected, serious adverse reaction (SUSAR) had not been anticipated by LPT or APOSCIENCE™. Before the NHP safety study, acute toxicity studies in rodents and a repeated-dose mouse study had shown no toxicity at 50–500 U/kg body weight.

By publishing these data together with the supplementary murine, rodent, and NHP study reports (Additional files 9-11), we aim to demonstrate that secretome-based investigational medicinal products may carry clinically relevant safety risks. Based on our previous investigations, we propose a scientific explanation for the vasoplegia observed in NHPs. We then compare APOSEC™ development with that of other GMP-produced cell-derived secretomes. Finally, we argue that IMP developers must comply with ICH requirements before administering effective secretome-based investigational medicinal products to humans.

**Preclinical definition of the APOSEC™ dosing regimen in AMI research:
scientific rationale for GLP safety studies**

Infusion or injection of $2\text{--}5 \times 10^6$ syngeneic or allogeneic stem cells attenuated acute myocardial infarction (AMI) in murine and rodent models. Between 2005 and 2008, we experimentally showed that medium conditioned by 8.5×10^6 apoptotic PBMCs prevented AMI under defined conditions: rat PBMCs were irradiated with 45 Gy at 25×10^6 cells/mL, cultured for 24 h, and 0.3 mL of the resulting cell suspension was infused via tail vein (i.v. route) (BMBWK-66Æ009/0278-BrGT/2005) (20). In 2009, we reported apoptotic PBMC suspensions as a new regenerative-medicine approach. Reanalysis of these data challenged the assumption that the cellular compartment itself was the curative agent in this experimental setting. In a confirmatory experiment, we showed that secretome derived from 8.5×10^6 PBMCs—equivalent to 8.5 U of APOSEC™ in a 0.30 kg rodent, or 28 U/kg body weight (1 U corresponds to 1×10^6 PBMC secretome)—prevented myocardial damage in rodents and corroborated our PBMC secretome hypothesis. To assess the clinical relevance of these rodent findings, we designed experiments with Univ. Prof. Mariann Gyöngyösi in a porcine AMI model (35). We subsequently showed that a single APOSEC™ infusion at 33 U/kg body weight prevented cardiac remodelling (11). These preclinically defined dose ranges provided the basis for our GLP safety programme.

Scientific rationale for vasoplegia in APOSEC™-exposed Cynomolgus monkeys (NHPs): the Hagen–Poiseuille equation as an explanation for a preclinical SUSAR

APOSEC™ prevents cardiac remodelling after experimental AMI by limiting microvascular obstruction (MVO). It attenuates platelet activation and induces vasodilation *in vivo*. Using catheter-based angiography, we showed that the IMP rapidly reduced the TIMI frame count and increased myocardial blush during reperfusion. Holter ECG monitoring showed fewer persistent ST-segment abnormalities and post-AMI arrhythmias. Prof. Heusch, a leading figure in German experimental cardiology and Editor-in-Chief of *Basic Research in Cardiology*, helped interpret these marked biological effects through a rigorous review process. Following his suggestions, we demonstrated that APOSEC™ induces iNOS and p-eNOS in primary cultured HUVECs *in vitro* and directly affects vascular tone in isolated porcine coronary vessel rings *ex vivo*. At experimental concentrations of 0.5, 1, and 10 U per testing unit, APOSEC™ dilated coronary arteries dose-dependently by up to 40% (12).

The Hagen–Poiseuille equation provides a physiological and mathematical rationale for the strong dependence of flow on microvascular radius and resistance, with flow varying with the fourth power of the radius (r^4). Thus, even small changes in vessel radius can markedly alter blood flow *in vivo*; for example, doubling the radius increases flow 16-fold at the same pressure. We therefore propose that administration of APOSEC™ at 10 times the anticipated human intended dose (HID) triggered vasoplegic shock. Consequently, 2 of 5 Cynomolgus monkeys had to be sacrificed in this GLP study. The rapid onset and reversibility of the signs, together with the subsequent dose-reduction protocol, underscore the need for careful pharmacodynamic monitoring during early clinical translation. Based on our

preclinical AMI data, vasodilation during reperfusion injury appears to be a key mechanism by which APOSEC™ prevents cardiac remodelling (34).

Fractionated microvesicle-enriched secretome (MVECS) versus complete stressed PBMC secretome in regenerative medicine: an evolving development pathway

In 2005, Gnecchi et al. first reported that concentrated MSC secretome attenuated hypoxia-induced myocardial damage (32). Today, most regenerative-medicine experts accept that ATMPs and secretome-based therapies may have clinical value. However, the optimal cellular source for secretome-based therapeutics remains unresolved and may include manipulated mesenchymal stem cells, cardiovascular induced pluripotent stem cells (iPSCs), HUVECs, and peripheral blood mononuclear cells (PBMCs). We believe that market authorisation will require rigorously conducted phase III GCP trials supported by demonstrated cost-effectiveness.

The APOSEC™ GMP production process offers several advantages for researchers, pharmaceutical developers, and investors: a) the IMP manufacturing process has changed only marginally since 2005; b) APOSCIENCE™ uses an abundant cell source as a bioreactor, namely a current waste product of blood banks worldwide; c) PBMCs are stressed to enrich lipid, protein, and exosome content (4); d) the cost of goods (COGs) for GMP-grade APOSEC™ is very low, with 50 U costing EUR 80 in 2026; and e) medical-grade albumin and insulin are integral IMP components. Importantly, fractionating APOSEC™ into exosome, lipid, or protein components, or culturing PBMCs without albumin and insulin, abolishes biological activity (5).

This publication responds directly to the important work of Humbert et al. and Menasché et al. (27,28). They reported that an iPSC-derived secretome undergoes tangential flow filtration (TFF; 30 kDa molecular weight cut-off, MWCO) to generate an off-the-shelf EV-enriched concentrate. However, they also acknowledged a major limitation: more restrictive EV isolation using a higher MWCO reduced biological activity *in vitro* (unpublished data). This observation aligns with our findings. In our GMP process, we avoided secretome concentration and used lyophilisation instead. APOSEC™ lyophilizate retained biological potency and stability for up to 72 months (APOSCIENCE™ GMP stability trial, unpublished data). Under ICH guidance, IMP potency assays should reflect an identified mode of action (MOA). We therefore question whether a non-standardisable HUVEC-based proliferation assay can serve as a validated potency assay. Validation should demonstrate sensitivity, specificity, dose dependence, and inhibition of biological activity; in this setting, exosome depletion of MVECS should prevent HUVEC proliferation. The reported potency assay was also not benchmarked against an internal MVECS reference batch. Finally, we question whether exosome content alone, rather than biological activity measured in a validated cell-based potency assay, can reliably demonstrate batch-to-batch comparability.

Defining “similar toxicities” in secretome therapy: murine and rodent models are not non-human primates (NHPs)

The three intravenous APOSEC™ GLP toxicology reports are provided as Additional files 9-11. In murine and rodent models, the NOAEL exceeded 500 U/kg body weight. By contrast, at 10 times the anticipated human intended dose of APOSEC™

(350 U/kg body weight), 2 of 5 Cynomolgus monkeys died, showing that APOSEC™, like other approved therapeutics, can cause severe adverse effects. From a clinically informed historical perspective, three major medical safety crises are particularly relevant. First, the public health consequences of the thalidomide tragedy remain evident today; use of an NHP model might have detected its teratogenicity. Since then, Cynomolgus monkeys have been widely used in safety toxicology (35). Second, CD40L (CD154) monoclonal antibodies were extensively studied for transplantation and autoimmune disease, but a first-in-human trial was stopped prematurely because of thromboembolic and cardiovascular events (36). We previously proposed that CD40L–FCγRIIA (CD32) receptor interaction might explain this observation (37,38), a hypothesis later supported by Robles-Carrillo et al. in FCγRIIA-transgenic mice (39). Third, more than two decades ago, the CD28 superagonist TGN1412 was evaluated preclinically for T-cell deficiency syndromes, autoimmune disease, and B-cell lymphoma. Although repeated-dose NHP toxicology suggested an acceptable safety profile, the subsequent first-in-human trial ended tragically (40,41). Together, these examples show that murine, rodent, and NHP models each have limitations in predicting adverse events in humans (42,43).

Conclusion and interpretation

Secretome-based preclinical research offers credible hope for patients with substantial unmet medical needs. Regulatory authorities classify APOSEC™ as a biological medicinal product under Directive 2001/83/EC. To protect patients and support animal welfare, IMP developers must comply with ICH-aligned GMP, GLP,

and GCP requirements. In this context, the author considers it irresponsible, and potentially scientific misconduct, to withhold GLP safety studies that identify clinically relevant risks. APOSCIENCE™ has shown that comprehensive GLP toxicology studies in NHPs are necessary to detect safety risks associated with secretome therapy. Our GLP data demonstrate that mouse and rodent models are only partly comparable to Cynomolgus monkeys; therefore, all developers of secretome-based IMPs should follow ICH guidelines throughout development.

Literature

1. Beer L, Nemec L, Wagner T, Ristl R, Altenburger LM, Ankersmit HJ, et al. Ionizing radiation regulates long non-coding RNAs in human peripheral blood mononuclear cells. *J Radiat Res (Tokyo)*. 2017 Mar 1;58(2):201–9. doi:10.1093/jrr/rrw111 PubMed PMID: 27974506; PubMed Central PMCID: PMC5603904.
2. Beer L, Seemann R, Ristl R, Ellinger A, Kasiri MM, Mitterbauer A, et al. High dose ionizing radiation regulates micro RNA and gene expression changes in human peripheral blood mononuclear cells. *BMC Genomics*. 2014 Sep 25;15(1):814. doi:10.1186/1471-2164-15-814 PubMed PMID: 25257395; PubMed Central PMCID: PMC4182888.
3. Kasiri MM, Beer L, Nemec L, Gruber F, Pietkiewicz S, Haider T, et al. Dying blood mononuclear cell secretome exerts antimicrobial activity. *Eur J Clin Invest*. 2016

598 Oct;46(10):853–63. doi:10.1111/eci.12667 PubMed PMID: 27513763; PubMed
599 Central PMCID: PMC5113772.

600 4. Beer L, Zimmermann M, Mitterbauer A, Ellinger A, Gruber F, Narzt MS, et al.
601 Analysis of the Secretome of Apoptotic Peripheral Blood Mononuclear Cells:
602 Impact of Released Proteins and Exosomes for Tissue Regeneration. Sci Rep.
603 2015 Nov 16;5:16662. doi:10.1038/srep16662 PubMed PMID: 26567861;
604 PubMed Central PMCID: PMC4645175.

605 5. Wagner T, Traxler D, Simader E, Beer L, Narzt MS, Gruber F, et al. Different pro-
606 angiogenic potential of γ -irradiated PBMC-derived secretome and its
607 subfractions. Sci Rep. 2018 Dec 20;8(1):18016. doi:10.1038/s41598-018-
608 36928-6

609 6. Mildner M, Hacker S, Haider T, Gschwandtner M, Werba G, Barresi C, et al.
610 Secretome of peripheral blood mononuclear cells enhances wound healing.
611 PloS One. 2013;8(3):e60103. doi:10.1371/journal.pone.0060103 PubMed PMID:
612 23533667; PubMed Central PMCID: PMC3606336.

613 7. Hacker S, Mittermayr R, Nickl S, Haider T, Leberherz-Eichinger D, Beer L, et al.
614 Paracrine Factors from Irradiated Peripheral Blood Mononuclear Cells Improve
615 Skin Regeneration and Angiogenesis in a Porcine Burn Model. Sci Rep. 2016
616 Apr 29;6(1):25168. doi:10.1038/srep25168

617 8. Hacker S, Mittermayr R, Traxler D, Keibl C, Resch A, Salminger S, et al. The
618 secretome of stressed peripheral blood mononuclear cells increases tissue

619 survival in a rodent epigastric flap model. *Bioeng Transl Med*. 2021
620 Jan;6(1):e10186. doi:10.1002/btm2.10186 PubMed PMID: 33532586; PubMed
621 Central PMCID: PMC7823127.

622 9. Vorstandlechner V, Copic D, Klas K, Direder M, Golabi B, Radtke C, et al. The
623 Secretome of Irradiated Peripheral Mononuclear Cells Attenuates Hypertrophic
624 Skin Scarring. *Pharmaceutics*. 2023 Mar 25;15(4):1065.
625 doi:10.3390/pharmaceutics15041065 PubMed PMID: 37111549; PubMed
626 Central PMCID: PMC10143262.

627 10. Altmann P, Mildner M, Haider T, Traxler D, Beer L, Ristl R, et al. Secretomes of
628 apoptotic mononuclear cells ameliorate neurological damage in rats with focal
629 ischemia. *F1000Research*. 2014;3:131. doi:10.12688/f1000research.4219.2
630 PubMed PMID: 25383184; PubMed Central PMCID: PMC4215751.

631 11. Lichtenauer M, Mildner M, Hoetzenecker K, Zimmermann M, Podesser BK,
632 Sipos W, et al. Secretome of apoptotic peripheral blood cells (APOSEC) confers
633 cytoprotection to cardiomyocytes and inhibits tissue remodelling after acute
634 myocardial infarction: a preclinical study. *Basic Res Cardiol*. 2011
635 Nov;106(6):1283–97. doi:10.1007/s00395-011-0224-6 PubMed PMID:
636 21952733; PubMed Central PMCID: PMC3228946.

637 12. Hoetzenecker K, Assinger A, Lichtenauer M, Mildner M, Schweiger T, Starlinger
638 P, et al. Secretome of apoptotic peripheral blood cells (APOSEC) attenuates
639 microvascular obstruction in a porcine closed chest reperfused acute myocardial
640 infarction model: role of platelet aggregation and vasodilation. *Basic Res Cardiol*.

641 2012 Sep;107(5):292. doi:10.1007/s00395-012-0292-2 PubMed PMID:
 642 22899170; PubMed Central PMCID: PMC3442164.

643 13. Klas K, Ondracek AS, Hofbauer TM, Mangold A, Pfisterer K, Laggner M, et al.
 644 The Effect of Paracrine Factors Released by Irradiated Peripheral Blood
 645 Mononuclear Cells on Neutrophil Extracellular Trap Formation. Antioxidants.
 646 2022 Aug 11;11(8):1559. doi:10.3390/antiox11081559 PubMed PMID:
 647 36009277; PubMed Central PMCID: PMC9405389.

648 14. Laggner M, Copic D, Nemec L, Vorstandlechner V, Gugerell A, Gruber F, et al.
 649 Therapeutic potential of lipids obtained from γ -irradiated PBMCs in dendritic cell-
 650 mediated skin inflammation. EBioMedicine. 2020 May;55:102774.
 651 doi:10.1016/j.ebiom.2020.102774 PubMed PMID: 32403085; PubMed Central
 652 PMCID: PMC7218268.

653 15. Laggner M, Acosta GS, Kitzmüller C, Copic D, Gruber F, Altenburger LM, et al.
 654 The secretome of irradiated peripheral blood mononuclear cells attenuates
 655 activation of mast cells and basophils. EBioMedicine. 2022 Jul;81:104093.
 656 doi:10.1016/j.ebiom.2022.104093 PubMed PMID: 35671621; PubMed Central
 657 PMCID: PMC9168057.

658 16. Panahipour L, Kochergina E, Laggner M, Zimmermann M, Mildner M, Ankersmit
 659 HJ, et al. Role for Lipids Secreted by Irradiated Peripheral Blood Mononuclear
 660 Cells in Inflammatory Resolution in Vitro. Int J Mol Sci. 2020 Jun 30;21(13):4694.
 661 doi:10.3390/ijms21134694 PubMed PMID: 32630157; PubMed Central PMCID:
 662 PMC7370068.

17. Haider T, Höftberger R, Rüger B, Mildner M, Blumer R, Mitterbauer A, et al. The secretome of apoptotic human peripheral blood mononuclear cells attenuates secondary damage following spinal cord injury in rats. *Exp Neurol*. 2015 May;267:230–42. doi:10.1016/j.expneurol.2015.03.013 PubMed PMID: 25797576.
18. Hoetzenecker K, Zimmermann M, Hoetzenecker W, Schweiger T, Kollmann D, Mildner M, et al. Mononuclear cell secretome protects from experimental autoimmune myocarditis. *Eur Heart J*. 2015 Mar 14;36(11):676–85. doi:10.1093/eurheartj/ehs459 PubMed PMID: 23321350; PubMed Central PMCID: PMC4359357.
19. Copic D, Direder M, Schossleitner K, Laggner M, Klas K, Bormann D, et al. Paracrine Factors of Stressed Peripheral Blood Mononuclear Cells Activate Proangiogenic and Anti-Proteolytic Processes in Whole Blood Cells and Protect the Endothelial Barrier. *Pharmaceutics*. 2022 Jul 30;14(8):1600. doi:10.3390/pharmaceutics14081600 PubMed PMID: 36015226; PubMed Central PMCID: PMC9415091.
20. Ankersmit HJ, Hoetzenecker K, Dietl W, Soleiman A, Horvat R, Wolfsberger M, et al. Irradiated cultured apoptotic peripheral blood mononuclear cells regenerate infarcted myocardium. *Eur J Clin Invest*. 2009 Jun;39(6):445–56. doi:10.1111/j.1365-2362.2009.02111.x PubMed PMID: 19397690.
21. Pavo N, Zimmermann M, Pils D, Mildner M, Petrás Z, Petneházy Ö, et al. Long-acting beneficial effect of percutaneously intramyocardially delivered secretome

of apoptotic peripheral blood cells on porcine chronic ischemic left ventricular dysfunction. *Biomaterials*. 2014 Apr;35(11):3541–50. doi:10.1016/j.biomaterials.2013.12.071 PubMed PMID: 24439416.

22. Simader E, Traxler D, Kasiri MM, Hofbauer H, Wolzt M, Glogner C, et al. Safety and tolerability of topically administered autologous, apoptotic PBMC secretome (APOSEC) in dermal wounds: a randomized Phase 1 trial (MARSYAS I). *Sci Rep*. 2017 Jul 24;7(1):6216. doi:10.1038/s41598-017-06223-x

23. Gugerell A, Gouya-Lechner G, Hofbauer H, Laggner M, Trautinger F, Almer G, et al. Safety and clinical efficacy of the secretome of stressed peripheral blood mononuclear cells in patients with diabetic foot ulcer-study protocol of the randomized, placebo-controlled, double-blind, multicenter, international phase II clinical trial MARSYAS II. *Trials*. 2021 Jan 6;22(1):10. doi:10.1186/s13063-020-04948-1 PubMed PMID: 33407796; PubMed Central PMCID: PMC7789696.

24. Laggner M, Gugerell A, Bachmann C, Hofbauer H, Vorstandlechner V, Seibold M, et al. Reproducibility of GMP-compliant production of therapeutic stressed peripheral blood mononuclear cell-derived secretomes, a novel class of biological medicinal products. *Stem Cell Res Ther*. 2020 Jan 3;11(1):9. doi:10.1186/s13287-019-1524-2 PubMed PMID: 31900195; PubMed Central PMCID: PMC6942406.

25. Gugerell A, Sorgenfrey D, Laggner M, Raimann J, Peterbauer A, Bormann D, et al. Viral safety of APOSECTM: a novel peripheral blood mononuclear cell derived-biological for regenerative medicine. *Blood Transfus Trasfus Sanguie*.

707 2020 Jan;18(1):30–9. doi:10.2450/2019.0249-18 PubMed PMID: 30865581;
 708 PubMed Central PMCID: PMC7053523.

709 26. Wuschko S, Gugerell A, Chabicovsky M, Hofbauer H, Laggner M, Erb M, et al.
 710 Toxicological testing of allogeneic secretome derived from peripheral
 711 mononuclear cells (APOSEC): a novel cell-free therapeutic agent in skin disease.
 712 Sci Rep. 2019 Apr 3;9(1):5598. doi:10.1038/s41598-019-42057-5 PubMed
 713 PMID: 30944367; PubMed Central PMCID: PMC6447581.

714 27. Humbert C, Cordier C, Drut I, Hamrick M, Wong J, Bellamy V, et al. GMP-
 715 Compliant Process for the Manufacturing of an Extracellular Vesicles-Enriched
 716 Secretome Product Derived From Cardiovascular Progenitor Cells Suitable for
 717 a Phase I Clinical Trial. J Extracell Vesicles. 2025 Aug;14(8):e70145.
 718 doi:10.1002/jev2.70145 PubMed PMID: 40831309; PubMed Central PMCID:
 719 PMC12365392.

720 28. Menasché P, Renault NK, Hagège A, Puscas T, Bellamy V, Humbert C, et al.
 721 First-in-man use of a cardiovascular cell-derived secretome in heart failure.
 722 Case report. EBioMedicine. 2024 May;103:105145.
 723 doi:10.1016/j.ebiom.2024.105145 PubMed PMID: 38713924; PubMed Central
 724 PMCID: PMC11096705.

725 29. Spannbaauer A, Mester-Tonczar J, Traxler D, Kastner N, Zlabinger K,
 726 Hašimbegović E, et al. Large Animal Models of Cell-Free Cardiac Regeneration.
 727 Biomolecules. 2020 Sep 29;10(10):1392. doi:10.3390/biom10101392 PubMed
 728 PMID: 33003617; PubMed Central PMCID: PMC7600588.

- 729 30. Desgres M, Lima Correa B, Petrusca L, Autret G, Pezzana C, Marigny C, et al.
730 Therapeutic potential of extracellular vesicles derived from cardiac progenitor
731 cells in rodent models of chemotherapy-induced cardiomyopathy. *Front*
732 *Cardiovasc Med.* 2023;10:1206279. doi:10.3389/fcvm.2023.1206279 PubMed
733 PMID: 37485274; PubMed Central PMCID: PMC10360184.
- 734 31. Wollert KC, Drexler H. Cell therapy for the treatment of coronary heart disease:
735 a critical appraisal. *Nat Rev Cardiol.* 2010 Apr;7(4):204–15.
736 doi:10.1038/nrcardio.2010.1 PubMed PMID: 20177405.
- 737 32. Gnecci M, He H, Liang OD, Melo LG, Morello F, Mu H, et al. Paracrine action
738 accounts for marked protection of ischemic heart by Akt-modified mesenchymal
739 stem cells. *Nat Med.* 2005 Apr;11(4):367–8. doi:10.1038/nm0405-367 PubMed
740 PMID: 15812508.
- 741 33. Lai RC, Arslan F, Lee MM, Sze NSK, Choo A, Chen TS, et al. Exosome secreted
742 by MSC reduces myocardial ischemia/reperfusion injury. *Stem Cell Res.* 2010
743 May;4(3):214–22. doi:10.1016/j.scr.2009.12.003 PubMed PMID: 20138817.
- 744 34. Mildner CS, Copic D, Zimmermann M, Lichtenauer M, Direder M, Klas K, et al.
745 Secretome of Stressed Peripheral Blood Mononuclear Cells Alters
746 Transcriptome Signature in Heart, Liver, and Spleen after an Experimental Acute
747 Myocardial Infarction: An In Silico Analysis. *Biology.* 2022 Jan 13;11(1):116.
748 doi:10.3390/biology11010116 PubMed PMID: 35053121; PubMed Central
749 PMCID: PMC8772778.

35. Korte R, Vogel F, Osterburg I. The primate as a model for hazard assessment of teratogens in humans. *Arch Toxicol Suppl Arch Toxikol Suppl*. 1987;11:115–21. doi:10.1007/978-3-642-72558-6_16 PubMed PMID: 3477153.
36. Barrile R, van der Meer AD, Park H, Fraser JP, Simic D, Teng F, et al. Organ-on-Chip Recapitulates Thrombosis Induced by an anti-CD154 Monoclonal Antibody: Translational Potential of Advanced Microengineered Systems. *Clin Pharmacol Ther*. 2018 Dec;104(6):1240–8. doi:10.1002/cpt.1054 PubMed PMID: 29484632.
37. Ankersmit HJ, Roth GA, Moser B, Zuckermann A, Brunner M, Rosin C, et al. CD32-mediated platelet aggregation in vitro by anti-thymocyte globulin: implication of therapy-induced in vivo thrombocytopenia. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2003 Jun;3(6):754–9. doi:10.1034/j.1600-6143.2003.00150.x PubMed PMID: 12780568.
38. Roth GA, Zuckermann A, Klepetko W, Wolner E, Ankersmit HJ, Moser B, et al. Thrombophilia associated with anti-CD154 monoclonal antibody treatment and its prophylaxis in nonhuman primates. *Transplantation*. 2004 Oct 27;78(8):1238–9; author reply 1239. doi:10.1097/01.tp.0000135457.69220.5b PubMed PMID: 15502729.
39. Robles-Carrillo L, Meyer T, Hatfield M, Desai H, Dávila M, Langer F, et al. Anti-CD40L immune complexes potently activate platelets in vitro and cause thrombosis in FCGR2A transgenic mice. *J Immunol*. 2010 Aug 1;185(3):1577–83. doi:10.4049/jimmunol.0903888 PubMed PMID: 20585032.

- 772 40. Attarwala H. TGN1412: From Discovery to Disaster. *J Young Pharm JYP*. 2010
773 Jul;2(3):332–6. doi:10.4103/0975-1483.66810 PubMed PMID: 21042496;
774 PubMed Central PMCID: PMC2964774.
- 775 41. Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD,
776 et al. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody
777 TGN1412. *N Engl J Med*. 2006 Sep 7;355(10):1018–28.
778 doi:10.1056/NEJMoa063842 PubMed PMID: 16908486.
- 779 42. Shen H, Yang Z, Rodrigues AD. Cynomolgus Monkey as an Emerging Animal
780 Model to Study Drug Transporters: In Vitro, In Vivo, In Vitro-to-In Vivo
781 Translation. *Drug Metab Dispos Biol Fate Chem*. 2022 Mar;50(3):299–319.
782 doi:10.1124/dmd.121.000695 PubMed PMID: 34893475.
- 783 43. Son YW, Choi HN, Che JH, Kang BC, Yun JW. Advances in selecting
784 appropriate non-rodent species for regulatory toxicology research: Policy,
785 ethical, and experimental considerations. *Regul Toxicol Pharmacol RTP*. 2020
786 Oct;116:104757. doi:10.1016/j.yrtph.2020.104757 PubMed PMID: 32758521.

787

788 Declarations

789 Consent for publication

790 Not applicable

791 Availability of data and materials

792 All data generated or analysed during this study are included in this published article
793 [and its supplementary information files].

794 Competing interests

795 The Medical University of Vienna has claimed financial interest. Aposcience AG
796 holds patents related to this work (EP20080450198, EP20080450199, and
797 EP17209165). H.J.A. hold patents related to this work (WO 2026/052783, WO
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805 Authors' contributions

806 H.J.A. wrote the main manuscript text, was responsible for the test substance and
807 coordinated the study.

808 Acknowledgements

809 Not applicable



MEETING MINUTES

Secretome of human apoptotic peripheral blood mononuclear cells (APOSEC TM)

SCIENTIFIC ADVICE

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Dirk Sorgenfrey Quality

Meeting

Date: 20.04.2017
Time: 13:30-15:30
Meeting place: AGES, Traisengasse 5, A-1200 Vienna

Details on the medicinal product

Substance	Secretome of human apoptotic peripheral blood mononuclear cells (APOSEC TM)
Therapeutic indication	Diabetic foot ulcers (DFU)
Therapeutic classification (group/ ATC code)	Not applicable
Dosage form	Gel
Route of administration	Topical
Type of Produkt	Other biological

Geschäftszahl – 701427-01-2017-BGA



MEETING MINUTES

Secretome of human apoptotic peripheral blood mononuclear cells (APOSEC™)

Question 1 (CMC)

The drug substance is a biological substance consisting of a complex mix of components that in their entirety mediate the desired pharmacological effect. Aposcience considers defining and controlling the complex mix of active components at a molecular level is not applicable for APOSEC™. For this reason, the quality of APOSEC™ is primarily defined by a well-established production process and assured by controlling critical starting materials, critical process parameters, in-process controls, and batch release testing.

Does the Agency agree with this approach?

AGES response

- The agency agrees that APOSEC™ is a biological medicinal product according to Directive 2001/83/EC.
- Essentially, the agency agreed to the described approach.
- It was accepted that APOSEC™ cannot be completely characterised at the molecular level. Aposcience provided characterization data on the allogeneic product. However, it is expected that the product quality of APOSEC™ (allogeneic), which will be used to supply the intended phase II study, will be characterized extensively. The agency recommends to define a) key components (based on scientific literature and own research data) which mediate the desired biological effect in the intended indication and b) components which are supportive. For proof of batch-to-batch consistency any suitable component (or marker) could be used.
- Apart from the characterisation, the sponsor should describe (based on scientific literature) the correlation between the claimed mode of action(s) and APOSEC™ key components in more detail.
- The sponsor should demonstrate that the potency assays applied reflect the biological effect of APOSEC™. It is expected that the potency is sensitive to detect differences in in vitro potency due to potential heterogeneity in the composition of APOSEC™.
- Data on donor variability (prior to pooling) should be provided, employing the developed in vitro potency assays.
- In general: data based on autologous APOSEC™ can only be used as supportive for allogeneic APOSEC™ from a scientific point of view. From a regulatory aspect autologous and allogeneic APOSEC™ are two different products.

Question 2 (CMC)

Aposcience maintains a **risk-based quality assurance concept** for the APOSEC™ drug product, which reflects the complex nature of the product and its manufacturing process. The main pillars include **viral and microbial safety** and assurance of **batch to batch consistency**. The Company considers this quality assurance strategy for the drug product adequate and sufficient to supply IMP for the proposed Phase II study.

Does the Agency agree?

AGES response

- Essentially, the agency agreed to the described approach, i.e. quality assurance concept should be based on assurance of viral and microbial safety and of batch-to-batch consistency.
- The justification for the selection of a proxy to demonstrate batch-to-batch consistency should be described in more detail.
- Potency assays applied should be sensitive enough to detect batch-to-batch differences of APOSEC™.
- Regarding viral safety the AGES raised concerns over viral clearance of non-enveloped viruses as both viral clearance steps that are applied (methylene blue/illumination & gamma-irradiation) are known to have



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limited efficacy against this viral group. The viral safety has to be justified based on a risk assessment, i.e. it needs to be demonstrated that all (reasonable) options have been exhausted.

- In the IMPD all available viral clearance methods have to be discussed regarding their suitability for APOSEC™ in accordance with Guideline "Virus safety evaluation of biotechnological investigational medicinal products (EMA/CHMP/BWP/398498/2005)".
- In the IMPD prion hazard has to be considered. Literature data are sufficient as long as the manufacturing process of APOSEC™ does show analogies to another already authorized product.
- For release testing a single well justified assay/potency test is sufficient.
- *Post meeting notes:*
 - a) *In future regulatory submissions, it should be clarified if there are specific selection criteria for donors and whether special key parameters (for example parameters selected for characterization/batch release) are determined prior to pooling with a view to selection of donations complementing each other for pooling or elimination of others? This information is relevant in the context of batch-to-batch consistency.*
 - b) *For prion safety the respective EMA-Guidelines (applicable to human plasma products) might be considered, as far as applicable: "Position Statement Creutzfeldt-Jakob disease and plasma-derived and urine-derived medicinal products (CHMP/BWP/303353/2010)" and "Investigation of manufacturing processes for plasma-derived medicinal products with regard to variant Creutzfeldt-Jakob disease risk (CPMP/BWP/5136/03)"*

Question 3 (CMC)

APOSEC™ dosing nomenclature: lyophilisate of 1 mL supernatant (contains the secretome of 25 Mio PMBCs) will be referred to as 25 U (U = Units) hereafter.

Does the Agency support this rationale and approach?

AGES response

- The AGES recommends NOT to use units (U) because units are generally related to a clearly defined and quantifiable reference standard.
- The AGES suggested to use the term 1 dose for the equivalent of 1 mL secretome derived from 25×10^6 PBMCs. Other dose definitions are applicable. A justification for the choice of nomenclature should be provided.

Question 4 (pharmaco-toxicological development)

Aposcience considers that the conducted and proposed non-clinical pharmacology and safety program is acceptable and that there are no further requirements for non-clinical testing of APOSEC™ prior to the inclusion and treatment of DFU patients in Phase II clinical studies, assuming that the following, planned non-clinical studies are performed and the results do not warrant further investigations.

- 4-week toxicity study of APOSEC™ *via* i.v. administration three times weekly to rats (GLP – Study, planned 2017)
- 4-week toxicity study of APOSEC™ *via* s.c. administration three times weekly to dogs, including respiratory and cardiovascular safety pharmacology parameters (GLP – Study, planned 2017)

Does the Agency support this rationale and approach?



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AGES response

In general, the AGES consider the proposed non-clinical testing strategy as appropriate and adequate, however, following aspects were pointed out by AGES:

Concerning pharmacology the hypothesized pleiotropic mechanism of action is well taken, but demands a scientific rationale to bridge quality/CMC aspects to clinical aspects. An appropriately selected potency assay represents an essential element in this regards, which is also required to calculate safety margins derived from nonclinical studies. Beside the concerns addressed in Question 3 above, the currently chosen potency (with 25 Us containing the secretome of 25 Mio PBMCs) presents limitations (is considered more a process parameter than a quality attribute), and demands appropriate data-driven justification.

No justification for the relevance of the selected tox species is provided with the briefing book, but is required for ICH S6(R1) compliance: a relevant species is one in which the test material is pharmacologically active. Based on data obtained from the wound healing study in the porcine burn model, the mini-pig seems to qualify as relevant species and the AGES further emphasized, that human and porcine skin are similar with regard to thickness and general morphology. In contrast, no data confirming the dog and rat as pharmacological relevant model for human derived APOSEC™ has been provided and such data are not available.

It was further emphasized, that one relevant species may even suffice for non-clinical safety testing according to ICH S6(R1), but certainly depends on the scientific rationale prepared by the developer regarding availability of relevant animal species. Aposcience mentioned plans for a s.c. study in one pharmacological relevant species.

Post-meeting note: The mouse was also confirmed as pharmacological relevant model as shown in a diabetic mouse model (Traxler et al. in preparation; abstract attached) and in a wild type mouse model (Mildner et al. 2013; attached). As for the pig study, the pharmacology studies in mice were also conducted with human derived APOSEC™. If the mouse model will be selected for toxicity testing, the data confirming the pharmacological relevance of this species will be discussed in detail in the IB.

No further i.v. studies are planned to support the topical application of APOSEC™ indicated for the treatment of DFU.

- Of note: Intravenous toxicity testing is planned as part of a safety program, intended to support i.v. use in cardiomyofarct patients.

Post-meeting note AGES: The Company is reminded that this approach still requires argumentation to satisfy following aspects:

(i) Due to significant differences in skin morphology the mouse is considered suboptimal in its translational value if compared with mini-pig – facing the targeted DFU indication.

(ii) according to ICH S6(R1) single species testing is justified, if the clinical candidate is pharmacologically active in only one species. According to the presented argumentation mini-pig as well as mouse in principle qualify as relevant species, as such one rodent and one non-rodent species seem to be available.

Reference to ICH S6(R1) is made:

2.2. One or two species

"If there are two pharmacologically relevant species for the clinical candidate (one rodent and one non-rodent), then both species should be used for short-term (up to 1 month duration) general toxicology studies. If the toxicological findings from these studies are similar or the findings are understood from the mechanism of action of the product, then longer-term general toxicity studies in one species are usually considered sufficient. The rodent species should be considered unless there is a scientific rationale for using non-rodents. Studies in two non-rodent species are not appropriate."



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Secretome of human apoptotic peripheral blood mononuclear cells (APOSEC TM)

*The use of one species for all general toxicity studies is justified when the clinical candidate is **pharmacologically active in only one species**. Studies in a second species with a homologous product are not considered to add further value for risk assessment and are not recommended."*

The AGES asked, if it can be excluded, that the residual amount of methylene blue in the final product induces a pharmacological or toxicological effect. Aposcience is confident, that the residual amount of methylene blue is safe and will provide adequate information as part of the CTA documentation.

- Traxler et al. Improved wound healing by topical application of APOSEC™ in a diabetic mouse model. European Cells and Materials Vol. 31. Suppl. 1, 2016.
- Mildner et al. Secretome of peripheral blood mononuclear cells enhances wound healing. PloS one. 2013;8(3).

Question 5 (clinical trials)

For moving into Phase III, Aposcience considers it sufficient conducting a single combined Phase II efficacy and dose ranging study. Does the Agency agree with this approach?

AGES response

Phase II study:

- The intended phase II study will be the first in human study for the allogeneic APOSEC™ and should be named accordingly as FIRST in Human Phase II study.

Design:

- The overall design was accepted by the AGES in terms of study population/ run in period.
- For proceeding to the main study after completion of the SAFETY lead-in study (FIH study) clear safety criteria will need to be predefined in the protocol under which circumstances the study might continue into the main study part OR an interim report on the findings of the SAFETY lead-in study will be required.

Dose groups:

- The AGES agreed to the intended safety margin and dose selection. However, careful attention should be paid to discriminating among the three APOSEC™ dose groups according to wound size. It is recommended to adapt the APOSEC™ gel dosing to amount/cm² wound surface or to identify a better dosing scheme. With the current dosing scheme there is a risk of underdosing of large wounds. Only a clear discrimination of dose groups will allow reproducible treatment effect size.
- Careful attention should be paid to recruiting comparable patient cohorts within the different dose groups in particular in terms of wound size and severity.
- Comparator:
No objection for the use of parallel induced cell-free control lyophilisate formulated in NU-GEL® for topical administration as the comparator product for APOSEC™.

Study population:

- Superinfected wounds as an exclusion criteria was accepted, though criteria should be defined in the protocol such as clinical signs of infected wound and systemic rise in inflammatory parameters. The agency agrees that no microbiological smear needs to be taken from the wound to rule out superinfection.
- Treatment duration:
The proposed treatment duration of 4 weeks was considered acceptable for the Phase II study. However, a more detailed rationale for the 4 week treatment duration shall be provided for the Phase III study. Aposcience referred to a previously published manuscript by Holzinger et al. (6) where a 4 week treatment duration was sufficient to achieve wound closure for patients with DFU and venous ulcers.



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Secretome of human apoptotic peripheral blood mononuclear cells (APOSEC TM)

- Based on the assumption that a 4 week treatment duration would suffice to achieve complete wound closure, the entire preclinical toxicology program has been based on a period of 4 weeks.

Endpoint:

- For the early stage of the clinical FIH/ phase II study AGES agreed to the primary endpoint: wound area reduction at 4 weeks. The assessment of epithelialization is crucial and should be clearly defined.
- The agency agrees to the list of secondary endpoints including wound closure during a 12 week study period for the phase II trial and recommends to use this endpoint for the pivotal studies as primary endpoint with a longer FU period.

Question 6 (clinical trials)

In Phase III, two confirmatory double blind, randomized, placebo controlled efficacy and safety studies are planned in patients with DFU and in a cohort of diabetic patients with advanced wound-healing problems. All trial participants will receive standardized best practice wound care. The primary trial endpoint of full wound closure will be measured at 3 months.

Does the Agency consider this approach appropriate?

AGES response

Clinical development program:

- For market authorization with only one pivotal phase III study, Aposcience will need to fulfill the criteria defined in the EMA guidance for „application with one pivotal trial guidance“. A single pivotal phase III study might be considered if the results of the phase II and the one phase III meet the EMA guidance criteria (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003657.pdf). The AGES had no general objections against the strategy to plan for a single pivotal trial only.

Study population:

- Overall no objection were raised regarding the presented study population and the intended expansion of indication into Wagner 3/(4) in a separate phase III trial where the highest medical need is considered. A homogenous distribution of patients among groups should be considered. A clear line should be drawn between ulcers and very severe wound damage.

Groups of study population:

- A comparable distribution of subgroups should be guaranteed in phase III trials.

Timepoint for the primary endpoint:

- The timepoint chosen for the primary endpoint of complete wound closure 8 weeks after termination of the IMP treatment (week 12) might be affected by endogenous and exogenous factors and would probably not reflect the effect size of the IMP. It is recommended to choose a timepoint which would be clinically reasonable to have achieved the maximum treatment effect size shortly after the 4 week treatment duration, alternatively a longer treatment duration could be considered. Complete wound closure as primary efficacy measure should ideally be confirmed in terms of durability, e.g. by a second assessment two weeks after primary endpoint.

Secondary endpoint

- Additional secondary endpoints should be considered to allow evaluation of the magnitude of effect size such as recurrence of DFU, number of amputations etc. with an extended follow-up period > 12 weeks.



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Secretome of human apoptotic peripheral blood mononuclear cells (APOSEC TM)

General AGES recommendations

Centralised procedure for marketing authorization

- Since a central application is considered a scientific advice at the EMA is recommended prior to initiation of pivotal clinical trials.
- In briefing book page 14 „The cells are not subjected to substantial manipulation...” should be deleted as cultivation is regarded as substantial manipulation.
- Aposcience should reconsider the starting material (more in line with ATMPs): e.g. PMBC from whole blood and NOT whole blood itself. This might circumvent regulatory hurdles in the future (discrimination from plasma products).

Vienna, 08.05.2017



Dr. René Anour

On behalf of Austrian Federal Office for Safety in Health Care

 Aposcience AG Mariannengasse 14 Top 9 A-1090 Wien Tel: +43 1 7966296-0 Fax: +43 1 7966296-222	Protokoll Nr. 1/2017 Version 1	Datum: 8.12.2017, 10:00-12:00 Ort: Paul-Ehrlich-Institut, Paul-Ehrlich-Straße 51-59, 63225 Langen, Deutschland
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MEETING MINUTES Secretome of human apoptotic peripheral blood mononuclear cells APOSEC™)

	Paul-Ehrlich-Institut (PEI) Participants: Dr. Eva-Maria Schneider Transfusion Medicine Dr. Anneliese Hilger Coagulation Products I Dr. Ute Vahlensieck Coagulation products I Dr. Johannes Blümel Viral Safety
	Aposcience AG Participants: Hendrik Jan Ankersmit COO Andreas Kronberger CFO Ghazaleh Gouya Clinical Michael Mildner Scientific development Anja Peterbauer-Scherb Production Silvio Wuschko Non-clinical Tobias Ostler Quality, tech. Regulatory Dirk Sorgenfrey Quality, tech. Regulatory Christiane Bachmann Quality, tech. Regulatory Helmut Hofbauer Administration
	Meeting Date: 08.12.2017 Time: 10:00-12:00 Meeting place: PEI, Paul-Ehrlich-Straße 51-59, 63225 Langen, Deutschland
	Details on the medicinal product

Question 1 (CMC)

The drug substance is a biological substance consisting of a complex mix of components that in their entirety mediate the desired pharmacological effect, including proteins, peptides, lipids, and exosomes. For this reason, **the quality of APOSEC™, as for other biologics, is primarily defined by the production process and its control.** In addition to the production of APOSEC™ by a well-established manufacturing process, its quality is assured via a combination of controlling critical starting materials, critical process parameters, in-process controls, and batch release testing.

Aposcience considers defining and controlling the complex mix of active components at a molecular level is not applicable for APOSECTM.

Does the Agency agree with this approach?

PEI response to Question 1

- The agency agrees with the approach that the product is primarily defined by the production process and its control. However, this approach requires a well-controlled, stable production process in order to assure batch to batch consistency.
- It is understood that APOSECTM is such a complex product that it cannot be characterized to the smallest detail. The regulatory classification of biological medicinal products depends on a pharmaceutically active substance, therefore it is essential to identify, quantify and characterize the main substance of the drug causing a certain pharmacological, immunological or metabolic action being responsible for its biologic effect (i.e. mode or mechanism of action, MoA). In addition, non-active components needed in the final formulation of the drug (excipients) have to be characterized.
- Defining the active substance responsible for the MoA will determine the pharmaceutical control strategy. It is important to justify the basis on which the controls, in particular the potency assays, are developed. The controls should be scientifically linked to the hypothesized MoA for the treatment depending on specific medicinal indication. Aposcience should demonstrate that the potency assays applied reflect the biological effect of APOSECTM and that the potency assay is sufficiently sensitive to detect differences in potency due to variability of the donor raw material (cell culture supernatant prior to pooling) and due to potential heterogeneity in the composition of the final APOSECTM drug product.
- Reducing the risk of viral and prion contamination to a minimum is essential. However, the authority acknowledged that the nature of the product precludes preferred methods of viral and prion reduction/inactivation, such as pasteurization or nanofiltration. While these methods are not feasible in case of APOSECTM, the agency conceded that it is difficult to offer clear guidance as to which additional removal or inactivation steps to include in the production process.
- It should be justified why all fractions of APOSECTM are required for the therapeutic effect. Background: preferred viral or prion depletion/inactivation methods could be employed, if fractions in APOSECTM sensitive to these methods were not essential. In particular, the importance of exosomes (which are considered critical with regards to viral and prion safety) for the anticipated mode of action should be justified.
- Based on literature as well as on the starting material, the manufacturing process and the resulting product components, a risk analysis should address prion safety and be included in the clinical trial application for the intended FIM/Phase II trial. The product will be judged by the Agency based on a benefit-risk analysis.
(An additional post meeting expert statement is attached regarding prion risk evaluation and mitigation).

Question 2 (CMC)

Aposcience maintains a **risk-based quality assurance concept** for the APOSECTM drug product, which reflects the complex nature of the product and its manufacturing process. The main pillars include **viral and microbial safety** and assurance of **batch to batch consistency**.

Several production steps assure the microbial and viral safety of the product. In addition, the quality of APOSECTM in terms of an absence of microbial and viral contamination is assured by in-process controls and batch release tests. Batch to batch consistency will be demonstrated by controlling selected components of APOSECTM and potency assessments.

The company considers this quality assurance strategy for the drug product adequate and sufficient to supply IMP for the proposed Phase II-study.

Does the Agency agree?

PEI response to Question 2

- Essentially, the agency agrees to the described approach. In particular, PEI agrees with the proposed quality assurance strategy under the condition that the quality of APOSEC™ used to supply the intended phase II study will be characterized by control of the starting material, control of the analytical markers to monitor batch to batch consistency, and control of the potency reflecting the representative modes of actions for APOSEC™.
- Question PEI: Did you contemplate the development of potency assays which cover the presented mode of actions “neoangiogenesis” and “anti-microbial activity”? This should be considered for further development (beyond phase II).
- It should be demonstrated that the potency assay(s) applied to batch release testing are sensitive to detect quality difference with respect to the intended indication of APOSEC™. Question PEI: Is there a correlation between the test results of the protein proxies (IL-8, EGF, TGF-β) and those of the potency assays? At the same time the PEI agreed that there was no obvious relationship discernable from the data set.
- Question PEI: One IL-8 value was outside (above) its specified range. (Response from Aposcience AG (Ankersmit): If protein proxies are outside the range, the batches are discarded. However, in this case the batch was released for a toxicology study anyway, because the IL-8 value was barely out of specification.)
- APOSEC™ is a new product. In the blood plasma industry there is a continued discussion on prion safety. The purification process of plasma proteins reduces potential prion contamination (CHMP position statement EMA/CHMP/BWP/303353/2010). However, this cannot be expected in the same way for Aposec as the product does not represent purified proteins. While a leucodepletion step might remove leukocyte-associated infectivity, infectivity also been found associated with platelet fraction and plasma. Exosomes have been found to harbor infectivity. If exosomes and lipids are needed for the therapeutic effect of APOSEC™, the options of prion and viral clearance are limited (e.g. nanofiltration is not possible). The Agency will judge APOSEC™ in comparison to other existing products regarding its benefit/risk ratio.
- In general, the agency stated that it is desired to implement two steps for virus inactivation or virus removal as it is the case for plasma-derived medicinal products. Gamma- irradiation is not expected to efficiently inactivate Hepatitis B virus and the effect of methylene blue treatment is not clear. However, for APOSEC™ the risk of infection with Hepatitis B viruses (HBV) is minimized, since all blood donations are individually tested for HBV with quantitative PCR and discarded, if found positive for HBV. Suggestion PEI: The current standard irradiation dose recommended as per Ph. Eur. 5.1.2 was established for microbial contamination. However, it is expected that the minimal irradiation dose will have to be increased from 25 kGy to 30 kGy or even 35 or 40 kGy to achieve 4 log inactivation of a broad range of viruses including retroviruses and parvoviruses. If a dose significantly higher than ≤25 kGy were to be used, the effect on the product quality would have to be evaluated, e.g. using Aposcience's potency assays. Viral inactivation studies are expected for clinical trial applications. Post meeting note: For definition of the minimum irradiation dose, validation of the distribution of gamma irradiation in the chamber should be considered.
- Filtration utilizing smaller filters would improve the product's viral and microbial risk profile. However, this is impossible without filtering out some of APOSEC™ 's fractions needed for its full efficacy. Therefore, justification for the existence of the different fractions within the product regarding its therapeutic effect is required.
- PEI question: There is no additional virus testing of the buffy coats during APOSEC™ production, correct? Response from Aposcience AG: Correct, all virus tests are done on the

whole blood donations. Material obtained from donations tested positive is eliminated during production prior to pooling of material. The verification of viral safety of the blood donations has to be realized in accordance with the German requirements for blood donor screening (www.pei.de/spendertestung).

- APOSEC™ 's risk profile seems to be appropriate to the Agency for the performance of phase II studies due to the limited patient pool. However, market authorization will require a more diligent reflection regarding the risks to public health as far more patients will be exposed.
- The difference between APOSEC™ and blood products (which also carry prion risk) lies in the fact that APOSEC™ is not a life-saving treatment and for the current indication (DFU) there are alternative products.
- The agency mentioned that - in general - smaller batch sizes reduce the viral and prion risk of the product, because only a limited number of patients would be affected by a batch which post release would turn out to be infectious. The PEI has been informed of the current batch size as well as the plan to pool blood from 7x10 donors in order to allow a suitable strategy for release and stability testing.
- The Agency discourages prion testing in the end product (the lyophilized powder) for reasons of dilution, the same is valid for testing of intermediates in the production process. It would be ideal to test every donor for prions, however tests for blood donor screening are currently not available.
- It should be considered to subject the manufacturing process to further studies regarding prion safety, particularly for submission of the MAA. Conventional reduction studies using brain-derived prion spike seem of limited value for such a complex product without extensive purification steps. The relevance of such spiking material for blood associated infectivity is questionable. As a potential approach the PEI suggested to evaluate whether prion infected blood (scrapies) from sheep or hamsters could be used to address this issue. However, infectivity has been found associated to platelets from both rodents and scrapie affected sheep and it seems uncertain whether significant prion reduction can be expected from the current manufacturing process.

(An additional post meeting expert statement is attached regarding prion risk evaluation and mitigation).

Considering the attached expert statement, it is agreed that it is difficult to expect significant prion reduction from the manufacturing process. The suggestion to limit the age of donors is endorsed as a risk reducing measure and the age should be limited towards 40 years. It is noted that, in very rare cases, sCJD has been found with younger patients and that the duration of a potential infectious incubation phase is not known.

Question 3 (units)

The APOSEC™ drug substance is produced from the supernatant of standardized cultures of PBMCs with a cell density of 25 Mio PBMCs/mL. The lyophilisate of 1 mL supernatant contains the secretome of 25 Mio PMBCs, which will be referred to as 25 U (U = Units) hereafter. This approach provides a clear dose definition and avoids misunderstandings because the final product does not contain any cells.

Aposcience plans to use this nomenclature for the planned clinical development program.

Does the Agency support this rationale and approach?

PEI response to Question 3

- The Agency does not support this approach. "Units" is an inadequate expression in the context of APOSEC™ because the term implies an entity that can be measured to which another entity is proportional to. Likewise, the Agency also does not recommend expressions like "equivalent" or artificial words.

- The Agency recommends expressing the package size on the basis of mass, e.g. in gram or milligrams.
- The use of “units” in the Briefing Book was not consistent: In some cases Aposcience AG expressed the dose in U/kg, in others in U/cm².
- However, for the planned phase II studies the term “units” is deemed acceptable by the Agency. A clear correlation needs to be given when changing the definition for dose or strength during product development to allow for an accurate comparison between studies.

Question 4 (pharmaco-toxicological development)

Aposcience considers that the conducted and proposed non-clinical pharmacology and safety program is acceptable and that there are no further requirements for non-clinical testing of APOSECTM prior to the inclusion and treatment of DFU patients in Phase II clinical studies, assuming that the following, planned non-clinical studies are performed and the results do not warrant further investigations. Does the Agency support this rationale and approach?

PEI response to Question 4

- The non-clinical program is deemed comprehensive and convincing to the Agency, this is also true for the safety pharmacology.
- The agency recommends to consider the execution of genotoxicity investigations prior phase III or marketing authorization.

Question 5 (clinical trials)

For moving into Phase III, Aposcience considers it sufficient conducting a single combined Phase II efficacy and dose ranging study. Does the Agency agree with this approach?

PEI response to Question 5

- The Agency has no objection to the overall design of the study. However, the statistical power with 80 % could be optimized but acceptable for an exploratory approach.
- Wound size:
 - o Wound size in healthy volunteers (MARSYAS I study) was 4 mm at baseline and 6 mm re-biopsy after the 7-day completion of treatment; the study was performed utilizing autologous APOSECTM)
 - o A broad range has been taken for wound size of 1cm² -8 cm² in Marsyas II study to ensure wound size is represented equally among dose groups, however an additional strata for wound size (eg. Stratum 1: Wound size 1-4cm², and Stratum 2: wound size 4,1-8cm²) should be considered
- Standard of care should be harmonized across all study sites by providing guidance in the protocol, i.e. e.g. appropriate training, and monitoring.

Question 6 (Phase III study)

In Phase III, one confirmatory double blind, randomized, placebo controlled efficacy and safety study is planned in patients with DFU and in a cohort of diabetic patients with advanced wound-healing

problems. All trial participants will receive standardized best practice wound care. The primary trial endpoint of full wound closure will be measured at 3 months.

Does the Agency consider this approach appropriate?

PEI response to Question 6

- The Agency expresses no objection towards the approach of obtaining marketing approval with one pivotal phase III study as far as the criteria of the EMA guidance are fulfilled
- Critical issue might be to extend the inclusion criteria to patients with more advanced wound healing problems as it might bear the risk not to meet the primary endpoint as planned based on lack of sufficient information from previous trials
- It has been suggested to add a separate phase II trial in patients with WAGNER 3 and 4 before enrolling the whole spectrum of patients with wound healing in the pivotal study or to adhere to the same study population as already enrolled in Phase II

Attachment

2018-01-12-APOSEC-prion-ExpertOpinion-KovacsGG

Post Meeting Note Aposcience Regarding Hepatitis B Virus:

In der Methylenblau Virusinaktivierungsstudie wurde Pseudorabies Virus als Surrogat für das Hepatitis B Virus verwendet.

Table 5

Plasma-borne viruses and their models

Virus	Examples of viruses used to model inactivation/removal studies
Hepatitis B virus	Duck hepatitis B virus, pseudorabies virus ^a
Hepatitis C virus	Bovine viral diarrhoea virus, Sindbis virus, Semliki forest virus, Yellow fever virus
Human immunodeficiency virus	Human immunodeficiency virus
Hepatitis A virus	Hepatitis A virus, encephalomyocarditis virus
Parvovirus B19	Canine parvovirus, porcine parvovirus

^a Because there are no convenient models for hepatitis B virus, pseudorabies virus is frequently used: both pseudorabies virus and hepatitis B virus are enveloped, double-stranded DNA viruses.

Source: http://www.who.int/bloodproducts/publications/WHO_TRS_924_A4.pdf



GMP-ZERTIFIKAT / CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

Zertifikat Nr.: / *Certificate No.:* INS-482918-0001-014

Teil 1 / Part 1

Ausgestellt auf Basis einer Inspektion in Übereinstimmung mit /
Issued following an inspection in accordance with

- ☒ **Art. 111(5) of Directive 2001/83/EC**
☐ **Art. 80(5) of Directive 2001/82/EC**
☒ **Art. 15 of Directive 2001/20/EC**

Die zuständige Behörde **Österreichs** bestätigt wie folgt: /
*The competent authority of **Austria** confirms the following:*

Der Betrieb / *The manufacturer*

Aposcience AG
Wenzgasse 25
1130 Wien

wurde im Rahmen des nationalen Inspektionsprogramms inspiziert, in Verbindung mit der Geschäftszahl
(Hersteller-Lizenznummer) / *has been inspected under the national inspection programme in connection*
*with manufacturing authorisation no. **482918***

in Übereinstimmung mit / *in accordance with*

- ☒ **Art. 40 of Directive 2001/83/EC**
☐ **Art. 44 of Directive 2001/82/EC**
☒ **Art. 13 of Directive 2001/20/EC**

umgesetzt in folgende nationale Gesetzgebung / *transposed in the following national legislation:*
'Verordnung der Bundesministerin für Gesundheit und Frauen betreffend Betriebe, die Arzneimittel
herstellen, kontrollieren oder in Verkehr bringen (Arzneimittelbetriebsordnung 2009 - AMBO 2009),
BGBl. II Nr. 324/2008, in der geltenden Fassung'.



GMP-ZERTIFIKAT / CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

Zertifikat Nr.: / Certificate No.: INS-482918-0001-014

Aus der während der Inspektion des betreffenden Herstellers gewonnenen Kenntnis, zuletzt durchgeführt am /

From the knowledge gained during inspection of this manufacturer, the latest of which was conducted on

15.02.2019 , für/for 0,5 Tag(e) / day(s)

kann angenommen werden, dass /

it is considered that it complies with

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☒ **Directive 2003/94/EC**

☐ **Directive 91/412/EEC**

☐ **der Richtlinie der GMP für Wirkstoffe (Art. 47 of Directive 2001/83/EC und Art. 51 of Directive 2001/82/EC) / The principles of GMP for active substances (Art. 47 of Directive 2001/83/EC and Art. 51 of Directive 2001/82/EC).**

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¹ These requirements fulfil the GMP recommendations of WHO.
(*) Nichtzutreffendes streichen / delete that which does not apply



GMP-ZERTIFIKAT / CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER

Zertifikat Nr.: / Certificate No.: INS-482918-0001-014

Teil 2 / Part 2

☒ Humanarzneimittel / *Human Medicinal Products*

☐ Veterinärarzneimittel / *Veterinary Medicinal Products*

Prüfpräparate zur klinischen Prüfung / *Human Investigational Medicinal Products*

☒ Phase I ☒ Phase II ☒ Phase III ☐ Phase IV

Teil 1 – HERSTELLUNGSTÄTIGKEITEN / Part 1 – MANUFACTURING OPERATIONS

1.1 Sterile Produkte / Sterile products

1.1.3 Chargenfreigabe / Batch certification

1.3 Biologische Arzneimittel / Biological medicinal products

1.3.2 Chargenfreigabe (Liste der Produktarten) / Batch certification (list of product types)

1.3.2.6 Produkte menschlicher oder tierischer Herkunft / *Human or animal extracted products*

1.3.2.8 Andere biologische Arzneimittel / *Other biological medicinal products*

Sekretom aus apoptotischen peripheren mononuklearen Zellen aus menschlichem Blut/ *Secretome of human apoptotic peripheral blood mononuclear cells (APOSEC)*

Mögliche Einschränkungen oder Erklärungen bezüglich des vorliegenden Zertifikats /

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Für das Bundesamt für Sicherheit im Gesundheitswesen /
For the Federal Office for Safety in Health Care

Kraßnigg Andreas
am 16.7.2019

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GMP-ZERTIFIKAT / CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER^{1,2}

Zertifikat-Nr.: / Certificate No.: INS-482918-102482868-19488291

Teil 1 / Part 1

Ausgestellt auf Basis einer Inspektion in Übereinstimmung mit /
Issued following an inspection in accordance with

Art. 63(4) of Regulation (EU) No 536/2014

Die zuständige Behörde **Österreichs** bestätigt wie folgt: /
*The competent authority of **Austria** confirms the following:*

Der Betrieb / *The manufacturer*

Aposcience AG
Dresdner Straße 87/A 21
1200 Wien

wurde im Rahmen des nationalen Inspektionsprogramms inspiziert, in Verbindung mit der Geschäftszahl
(Hersteller-Lizenznummer) / *has been inspected under the national inspection programme in connection*
*with manufacturing authorisation no. **482918***

in Übereinstimmung mit / *in accordance with*

Art. 61(1) of Regulation (EU) No 536/2014

umgesetzt in folgende nationale Gesetzgebung / *transposed in the following national legislation:*
'Verordnung der Bundesministerin für Gesundheit und Frauen betreffend Betriebe, die Arzneimittel
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Aus der während der Inspektion des betreffenden Herstellers gewonnenen Kenntnis, zuletzt
durchgeführt am / *From the knowledge gained during inspection of this manufacturer, the latest of*
which was conducted on

03.04.2024

kann angenommen werden, dass / *it is considered that it complies with*

den Richtlinien der Guten Herstellungspraxis entsprochen wird, festgehalten in /
The principles and guidelines of Good Manufacturing Practice laid down in

Commission Delegated Regulation (EU) 2017/1569

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46
47 ¹ *The certificate referred to in paragraph 111(5) of Directive 2001/83/EC and 94(1) of Regulation 2019/6, is also applicable to*
48 *importers.*

49 ² *Guidance on the interpretation of this template can be found in the Interpretation of the Union format for GMP certificate.*

50 ³ *These requirements fulfil the GMP recommendations of WHO.*

51 ⁴ *Nicht anwendbar auf Blutspendeeinrichtungen / Not applicable to blood establishments*



GMP-ZERTIFIKAT / CERTIFICATE OF GMP COMPLIANCE OF A MANUFACTURER^{1,2}

Zertifikat-Nr.: / Certificate No.: INS-482918-102482868-19488291

Teil 2 / Part 2

Hersteller klinischer Prüfpräparate / Manufacturer of investigational medicinal products

Phase I, Phase II, Phase III

Teil 1 – HERSTELLUNGSTÄTIGKEITEN / Part 1 – MANUFACTURING OPERATIONS

1.1 Sterile Produkte / Sterile products

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1.3.2.8 Andere biologische Arzneimittel / Other biological medicinal products: Sekretom aus apoptotischen peripheren Mononuclearen Zellen aus menschlichem Blut/ Secretome of human apoptotic peripheral blood mononuclear cells (APOSEC)

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Any restrictions or clarifying remarks related to the scope of this certificate:

Keine / None

Für das Bundesamt für Sicherheit im Gesundheitswesen /
For the Federal Office for Safety in Health Care

Meissner Christina
am 24.6.2024



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(54) Title: PHARMACEUTICAL PREPARATION

(57) Abstract: The present invention relates to a pharmaceutical preparation for treating an inflammatory condition, preferably a condition associated with ischemia comprising: a) a physiological solution comprising peripheral blood mononuclear cells (PBM-Cs) or a subset thereof, or b) a supernatant of the solution a), wherein the solution a) is obtainable by cultivating PBMCs or a subset thereof in a physiological solution free of PBMC-proliferating and PBMC-activating substances for at least 1 h.



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PHARMACEUTICAL PREPARATION

The present invention relates to a pharmaceutical preparation for treating internal inflammatory conditions, preferably internal conditions associated with ischemia.

Hypoxia, a state of reduced oxygen, can occur when the lungs are compromised or blood flow is reduced. Ischemia, reduction in blood flow, can be caused by the obstruction of an artery or vein by a blood clot (thrombus) or by any foreign circulating matter (embolus) or by a vascular disorder such as atherosclerosis. Reduction in blood flow can have a sudden onset and short duration (acute ischemia) or can have a slow onset with long duration or frequent recurrence (chronic ischemia). Acute ischemia is often associated with regional, irreversible tissue necrosis (an infarct), whereas chronic ischemia is usually associated with transient hypoxic tissue injury. If the decrease in perfusion is prolonged or severe, however, chronic ischemia can also be associated with an infarct. Infarctions commonly occur in the spleen, kidney, lungs, brain and heart, producing disorders such as intestinal infarction, pulmonary infarction, ischemic stroke and myocardial infarction.

Pathologic changes in ischemic disorders depend on the duration and severity of ischemia, and on the length of patient survival. Necrosis can be seen within the infarct in the first 24 h and an acute inflammatory response develops in the viable tissue adjacent to the infarct with leukocytes migrating into the area of dead tissue. Over succeeding days, there is a gradual breakdown and removal of cells within the infarct by phagocytosis and replacement with a collagenous or glial scar.

Hypoperfusion or infarction in one organ often affects other organs. For example, ischemia of the lung, caused by, for example, a pulmonary embolism, not only affects the lung, but also puts the heart and other organs, such as the brain, under hypoxic stress. Myocardial infarction, which often involves coronary artery blockage due to thrombosis, arterial wall vasospasms, or viral infection of the heart, can lead to congestive heart failure and systemic hypotension. Secondary complications such as global ischemic encephalopathy can develop if the cardiac arrest is prolonged with continued hypoperfusion. Cerebral ischemia, most commonly caused by vascular occlusion due to

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atherosclerosis, can range in severity from transient ischemic attacks (TIAs) to cerebral infarction or stroke. While the symptoms of TIAs are temporary and reversible, TIAs tend to recur and are often followed by a stroke.

Occlusive arterial disease includes coronary artery disease, which can lead to myocardial infarction, and peripheral arterial disease, which can affect the abdominal aorta, its major branches, and arteries of the legs. Peripheral arterial disease includes Buerger's disease, Raynaud's disease, and acrocyanosis. Although peripheral arterial disease is commonly caused by atherosclerosis, other major causes include, e.g., diabetes, etc. Complications associated with peripheral arterial disease include severe leg cramps, angina, abnormal heart rhythms, heart failure, heart attack, stroke and kidney failure.

Ischemic and hypoxic disorders are a major cause of morbidity and mortality. Cardiovascular diseases are responsible for 30% of deaths worldwide. Among the various cardiovascular diseases, ischemic heart disease and cerebrovascular diseases cause approximately 17% of deaths.

Currently, treatment of ischemic and hypoxic disorders is focused on relief of symptoms and treatment of causative disorders. For example, treatments for myocardial infarction include nitroglycerin and analgesics to control pain and relieve the workload of the heart. Other medications, including digoxin, diuretics, amrinone, beta-blockers, lipid-lowering agents and angiotensin-converting enzyme inhibitors, are used to stabilize the condition, but none of these therapies directly address the tissue damage produced by the ischemia and hypoxia.

Due to deficiencies in current treatments, there remains a need for methods that are effective in treating conditions involving hypoxia. There is also a need for methods that are effective in the prevention of tissue damage caused by ischemia that occurs due to, e.g., atherosclerosis, diabetes and pulmonary disorders.

Conditions associated with ischemia and hypoxia are usually accompanied by inflammation. Therefore means and methods are needed which also reduce inflammation.

It is an object of the present invention to provide means which allow the efficient treatment of internal inflammatory conditions, preferably conditions associated with ischemia.

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The present invention relates to a pharmaceutical preparation for treating an internal inflammatory condition, preferably an internal condition associated with ischemia, comprising

- a) a physiological solution comprising peripheral blood mononuclear cells (PBMCs) or a subset thereof, or
- b) a supernatant of the solution a), wherein the solution a) is obtainable by cultivating PBMCs or a subset thereof in a physiological solution free of PBMC-proliferating and PBMC-activating substances for at least 1 h.

It turned out that the administration of a pharmaceutical preparation as defined above to a patient suffering from an internal inflammatory condition, preferably an internal condition associated with ischemia, results in an alleviation of the respective symptoms and in a healing process.

The pharmaceutical preparation of the present invention comprises cultivated PBMCs or a subset thereof and/or the supernatant in which the PBMCs have been cultivated. In the course of the cultivation of PBMCs these cells express and secrete substances like cytokines which differ from those expressed and secreted in activated PBMCs. This means that the secretome of PBMCs of the present invention is different from the secretome of activated PBMCs. The cells of the present invention undergo a non-cell-surface moiety triggered secretome production. Therefore it is surprising that PBMCs which have not been contacted with PBMC activating substances like PHA or LPS can be employed to treat internal inflammatory conditions, in particular ischemic conditions, which shows that the secretome of these cells comprises substances supporting the treatment of such or similar conditions.

The PBMCs according to the present invention are obtainable by cultivating them in a physiological solution which does not comprise PBMC-proliferating and PBMC-activating substances. However, the PBMCs are incubated in the physiological solution for at least 1 h. This minimum time of cultivation is required to let the PBMCs secrete cytokines and other beneficial substances.

PBMCs part of the preparation according to the present invention can be obtained from whole blood using methods known in the art such as Ficoll gradient, hypotonic lysis etc.. These methods are well known in the art.

PBMCs of the pharmaceutical preparation may be obtained from

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a pool of donors or from the same individual to which the preparation will be administered.

The PBMCs or the subsets thereof are present in the preparation according to the present invention in their viable form.

The physiological solution from which the supernatant is obtained comprises at least 500, preferably at least 1000, more preferably at least 10^5 , even more preferably at least 10^6 , cells per ml solution or per dosage unit.

The preparation of the present invention may comprise at least 500, preferably at least 1000, more preferably at least 10^5 , even more preferably at least 10^6 , PBMCs per ml or per dosage unit.

"Physiological solution", as used herein, refers to a liquid solution in which PBMCs are cultivated prior their use in the pharmaceutical preparation according to the present invention.

"Physiological solution" refers also to a solution which does not lead to the death of PBMCs within an hour, preferably within 30 min. If the number of viable PBMCs is decreasing in a solution by 75%, more preferably by 90% within one hour, preferably within 30 min, the solution is not considered to be a "physiological solution" as defined herein. The "physiological solution" does not lead to a spontaneous lysis of PBMCs when contacted with said solution.

In this context the step of "cultivating" or "culturing" comprises or consists of the step of "incubating", a step in which the cells are contacted with a solution for a defined time (at least 1 h, preferably at least 4 h, more preferably at least 8 h, even more preferably at least 12 h) under conditions which are regularly used for cultivating PBMCs.

The term "condition associated with ischemia" in the context of the present invention can be used interchangeable with the term "ischemic conditions" and denotes any condition, disease or disorder in which regions of the human or animal body are deprived of adequate oxygen supply resultant damage or dysfunction of tissue. A pathological condition may be characterized by reduction or abolition of blood supply within an organ or part of an organ, which may be caused by the constriction or obstruction of a blood vessel. Such conditions are collectively referred to herein by the term "ischemia" or "ischemia related conditions" or "condition related to ischemia". In heart disease, for in-

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stance, ischemia is often used to describe the heart muscle that is not getting the proper amount of oxygen-rich blood because of narrowed or blocked coronary arteries. The symptoms of ischemia depend on the organ that is "ischemic". With the heart, ischemia often results in angina pectoris. In the brain, ischemia can result in a stroke. Ischemia conditions are accompanied by inflammation.

Non-limiting examples for pathological conditions which relate to inflammation, in particular to ischemia, include wounds, myocardial ischemia, limb ischemia, tissue ischemia, ischemia-reperfusion injury, angina pectoris, coronary artery disease, peripheral vascular disease, peripheral arterial disease, stroke, ischemic stroke, chronic wounds, diabetic wounds, myocardial infarct, congestive heart failure, pulmonary infarction, skin ulcer, etc..

Notwithstanding the above, a pathological condition in the context of the invention may be characterized by damage or dysfunction of endothelial cells, i.e. wound. Non-limiting examples of wounds which may be treated by the use of the preparation according to the present invention are chronic wounds, diabetic wounds, ulcer, burns, inflammatory skin disease and bowel disease.

The terms "internal condition", "internal inflammatory condition" and "internal conditions associated with ischemia" relate to conditions and diseases which occur inside the body of an individual that are caused by acute or latent hypoxia and inflammation in mammal end organs necessary for optimal functioning (e.g. bone, heart, liver, kidney, cerebrum, skin integrity).

"Physiological solution", as used herein, refers to a solution exhibiting an osmotic pressure which does not lead to the destruction of the PBMCs or subsets thereof and can be directly administered to an individual.

The term "free of PBMC-proliferating and PBMC-activating substances" refers to the physiological solution which does not comprise substances which activate PBMCs and induce the proliferation of PBMCs or subsets thereof. These substances include PHA, LPS etc..

According to a preferred embodiment of the present invention the inflammatory condition is selected from the group of mammal diseases that are related to hypoxia and inflammation of func-

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tional end organs.

According to a particularly preferred embodiment of the present invention the internal inflammatory condition, preferably the internal condition associated with ischemia, is selected from the group consisting of myocardial ischemia, limb ischemia, tissue ischemia, ischemia-reperfusion injury, angina pectoris, coronary artery disease, peripheral vascular disease, peripheral arterial disease, stroke, ischemic stroke, myocardial infarct, congestive heart failure, trauma, bowel disease, mesenterial infarction, pulmonary infarction, bone fracture, tissue regeneration after dental grafting, auto-immune diseases, rheumatic diseases, transplantation allograft and rejection of allograft.

The subset of peripheral blood mononuclear cells (PBMCs) is preferably T cells, B cells or NK cells. Of course it is also possible to use combinations of these cells: T cells and B cells; T cells and NK cells; B cells and NK cells; T cells, B cells and NK cells. Methods for providing and isolating said cells are known.

It surprisingly turned out that the PBMCs of the present invention can be cultivated in any kind of solution provided that said solution does not comprise substances which are not pharmaceutically acceptable, lead to an immediate death of the PBMCs, activate PBMCs and stimulate the proliferation of PBMCs (as defined above). Therefore the solution to be used at least exhibits osmotic properties which do not lead to lysis of the PBMCs. The physiological solution is preferably a physiological salt solution, preferably a physiological NaCl solution, whole blood, a blood fraction, preferably serum, or a cell culture medium.

The cell culture medium is preferably selected from the group consisting of RPMI, DMEM, X-vivo and Ultraculture.

According to a particularly preferred embodiment of the present invention the cells of the present invention are cultivated under stress inducing conditions.

The term "under stress inducing conditions", as used herein, refers to cultivation conditions leading to stressed cells. Conditions causing stress to cells include among others heat, chemicals, radiation, hypoxia, osmotic pressure (i.e. non-physiological osmotic conditions) etc..

Additional stress to the cells of the present invention leads to a further increase of the expression and secretion of

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substances beneficial for treating internal inflammatory conditions, preferably internal conditions associated with ischemia.

According to a preferred embodiment of the present invention the stress inducing conditions include hypoxia, ozone, heat (e.g. more than 2°C, preferably more than 5°C, more preferably more than 10°C, higher than the optimal cultivation temperature of PBMCs, i.e. 37°C), radiation (e.g. UV radiation, gamma radiation), chemicals, osmotic pressure (i.e. osmotic conditions which are elevated at least 10% in comparison to osmotic conditions regularly occurring in a body fluid, in particular in blood), pH shift or combinations thereof.

If radiation is used to stress the PBMCs of the present invention the cells are preferably irradiated with at least 10 Gy, preferably at least 20 Gy, more preferably at least 40 Gy, whereby as source Cs-137 Caesium is preferably used.

According to a preferred embodiment of the present invention the non-activated PBMCs or a subset thereof are cultivated in a medium for at least 4 h, preferably for at least 6 h, more preferably for at least 12 h.

The pharmaceutical preparation according to the present invention can be administered in various ways depending on the condition to be treated. Therefore said preparation is preferably adapted for subcutaneous administration, intramuscular administration, intra-organ administration (e.g. intramyocardial administration) and intravenous administration.

A pharmaceutical preparation according to the present invention may comprise pharmaceutically acceptable excipients such as diluents, stabilizers, carriers etc. Depending on the administration route the preparation according to the present invention is provided in a respective dosage form: injection solution, etc.. Methods for preparing the same are well known to the skilled artisan.

In order to increase the shelf-life of the preparation according to the present invention the solution a) or the supernatant b) is lyophilised. Methods for lyophilising such preparations are well known to the person skilled in the art.

Prior its use the lyophilised preparation can be contacted with water or an aqueous solution comprising buffers, stabilizers, salts etc..

Another aspect of the present invention relates to the use

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of a preparation as defined above for the manufacture of a medicament for treating an internal inflammatory condition, preferably an internal condition associated with ischemia.

Yet another aspect of the present invention relates to a method for preparing a pharmaceutical preparation as disclosed herein comprising the steps of

a) providing peripheral blood mononuclear cells (PBMCs) or a subset thereof,

b) culturing the cells of step a) in a physiological solution free of PBMC-proliferating and PBMC-activating substances for at least 1 h,

c) isolating the cells of step b) and/or the supernatant thereof, and

d) preparing the pharmaceutical preparation using the cells and/or the supernatant of step c).

The preparation according to the present invention can be obtained by incubating or culturing PBMCs in a physiological solution for at least 1 h, preferably at least 4 h, more preferably at least 8 h, even more preferably at least 12 h. In the course of this step the PBMCs begin to synthesize and to secrete substances which are useful in the treatment of internal inflammatory conditions. Prior, after and in the course of the culturing step the cells are not activated by adding PBMC activating substances like PHA or LPS. After the cultivation step the cells and/or the supernatant of the culture is isolated to be further used in the preparation of the final pharmaceutical preparation. As discussed above the pharmaceutical preparation may comprise cultivated PBMCs, the supernatant of the culture in which said cells had been incubated or both the cultivated PBMCs as well as the culture medium.

According to a preferred embodiment of the present invention the cells are subjected to stress inducing conditions before or in the course of step b), wherein said stress inducing conditions include hypoxia, ozone, heat, radiation, chemicals, osmotic pressure (e.g. induced by the addition of salt, in particular NaCl, in order to give an osmotic pressure higher than in blood), pH shift (i.e. pH change by adding acids or hydroxides to give a pH value of 6.5 to 7.2 or 7.5 to 8.0) or combinations thereof.

According to a preferred embodiment of the present invention

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the cells are irradiated before or in the course of step b) with at least 10 Gy, preferably at least 20 Gy, more preferably at least 40 Gy, with ozone, with elevated temperature or with UV radiation.

Another aspect of the present invention relates to a preparation obtainable by a method as described above.

Another aspect of the present invention relates to a method for treating internal inflammatory conditions, preferably internal conditions associated with ischemia, by administering to an individual in need thereof an appropriate amount of the pharmaceutical preparation according to the present invention. Depending on the condition to be treated the preparation of the present invention is administered intramuscularly, intravenously, intra-organly (e.g. intramyocardially) or subcutaneously.

In a preferred embodiment of the present invention the pharmaceutical preparation comprises at least 500, preferably at least 1000, more preferably at least 10^5 , even more preferably at least 10^6 PBMCs per ml obtainable by a method as outlined above. Correspondingly at least 500, preferably at least 1000, more preferably at least 10^5 , even more preferably at least 10^6 , PBMCs are administered to an individual to be treated.

The present invention is further illustrated by the following figures and examples, however, without being restricted thereto.

Fig. 1 shows: (a) the study protocol and the time points of evaluation of cardiac function by echocardiography, histology and immunohistology; (b) the percentage of irradiated and non-irradiated rat PBMC positively stained for Annexin after a culture period of 18h.

Fig. 2 (a): FACS analysis shows that irradiation leads to induction of apoptosis in human PBMC with a time dependent increase of Annexin expression over 48h. (b) Co-incubation of LPS stimulated PBMC or monocytes with irradiated apoptotic autologous PBMC demonstrates a reduced secretion of the pro-inflammatory cytokine IL- 1β in a dose dependent manner. (c) To a lesser extent this finding also correlates with the IL-6 secretion profile of LPS stimulated PBMC and monocytes in the presence of IA-PBMC. (d) Addition of autologous IA-PBMC in a mixed lymphocyte reaction with LPS stimulation decreases T-cell proliferation as measured by counts per minute (cpm). (e) RT-PCR

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RNA expression analysis of VEGF, IL-8/CXCL8 and MMP transcripts shows an upregulation of IL-8/CXCL8 and especially MMP9 in irradiated PBMC after a culture period of 24 h. (f) ELISA analysis of VEGF, IL-8/CXCL8 and MMP9 demonstrates that MMP9 is predominantly found in cell lysates whereas differences in VEGF and IL-8/CXCL8 protein secretion remain approximately at the same level in both viable cells and IA-PBMC. (g) Human fibroblasts incubated in supernatants obtained from cell cultures of viable or IA-PBMC exhibit a strong upregulation of VEGF, IL-8/CXCL8 and MMP9 transcripts in RT-PCR analysis, peak values were found in fibroblasts incubated in IA-PBMC supernatants.

Fig. 3 (a, b, c): CFSE labeled syngeneic PBMC administered via the tail vein in rats after artificial myocardial infarction were predominantly found in the spleen (b), to a lesser extent in the liver (a) and no cells in the infarcted heart (c). (d, e, f): HE stained infarct zones of rats injected with either medium (d) or viable PBMC (e) show a comparable pattern of ischemic myocardium infiltrated by immune cells, tissues obtained from rats receiving IA-PBMC indicate very dense infiltrations. (g, h, i): Rats treated with viable cells (h) reveal slightly more of CD68+ stained cells in the infarcted than in medium treated rats (g), but a 3-fold higher amount of CD68+ was detected in IA-PBMC injected animals. (j, k, l): Higher levels of S100 β + cells were found in rats receiving medium alone compared to the application of viable PBMC or IA-PBMC.

Fig. 4 (a, b, c): Almost 4-fold higher amounts of cells staining positive for VEGF were detected in infarcted myocardial tissue obtained from animals injected with IA-PCMC (c), in comparison with medium (a) or viable cell treatment (b). (d, e, f): A similar expression pattern was found for VEGF receptor KDR/FLK1 with peak values in the IA-PBMC group (f) compared to medium (d) and viable cells (e). (g, h, i): No differences were detected for CD34 in all three groups. (j, k, l) immunohistological analysis for the marker c-kit in infarcted hearts shows a high quantity of positively stained cells and dense localization in rats injected with IA-PBMC (l) and fewer cells in medium (j) and viable cell receiving animals (k).

Fig. 5 (a, b, c): Histological analysis of ischemic rat hearts explanted 6 weeks after induction of myocardial infarction (Elastica van Gieson staining), hearts from medium injected

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animals (a) appear more dilated and show a greater extension of fibrotic tissue, scar extension was reduced in viable cell injected rats (b) with fewer signs of dilatations, the least amount of scar tissue formation was detected in IA-PBMC injected animals (c). (d) statistical analysis of data obtained from planimetric analysis of specimen collected 6 weeks after LAD-ligation shows a mean scar extension of 24.95 ± 3.6 in medium, of 14.3 ± 1.3 in viable PBMC and 5.8 ± 2 in IA-PBMC injected animals (mean + SEM). (e, f, g): Assessment of cardiac function parameters shortening fraction, ejection fraction and endsystolic diameter by echocardiography evidences a better recovery after myocardial infarction in animals injected with IA-PBMC.

Fig. 6a shows that neither unstimulated viable PBMC or IA-PBMC secrete the mainly monocyte derived pro-inflammatory cytokine TNF- α . (Significances are indicated as follows: * $p=0.05$, ** $p=0.001$; $n=8$)

Fig. 6b demonstrates a strong induction of pro-inflammatory Interferon- γ secretion after activation as compared to unstimulated PBMC. (Significances are indicated as follows: * $p=0.05$, ** $p=0.001$; $n=8$)

Fig. 7a shows pooled results of flow cytometric analysis. PBMCs were gated for T cells and expression of activation markers CD69 and CD25 were evaluated. (Significances are indicated as follows: * $p=0.05$, ** $p=0.001$; $n=4$)

Fig. 7b displays a representative FACS analysis of PBMCs either activated (PHA, CD3 mAb). Gating represents % of positive cells.

Fig. 8 shows high proliferation rates as measured by ^3H -thymidine incorporation of stimulated PBMC when compared to viable PBMC cultured in RPMI without stimulation.

Fig. 9 shows inhibition of T cell response of PBMC secretoma in T cell proliferation assays.

Fig. 10 (a-f) shows supernatant levels of Interleukin-8, Gro- α , ENA-78, ICAM-1, VEGF and Interleukin-16. Apoptotic PBMC show a markedly different secretion pattern of these cytokines and chemokine related to angiogenesis and immunosuppression compared to viable cells. This effect was even more pronounced when cells were incubated at high densities.

Fig. 11 shows the extension of myocardial scar tissue 6 weeks after experimental LAD ligation (as % of the left ventri-

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cle). Animals that were infused with cell culture supernatants derived from apoptotic cells evidence a significant reduction of collagen deposition, less scar extension and more viable myocardium.

Fig. 12 (a-c) shows macroscopic appearance of rat hearts explanted 6 weeks after experimental myocardial infarction. Animals transfused with supernatants from irradiated apoptotic cells (c) evidenced reduced collagen deposition and much smaller infarcted areas compared to medium (a) or supernatants from viable cells (b). Scar tissue is coloured in green for better visualization.

Fig. 13 (a-d) shows representative echocardiographic analyses (M-Mode). Cardiac function was significantly better in rats transfused with IA-PBMC supernatants (c) compared to medium (a) and viable cell treated rats (b). Echocardiographic imaging from a sham operated rat is depicted in (d).

Fig. 14 (a, b) shows echocardiographic analyses conducted 6 weeks after myocardial infarction. Rats therapied with supernatants from irradiated apoptotic PBMC evidence a significantly better cardiac function compared to medium or viable cell culture supernatant infused animals.

Fig. 15 shows Kaplan-Meier survival curve for all four treatment groups. Both viable or apoptotic PBMC cell culture supernatant infused animals evidence a better survival compared to medium injected rats. ($p < 0.1$).

Fig. 16 shows anti-CD3 and PHA stimulation experiments performed with PBMC.

Fig. 17 shows the proliferation of PBMC upon stimulation with anti-CD3, PHA and mixed lymphocytes.

Fig. 18 shows the level of Annexin V and PI positivity of the supernatant of CD4⁺ cells inocubated with PBMC supernatants.

Fig. 19 shows the inhibition of the up-regulation of CD25 and CD69 in CD4⁺ cells by PBMC supernatant.

Fig. 20 shows that the demonetizing of IL-10 and TGF- β did not increase the proliferation rates of CD4⁺ cells.

EXAMPLES:

Example 1:

Acute myocardial infarction (AMI) often leads to congestive heart failure. Despite current pharmacological and mechanical revascularization no effective therapy is defined experimentally

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to replace infarcted myocardium. Integral component of the remodelling process after AMI are the inflammatory response and the development of neo-angiogenesis after AMI. These processes are mediated by cytokines and inflammatory cells in the infarcted myocardium that phagocytose apoptotic and necrotic tissue and initiate homing of interstitial dendritic cells (IDC) and macrophages. Clinical trials aimed to attenuate AMI induced inflammatory response were abandoned since systemic immune suppression (steroids) led to increased infarct size and delayed myocardial healing. From these data it was concluded that inflammatory response after AMI is responsible for tissue stabilization and scar formation. A new field in regenerative cardiovascular medicine emerged when investigators observed that distant stem cells sense sites of damage and promote structural and functional repair. By utilizing this approach, Orlic et al. injected c-kit positive endothelial progenitor cells (EPC) into the border zone of experimental AMI and increased neo-angiogenesis and regeneration of myocardial and vascular structures. This work ignited a plethora of publications that demonstrated a regenerative potential of "cell based therapy", however it still remains elusive whether this therapeutic effect is caused by the transplanted cells themselves, recruitment of resident cardiac stem cells, or by activation of, as yet, unidentified paracrine and immunologic mechanisms. Ischemia in infarcted myocardium causes apoptotic processes and initiates alterations of cell surface lipids on dying cells. The best-characterized modification is the loss of phospholipid asymmetry and exposure of phosphatidylserine (PS). These PS are recognized by macrophages and dendritic cells (antigen presenting cells, APC) via ligands such as thrombospondin, CD14 and CD36. Under physiological conditions these receptors serve to engulf apoptotic and necrotic debris and initiate a silent "clean up" process. This process of phagocytosis by APC leads to a phenotypic anti-inflammatory response as determined by augmented IL-10 and TGF- β production and impaired APC function. Of clinical relevance are reports that demonstrated that infusion of apoptotic cells lead in a hematopoietic cell (HC) transplantation model to allogeneic HC engraftment and to a delay of lethal acute graft-versus-host disease (GVHD). Moreover, in solid organ transplantation models infusion of donor apoptotic cells increased heart graft survival. Con-

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trary to inflammation and relevant to progenitor cell recruitment from bone marrow (BM) it was shown that opsonisation of apoptotic cells elicits enhanced VEGF and CXCR8/IL-8 production of APC. In addition to the latter cytokines MMP9 was also identified to be vital for EPC recruitment and liberation from the bone marrow.

The current "status quo" in AMI treatment is directed toward early reperfusion and reopening the acute occluded coronary artery and that myocardial inflammation post infarction is perceived beneficiary despite this condition increases myocardial damage and counteracts endogenous repair mechanisms.

Material and Methods

Induction of apoptosis of PBMC and generation of supernatants

For the in vivo experiments blood was drawn from healthy young volunteers. Apoptosis was induced by Cs-137 Caesium irradiation with 60 Gy (human PBMC) or with 45 Gy for in vivo (rat PBMC) experiments. Cells were resuspended in serum free Ultra Culture Medium (Cambrex Corp., USA) containing 0.2% gentamycin-sulfate (Sigma Chemical Co, USA), 0.5% β -mercapto-ethanol (Sigma, USA), 1% L-glutamin (Sigma, USA) and cultured in a humidified atmosphere for 24h for in vitro experiments (concentration of cells, 1×10^6 ml). Induction of apoptosis was measured by AnnexinV-fluorescein/propidium iodide (FITC/PI) co-staining (Becton Dickinson, USA) on a flow cytometer. Annexin-positivity of PBMCs was determined to be >70% and are consequently termed IA-PBMC. Non-irradiated PBMC served as controls and are termed viable-PBMC. From both experimental settings supernatants were collected and served as experimental entities as described below (SN-viable-PBMC, SN-IA-PBMC).

LPS-stimulation experiments

Human PBMCs and monocytes (purity >95%) were separated using a magnetic bead system (negative selection Miltenyi Biotec, USA). PBMCs and monocytes were co-incubated for 4 h with different concentrations of apoptotic autologous PBMCs (annexin positivity >70%) and Lipopolysaccharide (1 ng/ml LPS; Sigma Chemical Co, USA). Supernatants were secured and kept frozen at -80°C until further tests. IL-6 and IL-1 β release was determined using commercially available ELISA kits (BenderMedSystems, Austria).

Monocyte-derived DC preparation and T-cell stimulation

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PBMCs were isolated from heparinized whole blood of healthy donors by standard density gradient centrifugation with Ficoll-Paque (GE Healthcare Bio-Sciences AB, Sweden). T cells and monocytes were separated by magnetic sorting using the MACS technique (Miltenyi Biotec). Purified T cells were obtained through negative depletion of CD11b, CD14, CD16, CD19, CD33, and MHC class II-positive cells with the respective monoclonal antibody. Monocytes were enriched by using the biotinylated CD14 mAb VIM13 (purity 95%). DCs were generated by culturing purified blood monocytes for 7 days with a combination of GM-CSF (50 ng/ml) and IL-4 (100 U/ml). Subsequently, DCs were differently stimulated. Maturation was induced either by adding 100 ng/ml LPS from *Escherichia coli* (serotype 0127-B8, Sigma Chemie) for 24h alone or by adding LPS for 2h and further culturing the dendritic cells with apoptotic cells in a 1:1 ratio for 22h. Additionally, DCs were treated with apoptotic cells alone (1:1) for 24h. For the mixed leukocyte reaction (MLR), allogenic, purified T cells (1×10^5 /well) were incubated in 96-well cell culture plates (Corning Costar) with graded numbers of differently stimulated DCs for 6 days. The assay was performed in triplicate. Proliferation of T cells was monitored by measuring [methyl-3H]thymidine (ICN Pharmaceuticals) incorporation, added after 5 days. Cells were harvested after 18h and incorporated [methyl-3H]thymidine was detected on a microplate scintillation counter.

Cell culture, RNA isolation and cDNA preparation of viable PBMC, IA-PBMC and SN exposed fibroblasts

IA-PBMCs, viable-PBMC (1×10^6 cells, both conditions cultured for 24 h in Ultra Culture Medium) and fibroblasts exposed to SN-viable-PBMC/SN-IA-PBMC were investigated (1×10^5 fibroblasts obtained from Cascade Inc. (USA) were cultured in Dulbecco's modified Eagle medium (DMEM, Gibco BRL, USA) supplemented with 10% fetal bovine serum (FBS, PAA, Austria), 25 mM L-glutamine (Gibco, BRL, USA) and 1% penicillin/streptomycin (Gibco) and seeded in 12 well plates; fibroblasts were co-incubated with SN-viable-PBMC, SN-IA-PBMC for 4 and 24 h respectively). After RNA extraction of PBMC and fibroblasts (using RNeasy, QiIAGEN, Austria) following the manufacturer's instruction, cDNAs were transcribed using the iScript cDNA synthesis kit (BioRad, USA) as indicated in the instruction manual.

Quantitative real time PCR

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mRNA expression was quantified by real time PCR with LightCycler Fast Start DNA Master SYBR Green I (Roche Applied Science, Penzberg, Germany) according to the manufacturer's protocol. The primers for VEGF were: forward: 5'-CCCTGATGAGATCGAG-TACATCTT-3', reverse: 5'-ACCGCCTCGGCTTGTCAC-3'; for IL-8 forward: 5'-CTCTTGGCAGCCTTCCTGATT-3', reverse: 5'-TATGCACTGACATCTAAGTTCTTTAGCA-3'; for MMP9 forward: 5'-GGGAAGATGCTGGTGTTC-3', reverse: 5'-CCTGGCAGAAATAGGCTTC-3' and for β -2-microglobulin β 2M, forward: 5'-GATGAGTATGCCTGCCGTGTG-3', reverse: 5'-CAATCCAAATGCGGCATCT-3'. The relative expression of the target genes was calculated by comparison to the house keeping gene β 2M using a formula described by Wellmann et al. (Clinical Chemistry. 47 (2001) 654-660, 25). The efficiencies of the primer pairs were determined as described (A. Kadl, et al. Vascular Pharmacology. 38 (2002) 219-227).

Release of pro-angiogenetic factors and MMP9 by viable PBMC and IA-PBMC after culture

IA-PBMC (5×10^5) and viable PBMC were incubated in a humidified atmosphere for 24h. Supernatants were collected after 24h and immediately frozen at -80°C until evaluation. Lysates of respective cells served as controls. Release of pro-angiogenetic factors (VEGF-A, CXCL-8/IL-8, GM-CSF, G-CSF) and MMP9, an accepted liberating factor of c-kit cells, were analysed utilizing ELISA (R&D, USA) following the manufacturer's instructions. Plates were read at 450nm on a Wallac Multilabel counter 1420 (PerkinElmer, USA).

Acquisition of syngeneic IA-PBMC and viable-PBMC for AMI in vivo experiment

Syngeneic rat PBMC for in vivo experiments were separated by density gradient centrifugation from whole-blood obtained from prior heparinized rats by punctuation of the heart. Apoptosis was induced by Cs-137 Caesium irradiation with 45 Gy for in vivo experiments and cultured for 18h as described above. (annexin staining >80% IA-PBMC, annexin staining <30% viable PBMC, $1 \times 10^6/\text{ml}$).

Induction of myocardial infarction

Myocardial infarction was induced in adult male Sprague-Dawley rats by ligating the LAD as previously described (Tresscher K, et al. Cardiovasc Res. 2006; 69(3): 746-54). In short, animals were anesthetized intraperitoneally with a mixture of

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xylazine (1 mg/100 g bodyweight) and ketamine (10 mg/100 g bodyweight) and ventilated mechanically. A left lateral thoracotomy was performed and a ligature using a 6-0 prolene was placed around the LAD beneath the left atrium. Immediately after the onset of ischemia 8×10^6 apoptotic PBMCs suspended in 0.3 ml cell culture medium were infused through the tail vein. Infusion of cell culture medium alone, viable PBMC and sham operation respectively or served in this experimental setting as negative control. The rat experimental design is shown in Fig. 1 (Fig. 1a, b).

Tracking of apoptotic cells

8×10^6 syngeneic rat PBMC were labelled with 15 μ M Carboxy-fluorescein diacetate succinimidyl ester (CFSE, Fluka Bio-Chemika, Buchs, Switzerland) at room temperature for 10 min. Labelling was stopped by the addition of fetal calf serum (FCS). Apoptosis was induced (annexin V >70%) and cells were injected after ligation procedure. 72h after operation rats were sacrificed and liver, spleen and heart were processed following a standard procedure for frozen sections (n=4). Samples were analyzed by confocal laser scanning microscopy (ZEISS LSM 510 laser scanning microscope, Germany) as described previously (Kerjaschki D, J Am Soc Nephrol. 2004; 15: 603-12).

Histology and immunohistochemistry in vivo

All animals were sacrificed either 72 h or 6 weeks after experimental infarction. Hearts were explanted and then sliced at the level of the largest extension of infarcted area (n=8-10). Slices were fixed with 10% neutral buffered formalin and embedded in paraffin for (immune-)histological staining. The tissue samples were stained with hematoxylin-eosin (H&E) and elastic van Gieson (evg). Immunohistological evaluation was performed using the following antibodies directed to CD68 (MCA 341R, AbD Serotec, UK), VEGF (05-443, Upstate/Milipore, USA), Flk-1 (sc-6251, Santa Cruz Biotechnology, USA), CD34 (sc-52478, Santa Cruz Biotechnology, USA), c-kit (sc-168, Santa Cruz Biotechnology, USA), S100 beta (sc-58841, Santa Cruz Biotechnology, USA). Tissue samples were evaluated on a Olympus Vanox AHB3 microscope (Olympus Vanox AHB3, Olympus Optical Co. Ltd., Japan) at 200x magnification and captured digitally by using a ProgRes Capture-Pro C12 plus camera (Jenoptik Laser Optik Systeme GmbH, Germany).

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Determination of myocardial infarction size by planimetry

In order to determine the size of the infarcted area, Image J planimetry software (Rasband, W.S., Image J, U. S. National Institutes of Health, USA) was used. The extent of infarcted myocardial tissue (% of left ventricle) was calculated by dividing the area of the circumference of the infarcted area by the total endocardial and epicardial circumferenced areas of the left ventricle. Planimetric evaluation was carried out on tissue samples stained with evg for better comparison of necrotic areas. Infarct size was expressed as percent of total left ventricular area.

Cardiac function assessment by echocardiography

Six weeks after induction of myocardial infarction rats were anaesthetized with 100 mg/kg Ketamin and 20 mg/kg Xylazin. The sonographic examination was conducted on a Vivid 5 system (General Electric Medical Systems, USA). Analyses were performed by an experienced observer blinded to treatment groups to which the animals were allocated (EW). M-mode tracings were recorded from a parasternal short-axis view and functional systolic and diastolic parameters were obtained. Ventricular diameters and volumes were evaluated in systole and diastole. Fractional shortening was calculated as follow: $FS(\%) = ((LVEDD - LVESD) / LVEDD) * 100\%$

Statistical methods

Statistical analysis was performed using SPSS software (SPSS Inc., USA). All data are given as mean $\pm$ standard of the mean. Normal distribution was verified using the Kolmogorov-Smirnov test. Paired two-sided t-tests for dependent, unpaired t-tests for independent variables were utilized calculating significances. Bonferroni-Holm correction was used to adjust p-values for multiple testing. P-values <0.05 were considered statistically significant.

Results

Induction of apoptosis with caesium irradiation (IA-PBMC)

In order to evaluate the immunomodulatory potential of apoptotic cells, first the cellular response to induction of apoptosis by caesium irradiation of human peripheral blood mononuclear cells (PBMC) was determined by flow cytometry utilizing Annexin-V/PI staining on a flow cytometer. Irradiation caused positivity for Annexin on PBMC in a time dependent manner and

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peaked within 24 h as compared to viable PBMC. Viable cells served as controls (Fig. 2a). Since Annexin-V binding was highest after 24 h all further in vitro investigations were performed after this culture period (IA-PBMC). Viable PBMC served in RT-PCR and supernatant experiments as control.

IA-PBMC evidence immune suppressive features in vitro

Interleukin-1 β and IL-6 is recognized as the predominant pro-inflammatory mediator in myocardial infarction in vivo. To test the hypothesis whether IA-PBMC has an effect on cellular response human monocytes and PBMC were co-incubated with IA-PBMC and target cells were stimulated with LPS. A dose dependent decrease in secretion of IL-1 β and IL-6 in cultures of both cell types as evaluated by ELISA was found (Fig. 2b, c). To verify anti-proliferative effects of IA-PBMC in an allogeneic model a mixed lymphocyte reaction (MLR) was utilized. Allogenic, purified T-cells were utilized and these effector cells were incubated with graded doses of dendritic cells with/without addition of IA-PBMC. Fig. 2d evidences that co-incubation of IA-PBMC decreases proliferation rate in a dose-dependent manner.

IA-PBMC and viable PBMC evidence increased mRNA transcription of VEGF, IL-8/CXCL8, and MMP9

To substantiate whether irradiation leads to enhanced mRNA transcription of proteins known to be related to mobilization of EPC PBMC was analysed after separation, and after apoptosis induction (24 h). Viable PBMC served as control (viable PBMC or IA-PBMC). RNA transcription showed little difference VEGF expression as determined by RT-PCR, however a strong enhancement of IL-8/CXCL8 and MMP9. Peak induction for IL-8/CXCL8 in IA-PBMC was 6 fold versus 2 fold in viable cells, and 30 fold versus 5 fold for MMP9, respectively (Fig. 2e).

IA-PBMC and viable PBMC secrete paracrine factors that cause endothelial progenitor cells (EPC) liberation

SN derived from IA-PBMC and viable PBMC were quantified for VEGF, IL-8/CXCL8, GM-CSF, G-CSF and MMP9 utilizing ELISA after 24 h culture. As seen in Fig. 2f VEGF, IL-8/CXCL8 and MMP9 evidenced an increment. GM-CSF and G-CSF were not detectable. Of interest was the finding that MMP9 evidenced peak values in cell lysates.

SN derived from IA-PBMC and viable PBMC augment pro-angiogenic mRNA transcription in mesenchymal fibroblasts

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Since stromal cells in bone marrow are constitutively fibroblasts it was sought to investigate whether co-incubation of fibroblasts with SN derived from IA-PBMC and viable PBMC had the ability to increase VEGF, IL-8/CXCL8 and MMP9 mRNA transcription, factors responsible for EPC mobilization. RT-PCR was conducted at 4 and 24 h. Highest levels of induction were detected for IL-8/CXCL8 in cells cultivated in IA-PBMC SN, reaching an almost 120-fold induction at 4 h as compared to control. This response is also present at 24 h. A comparable response was found for VEGF, whereas MMP9 upregulation was predominantly found after 24 h. This data indicates that SN contains paracrine factors that enhance fibroblasts to augment mRNA products responsible for pro-angiogenic effects in the BM (Fig. 2g).

Adoptive transfer of CFSE labelled IA-PBMC in a rat myocardial infarction model

Because it could be proven that cultured IA-PBMC are both anti-inflammatory and pro-angiogenic in vitro IA-PBMC and viable PBMC were infused in an acute rat AMI model. First it was sought to determine where these cultured cells are homing after infarction. CFSE labelled IA-PBMC were injected into the rat's tail vein shortly after LAD artery ligation. A representative histology is seen in Fig. 3a, b, c. The majority of CFSE IA-PBMC were trapped in the spleen and liver tissue within 72 h. No cells were observed in the heart.

Diverted early inflammatory immune response in IA-PBMC treated AMI

Upon closer investigation in H.E. staining, control infarction and viable leucocytes (viable PBMC) treated AMI rats evidenced a mixed cellular infiltrate in the wound areas in accordance to granulation tissue with abundance of neutrophils, macrophages/monocytes, lymphomononuclear cells, fibroblasts and activated proliferating endothelial cells admixed to dystrophic cardiomyocytes (Fig. 3d, e) within 72 h after AMI. In contrast, AMI rats treated with IA-PBMC evidenced a dense monomorphic infiltrate in wound areas that consisted of medium sized monocytoïd cells with eosinophilic cytoplasm, dense nuclei and a round to spindle shaped morphology (Fig. 3f). In addition, few lymphomononuclear cells, especially plasmacells, fibroblasts and endothelial could be detected. Immunohistochemical analysis revealed that the cellular infiltrate in IA-PBMC AMI rats was composed of

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abundant CD68+ monocytes/macrophages (Fig. 3i) that were much weaker in the other two groups (MCI, Viable PBMC, IA-PBMC, high power field, HPF, 60.0 ± 3.6 , 78.3 ± 3.8 , 285.0 ± 23.0 (SEM), respectively) (Fig. 3g, h). Content on Vimentin positive mesenchymal cells was similar in all groups while S100+ dendritic cells were preferentially found in control infarction (AMI, Viable PBMC, IA-PBMC, HPF 15.6 ± 1.7 , 12.4 ± 2.3 , 8.4 ± 1.2 (SEM), respectively as compared to treated groups (Fig. 3j, k, h Representative histology, n=5)).

Early homing of VEGF+, Flk1+ and c-kit+ cells in IA-PBMC treated AMI

Since IA-PBMC evidenced a dense monomorphic infiltrate in wound areas that consisted of medium sized monocytoid cells with eosinophilic cytoplasm and dense nuclei multiple surface markers related to neo-angiogenesis and regenerative potency were explored. This cell population identified in the H.E. staining in IA-PBMC treated AMI group stained highly positive for vascular endothelial growth factor (VEGF α), Flk-1 and c-kit (CD 117) (Fig. 4c, f, i). Expression of both markers was reduced in control AMI and viable PBMC treated AMI group (Fig. 4a, b, d, e, j). Interestingly, IA-PBMC treated AMI evidenced increased CD34+ cells within the densely populated infarcted area which is attributed to vascular structure putatively referring to colonisation of 34+ cells (I) as compared to control (G, H) (Representative histology, n=5)

Attenuated infarct size in IA-PBMC treated AMI

In a planimetric analysis performed on EVG stained tissue samples from hearts explanted 6 weeks after myocardial infarction was induced, rats receiving saline show a collagenous scar extending to over $24.95\% \pm 3.58$ (SEM) of the left ventricle with signs of dilatation. In IA-PBMC treated rats these signs were almost abrogated with infarct sizes of $5.81\% \pm 2.02$ (SEM) as compared to $14.3\% \pm 1.7$ (SEM) treated with viable PBMC (Fig. 5a,b,c).

LV function improves in IA-PBMC treated AMI

Intravenous application of syngeneic cultured IA-PBMC significantly improves echocardiographic parameters as compared with viable PBMC or culture medium treated animals. Shortening fraction (SF) evidenced values of $29.16\% \pm 4.65$ (SEM) in sham operated animals, $18.76\% \pm 1.13$ (SEM) in medium treated AMI animals, $18.46\% \pm 1.67$ (SEM) in the viable PBMC AMI group and

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25.14%±2.66 (SEM) in IA-PBMC treated rats (Fig. 5e). Ejection fraction (EF) was 60.58%±6.81 (SEM) in sham operated rats and declined to 42.91%±2.14 (SEM) in AMI animals treated with medium, and to 42.24%±3.28 (SEM) in animals receiving viable PBMC, whereas rats treated with IA-PBMCs evidenced a EF of 53.46%±4.25.

Analysis of end-systolic and end-diastolic diameters (LVESD, LVEDD), end-systolic and end-diastolic volumes (LVESV, LVEDV) showed a comparable pattern to the previously observed values. Saline receiving animals and viable PBMC treated rats showed LVEDD values of 10.43mm±0.21 (SEM) and 11.03mm±0.40 respectively, IA-PBMC rats even represented a slightly reduced left-ventricular diastolic diameter of 8.99mm±0.32 compared to 9.47mm±0.64 in sham operated animals. Differences in systolic diameters were less pronounced, but in the same ranking (Panel 5 (a, b, c))

Conclusion:

These findings demonstrate that irradiated apoptotic PBMC (IA-PBMC) induces immune suppression in vitro and is associated to secretion of pro-angiogenic proteins. Therefore cultured viable-PBMC and IA-PBMC were infused in an acute rat AMI model and demonstrated that this treatment evoked massive homing of FLK1+/c-kit+ positive EPC into infarcted myocardium within 72 h and caused a significant functional recovery within 6 weeks.

Co-culture of IA-PBMC in immune assays resulted in reduced IL-1β and IL-6 production and attenuated allogeneic dendritic mixed lymphocyte reaction (MLR). Both immune parameters were described to have a role in inflammation after myocardial ischemia. In addition, it was evidenced that viable- and IA-PBMC secrete CXCL8/IL-8 and MMP9 into the culture medium within 24 h. These proteins were described to be responsible for neo-angiogenesis and recruitment of EPC from the BM to the ischemic myocardium. The CXCL8/IL-8 chemokine belongs to the CXCL family that consists of small (<10 kDa) heparin-binding polypeptides that bind to and have potent chemotactic activity for endothelial cells. Three amino acid residues at the N-terminus (Glu-Leu-Arg, the ELR motif) determine binding of CXC chemokines such as IL-8 and Gro-α to CXC receptors 1 and 2 on endothelial cells and are promoting endothelial chemotaxis and angiogenesis. In addition MMP9 secretion was identified to be pivotal in

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EPC mobilisation since this matrixproteinase serves as signal to release soluble kit-ligand (sKitL), a chemokine that causes the transition of endothelial and hematopoietic stem cells (EPC) from the quiescent to proliferative niche in the BM. In a further in vitro assay it could be demonstrated that the supernatant (SN) derived from cultured viable- and IA-PBMC had the ability to enhance mRNA transcription of CXCL8/IL-8 and MMP9 in mesenchymal fibroblasts. These data indicate that SN derived from viable and irradiated PBMC contain paracrine factors that confer a biological situation in the BM which results in elution of c-kit+ EPC into circulation.

In order to prove any beneficial effect of this culture-cell suspension in vivo a model of open chest myocardial injury and infused cultured viable- and IA-PBMC shortly after LAD ligation in rat animal model was utilized. In a first attempt it was proved that CFSE labelled IA-PBMC were trapped in majority in the spleen and the liver. These data indicate that "cell based therapy" does not home in infarcted myocardium. In contrary, it is much more likely that paracrine effects, either by "modified" culture medium alone or by evoked "immune mediated cytokine storm" due to cell-culture suspension exposure is causative for the regenerative effect in AMI. Since immediate inflammation after acute ischemia determines the road map to ventricular dilatation histological analysis after 72 h after AMI was performed. It could be shown that IA-PBMC treated rats evidenced massive homing of CD68+ and VEGFa/FLK1/c-kit+ positive EPC cell populations within this time period. In contrast, more S100 β positive dendritic cells were found in control AMI, indicating enhanced APC based inflammation in control AMI.

The results seen in IA-PBMC treated rats partly foil currently accepted knowledge about the natural course of myocardial infarction. In regards to inflammation: Under normal conditions remodeling processes are mediated by cytokines and inflammatory cells in the infarcted myocardium that initiate a wound reparation process that is landmarked by phagocytosis and resorption of the necrotic tissue, hypertrophy of surviving myocytes, angiogenesis and, to a limited extent, progenitor cell proliferation. Any experimental approach so far that intervened into inflammatory response post infarction was shown to be detrimental in AMI models. When interpreting the present histological short

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term data it is argued that IA-PBMC cell-medium suspension in AMI results in an advanced transitioning from inflammation to c-kit+ EPC repair phase. Previous work has confirmed that bone marrow of circulating progenitor cell therapy after AMI improve cardiac function, regardless of whether transdifferentiation of the cells to cardiomyocytes occurs or does not. In regard to c-kit+ EPC the bone marrow derived cells are considered as having a significant role as indispensable for cardiac repair. Pharmacological inhibition with imatinib mesylate and non-mobilization of c-kit+ EPC resulted in an attenuated myofibroblast response after AMI with precipitous decline in cardiac function.

These results show the regenerative potency of infusing "syngeneic" cultured IA-PBMC in patients suffering from AMI and indicate that patients who suffer from acute AMI would benefit from being transfused with autologous (=from the patient to be treated or from the same species) IA-PBMC.

**Example 2: Resting Peripheral Blood Mononuclear Cells (PBMC)
Evidence Low Activation Marker and Reduced Inflammatory Cytokine
Production**

Activated peripheral blood mononuclear cells (PBMCs) and their supernatants (SN) are supposed to be beneficial in wound regeneration (Holzinger C et al. Eur J Vasc Surg. 1994 May; 8(3): 351-6.). In example 1 it could be shown that non-activated PBMC and SN derived thereof has beneficial effects in an experimental acute myocardial infarct (AMI) and wounding model. Since non-activation of PBMC had to be verified experimentally it was investigated whether cultivation of PBMC leads to enhanced T-cell activation markers (CD69, CD25) or enhanced inflammatory cytokine secretion (monocyte activation=TNF α , T-cell activation=INF γ). In a control experiment cultured T cells were triggered by CD3 mAb stimulation or Phytohemagglutinin (PHA).

Methods and Results

Venous blood was collected in EDTA-tubes from healthy volunteers. After Ficoll-Hypaque density grade separation, PBMC were collected and divided into viable and irradiated apoptotic cells (IA-PBMC). To obtain apoptotic cells, PBMC were irradiated with 60 Gy (Caesium-137). For flow cytometric analysis 500,000 PBMC were cultivated in 200 μ l serum-free medium. Cells were either stimulated with PHA (7 μ g/mL) or CD3-mAb (10 μ g/mL) or were left unstimulated. After 24h of incubation cells were washed, stained

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for CD3, CD69 and CD25 (R&D System) and evaluated for surface activation markers on a FC500 (Coulter). For ELISA assays PBMC were cultivated overnight at a density of 2.5×10^6 cells/ml, either with or without PHA or CD3 stimulation. After 24h supernatants were harvested and frozen at -20°C . Commercially available ELISA kits for TNF- α (R&D) and INF- γ (Bender) were purchased. In short, MaxiSorp plates were coated with antibodies against TNF- α and INF- γ and stored overnight. After 24h, plates were washed and samples added in duplicates to each well. After incubation and addition of a detection antibody and Streptavidin-HRP, TMB-substrate was added to each well. After color development, the enzymatic reaction was stopped by addition of sulphuric acid. Optical density values were read on a Wallac Victor3 plate reader.

Results:

FACS analysis: CD3 and PHA stimulated T cells showed an upregulation of activation markers CD69 and CD25 after 24h of incubation. Unstimulated and apoptotic cells expressed only low amounts of CD69 and CD25 (Fig. 6a (representative sample, Fig. 6b, histogram, $n=4$). Statistical significance is indicated by asterisk (xx $p<0.001$, x $p<0.05$). ELISA analysis: Whereas neither TNF- α and INF- γ in unstimulated PBMC-derived supernatants were detected, supernatants from PHA or CD3 stimulated PBMC evidenced high values for these cytokines as indicated by ELISA analysis (asterisk ** $p<0.001$, * $p<0.05$, $n=8$). The results clearly show a different secretion pattern of inflammatory cytokines in comparison to unstimulated PBMC.

Conclusion:

These data indicate that "unstimulated PBMC" evidence a distinct different phenotype (activation marker, cytokine secretion) as compared to stimulated PBMCs (PHA and CD3 mAb).

Figure 6a indicates that neither unstimulated viable PBMC or IA-PBMC secrete the mainly monocyte derived pro-inflammatory cytokine TNF- α . (Significances are indicated as follows: * $p=0.05$, ** $p=0.001$, $n=8$)

Figure 6b demonstrates a strong induction of pro-inflammatory Interferon- γ secretion after activation as compared to unstimulated PBMC. (Significances are indicated as follows: * $p=0.05$, ** $p=0.001$; $n=8$)

Fig. 7a shows pooled results of flow cytometric analysis.

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PBMCs were gated for T cells and expression of activation markers CD69 and CD25 were evaluated. (Significances are indicated as follows: * $p=0.05$, ** $p=0.001$; $n=4$)

Fig. 7b displays a representative FACS analysis of PBMCs either activated (PHA, CD3 mAb). Gating represents % of positive cells.

Example 3: Proliferative activity of PBMC cultivated in a physiological solution

The aim of this example is to prove that PBMC have no proliferative activity as compared to immune assays that utilize specific (CD3), unspecific (lectin, PHA) and allogeneic T-cell triggering (mixed lymphocyte reaction, MLR) in a 2 day (CD3, PHA) and 5 day (MLR) stimulation assay.

Material and Methods

PBMC were separated from young healthy volunteers by Ficoll density gradient centrifugation and resuspended in RPMI (Gibco, USA) containing 0.2% gentamycinsulfate (Sigma Chemical Co, USA), 1% L-Glutamin (Sigma, USA) at 1×10^5 cells per 200 μ L. Responder cells were either stimulated by MoAb to CD3 (10 μ g/mL, BD, NJ, USA), PHA (7 μ L/mL, Sigma Chemical Co, USA) or with irradiated allogeneic PBMC at a 1:1 ratio (for MLR). Plates were incubated for 48h or 5 days and then pulsed for 18h with 3[H]-thymidine (3.7×10^4 Bq/well; Amersham Pharmacia Biotech, Sweden). Cells were harvested and 3[H]-thymidine incorporation was measured in a liquid scintillation counter.

Results

Stimulated PBMC showed high proliferation rates as measured by 3[H]-thymidine incorporation when compared to viable PBMC cultured in RPMI without stimulation (Fig. 8). This effect was observed by adding T cell specific stimuli (PHA, CD3) as well as in assays where proliferation was triggered by antigen presenting cells (MLR).

Conclusion

This set of experiments implicates that viable PBMC held in culture for up to 5 days did not proliferate whereas PBMC stimulated by different ways showed a marked proliferative response. It is concluded that culture of PBMC without stimulation does not lead to proliferative response.

Example 4: Secretoma of separated PBMC kept under sterile culture conditions possess neo-angionetic capacity

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Since neo-angiogenesis and inflammation are strongly linked in vivo it was investigated whether these secretoma of PBMC also exhibit anti-proliferative effects on T cells and therefore interfere with an inflammatory immune response.

Material and Methods

Secretoma were obtained by incubating PBMC (2.5×10^6 /mL) from young healthy volunteers separated by Ficoll density gradient centrifugation for 24h in RPMI (Gibco, CA, USA) containing 0.2% gentamycinsulfate (Sigma Chemical Co, USA), 1% L-Glutamine (Sigma, USA). Supernatants were separated from the cellular fraction and stored at -80°C . For proliferation assays allogeneic PBMC were resuspended at 1×10^5 cells per 200 μL RPMI after separation. Responder cells were either stimulated by MoAb to CD3 (10 $\mu\text{g}/\text{mL}$, BD, USA) or PHA (7 $\mu\text{L}/\text{mL}$, Sigma Chemical Co, USA). Different dilutions of supernatants were added. Plates were incubated for 48h and then pulsed for 18h with $^3\text{[H]}$ -thymidine (3.7×10^4 Bq/well; Amersham Pharmacia Biotech, Sweden). Cells were harvested and $^3\text{[H]}$ -thymidine incorporation was measured in a liquid scintillation counter.

Results:

Secretoma of allogeneic PBMC evidenced a significant reduction of proliferation rates measured by $^3\text{[H]}$ -thymidine incorporation when compared to positive controls (Fig. 9). This effect was dose-dependent and could be seen upon anti-CD3 as well as upon PHA stimulation.

Implication:

This set of experiments implicates that secretoma obtained from viable PBMC held in culture for 24h exhibit significant anti-proliferative effects in vitro. These data indicate that supernatant derived from PBMC or in lyophilised form may serve as potential therapeutic formula to treat human diseases that are related to hypoxia induced inflammation or other hyperinflammatory diseases (e.g. auto-immune diseases, inflammatory skin diseases).

Example 5: Paracrine factors secreted by peripheral blood mononuclear cells preserve cardiac function

In example 1 it was shown that transfusion of cultured irradiated apoptotic cells derived from peripheral blood significantly improved functional cardiac recovery after experimental myocardial infarction in rats. This improvement was based on im-

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munesuppressive features of apoptotic cells, pro-angiogenic effects and induction of augmented homing of c-kit⁺ endothelial progenitor cells (EPCs).

In the present example peripheral blood mononuclear cells (PBMC) either viable or irradiated with a dose of 60 Gray were incubated for 24 hours to generate conditioned cell culture supernatants. Supernatants were lyophilized and kept frozen until use in in vivo experiments. Myocardial infarction was induced in Sprague-Dawley rats by ligating the left anterior descending artery. After the onset of ischemia, lyophilized supernatants were resuspended and injected intravenously. Tissue samples for histological and immunohistological evaluations were obtained three days and six weeks after myocardial infarction. Cardiac function was assessed by echocardiography six weeks post AMI. Sham operated and untreated animals served as controls.

Rats that were infused with supernatants obtained from apoptotic PBMC evidenced increased myocardial angiogenesis and enhanced homing of endothelial progenitor cells within 72 hours as compared to controls. Planimetric evaluation of fibrotic areas indicated reduced infarction size in animals treated with supernatants from apoptotic cells. Furthermore, echocardiography showed a significant improvement regarding post AMI remodeling as evidenced by an attenuated loss of ejection fraction and preserved ventricular geometry. Left ventricular ejection fraction (LVEF) in rats receiving supernatants from apoptotic cells evidenced a mean value of $56 \pm 4\%$ compared to $60 \pm 5\%$ in sham operated animals, whereas untreated or viable cell supernatant infused animals showed a significant decline of LVEF to $44 \pm 3\%$ and $41 \pm 4\%$ respectively ($p < 0.001$).

These data indicate that infusion of supernatants derived from irradiated apoptotic PBMC in experimental AMI circumvented inflammation and caused preferential homing of regenerative EPC leading to preservation of ventricular function.

Methods

Cell culture of human PBMC for in vitro assays

Human peripheral blood mononuclear cells (PBMC) were obtained by Ficoll density grade centrifugation as described previously. To induce apoptosis in human PBMC, cells were irradiated with 60Gy (irradiation automat for human blood products, Department of Hematology, General Hospital Vienna). Both viable

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and irradiated apoptotic (IA-) PBMC were incubated at 37° Celsius for 24 hours at various cell densities (1×10^6 , 5×10^6 , 10×10^6 and 25×10^6 cells/milliliter, n=5). Then supernatants were obtained and levels of secreted proteins were measured by Enzyme-linked immunosorbent assay (ELISA, R&D Systems, Minneapolis, USA), according to the protocols supplied by the manufacturer.

Acquisition of syngeneic IA-PBMC and viable-PBMC for AMI in vivo experiment

Syngeneic rat PBMC for in vivo experiments were separated by density gradient centrifugation from whole-blood obtained from prior heparinized rats by puncturing of right atrium. Apoptosis was induced by Cs-137 cesium irradiation with 45Gy for in vivo experiments and cultured at 37° Celsius at a cell density of 25×10^6 cells/milliliter). Induction of apoptosis by irradiation was measured by flow cytometry (annexin V staining >80% for IA-PBMC, annexin V staining <20% for viable PBMC). Cells were incubated for 24hrs in a humidified atmosphere (5% CO₂, 37°C, relative humidity 95%). Supernatants were removed and dialysed with a 3.5 kDa cutoff (Spectrum laboratories, Breda, The Netherlands) against 50mM ammonium acetate overnight at 4°C. Then supernatants were sterile filtrated and lyophilized. Lyophilized secretoma were stored at -80°C and freshly resuspended for every experiment. Secretoma were radom sampled for their pH value. The lyophilized powder was stored at -80° Celsius until further experiments were conducted.

Induction of myocardial infarction

Animal experiments were approved by the committee for animal research, Medical University of Vienna. All experiments were performed in accordance to the Guide for the Care and Use of Laboratory Animals by the National Institutes of Health (NIH). Myocardial infarction was induced in adult male Sprague-Dawley rats by ligating the left anterior descending artery (LAD). In short, animals were anesthetized intraperitoneally with a mixture of xylazin (1 mg/100 g bodyweight) and ketamin (10 mg/100 g bodyweight) and ventilated mechanically. A left lateral thoracotomy was performed and a ligature using 6-0 prolene was placed around the LAD beneath the left atrium. Immediately after the onset of ischemia, lyophilized supernatants obtained from 8×10^6 apoptotic PBMC resuspended in 0.3 ml cell culture medium were infused over the femoral vein. Infusion of cell culture medium

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alone, viable PBMC supernatants and sham operation served as negative controls in this experimental setting, respectively. The experimental design is shown in Fig. 1.

Histology and immunohistochemistry in vivo

See example 1.

Determination of myocardial infarction size by planimetry

See example 1.

Cardiac function assessment by echocardiography

See example 1.

Statistical methods

Statistical analysis was performed using Graph Pad Prism software (USA). All data are given as mean $\pm$ standard error of the mean. Paired two-sided t-tests for dependent, unpaired t-tests for independent variables were utilized calculating significances.

Between-group differences regarding survival of acute myocardial infarction were compared by Kaplan-Meier actuarial analysis. Bonferroni-Holm correction was used to adjust p-values for multiple testing. P-values <0.05 were considered statistically significant.

Results

Determination of paracrine factors secreted by IA-PBMC and viable PBMC by ELISA

The results are shown in Fig. 10 to 15.

Example 6 Paracrine factors secreted by peripheral blood mononuclear cells posses immunosuppressive features

In Example 1 anti-inflammatory effects of PBMC secretoma in an acute myocardial infarction (AMI) animal model are evidenced. In this example it is shown that the application of PBMC secretoma after AMI induction inhibits the inflammatory damage of the heart muscle by massively down-regulating the immune response.

Based on these findings possible immunosuppressive effects of secretoma in in vitro experiments were investigated. CD4+ cells play a key role in the orchestration of the immune response as they are pivotal for the assistance of other leukocytes (e.g. macrophages, B cells, cytotoxic T cells) in immunological processes.

Material and Methods

Production of PBMC secretoma

PBMC from healthy volunteers were separated by Ficoll den-

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sity centrifugation. Cells were resuspended in Ultra Culture Medium (Lonza, Basel, Switzerland) at a concentration of 1×10^6 cells/mL (sup liv). For the production of secretoma from apoptotic PBMC apoptosis was induced by irradiation with 60Gy (sup APA). Cells were incubated for 24 h in a humidified atmosphere (5% CO₂, 37°C, relative humidity 95%). Supernatants were removed and dialysed with a 3.5 kDa cutoff (Spectrum laboratories, Breda, The Netherlands) against 50mM ammonium acetate overnight at 4°C. Then supernatants were sterile filtrated and lyophilized. Lyophilized secretoma were stored at -80°C and freshly resuspended for every experiment. Secretoma were radom sampled for their pH value.

Separation of CD4 cells

CD4+ cells were separated by depletion of non-CD4+ T cells utilizing a MACS bead system (Miltenyi, Bergisch Gladbach, Germany). Cells were freshly prepared and immediately used for each experiment.

Measurement of apoptosis

Apoptosis was detected by flow cytometry using a commercially available Annexin V/PI kit (BD, New Jersey, USA). Apoptosis were defined by Annexin positive staining, late apoptosis by PI positivity.

Proliferation experiments

PBMC or purified CD4+ cells were diluted in Ultra Culture supplemented with 0.2% gentamycinsulfate (Sigma, St. Louis, MO, USA), 0.5% β -mercapto-ethanol (Sigma, St Louis, MO, USA) and 1% GlutaMAX-I (Invitrogen, Carlsbad, CA, USA) to a concentration of 1×10^5 /well in a 96 round-bottom well plate. Cells were stimulated with either PHA (7 μ g/mL, Sigma, USA), CD3 (10 μ g/mL, BD, New Jersey, USA) IL-2 (10U/mL, BD, USA) or an 1:1 ratio of allogeneic irradiated (60 Gy) PBMC for MLR. Cells were incubated for 48 h or 5 days (MLR) with different concentrations of PBMC secretoma, IL-10 or TGF- β . Then cells were pulsed for 18 h with 3[H]-thymidine (3.7×10^4 Bq/well; Amersham Pharmacia Biotech, Uppsala, Sweden). Cells were harvested and 3[H]-thymidine incorporation was measured in a liquid scintillation counter.

Activation markers

Purified CD4+ cells were stimulated with anti-CD3 (10 μ g/mL) and co-incubated with different concentration of PBMC secretoma. Cells were stained for CD69 and CD25 following a standard flow

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cytometric staining protocol and analyzed on a flow cytometer FC500 (Beckman Coulter, Fullerton, CA, USA).

Results

In preliminary experiments the anti-proliferative properties of PBMC supernatants from viable cells (sup liv) were tested. In anti-CD3 and PHA stimulation experiments proliferations rates were significantly reduced by the addition of secretoma (n=10).

Based on these findings the effect of PBMC secretoma on the T-helper cell compartment was evaluated, since these cells play a pivotal role in launching and perpetuating an immune response. In analogy to Fig. 16 highly purified CD4⁺ cells lost their proliferative capacity by the addition of secretoma. This phenomenon was observed for the supernatant of living as well as of apoptotic, irradiated PBMC (Fig. 17, n=5).

The next step was to determine possible effects of the secretoma on cell viability. Therefore resting CD4⁺ cells were incubated with supernatant and Annexin V and PI positivity was evaluated. Supernatants from both, living and apoptotic PBMC, evidenced remarkable pro-apoptotic effects (Fig. 18, n=5).

To test if PBMC secretoma were able to inhibit CD4⁺ cell activation the T cell activation markers CD25 and CD69 following anti-CD3 stimulation of CD4⁺ cells was evaluated. The up-regulation of both markers was significantly and dose-dependent inhibited by PBMC secretoma (Fig. 19, n=5).

In a last set of experiments the effect of the immune-suppressive cytokines IL-10 and TGF- β by the addition of neutralizing antibodies in these experiments was examined. Neither IL-10 and TGF- β was found to be responsible for the anti-proliferative effects of our PBMC secretoma, since demonetizing these cytokines did not increase proliferation rates (Fig. 20, n=5).

Conclusion

These experiments evidence for the first time that PBMC secretoma posses immune-suppressive features in vitro. It was shown that supernatant a) reduces proliferation rates in anti-CD3, PHA and MLR stimulation experiments, b) has the potency to induce apoptosis and inhibits activation of CD4⁺ cells upon T cell triggering.

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Claims:

1. Pharmaceutical preparation for treating an internal inflammatory condition, preferably an internal condition associated with ischemia, comprising
 - a) a physiological solution comprising peripheral blood mononuclear cells (PBMCs) or a subset thereof, or
 - b) a supernatant of the solution a), wherein the solution a) is obtainable by cultivating PBMCs or a subset thereof in a physiological solution free of PBMC-proliferating and PBMC-activating substances for at least 1 h.
2. Preparation according to claim 1, characterised in that the inflammatory condition is selected from the group consisting of myocardial ischemia, limb ischemia, tissue ischemia, ischemia-reperfusion injury, angina pectoris, coronary artery disease, peripheral vascular disease, peripheral arterial disease, stroke, ischemic stroke, myocardial infarct, congestive heart failure, trauma, bowel disease, mesenterial infarction, pulmonary infarction, bone fracture, tissue regeneration after dental grafting, auto-immune diseases, rheumatic diseases, transplantation allograft and rejection of allograft.
3. Preparation according to claim 1 or 2, characterised in that the subset of peripheral blood mononuclear cells (PBMCs) is T cells, B cells or NK cells.
4. Preparation according to any one of claims 1 to 3, characterised in that the physiological solution is a physiological salt solution, preferably a physiological NaCl solution, whole blood, a blood fraction, preferably serum, or a cell culture medium.
5. Preparation according to claim 4, characterised in that the cell culture medium is selected from the group consisting of RPMI, DMEM, X-vivo and Ultraculture.
6. Preparation according to any one of claims 1 to 5, characterised in that the cells are cultivated under stress inducing conditions.

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7. Preparation according to claim 6, characterised in that the stress inducing conditions include hypoxia, ozone, heat, radiation, chemicals, osmotic pressure, pH shift or combinations thereof.

8. Preparation according to any one of claims 1 to 7, characterised in that the PBMCs or a subset thereof are stressed during cultivation with at least 10 Gy, preferably at least 20 Gy, more preferably at least 40 Gy, with ozone, with elevated temperature or with UV radiation.

9. Preparation according to any one of claims 1 to 8, characterised in that said preparation is adapted for subcutaneous administration, intramuscular administration, intra-organ administration and intravenous administration.

10. Preparation according to any one of claims 1 to 9, characterised in that the solution a) or the supernatant b) is lyophilised.

11. Preparation according to any one of claims 1 to 10, characterised in that the PBMCs or a subset thereof are cultivated in said solution for at least 4 h, preferably for at least 6 h, more preferably for at least 12 h.

12. Use of a preparation as defined in any one of claims 1 to 11 for the manufacture of a medicament for treating an internal inflammatory condition, preferably an internal condition associated with ischemia.

13. Method for preparing a pharmaceutical preparation according to any one of claims 1 to 11 comprising the steps of

a) providing peripheral blood mononuclear cells (PBMCs) or a subset thereof,

b) culturing the cells of step a) in a physiological solution free of PBMC-proliferating and PBMC-activating substances for at least 1 h,

c) isolating the cells of step b) and/or the supernatant thereof, and

d) preparing the pharmaceutical preparation using the cells

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and/or the supernatant of step c).

14. Method according to claim 13, characterised in that the cells are subjected to stress inducing conditions before or in the course of step b), wherein said stress inducing conditions include hypoxia, ozone, heat, radiation, chemicals, osmotic pressure, pH shift or combinations thereof.

15. Method according to claim 13 or 14, characterised in that the cells are irradiated before or in the course of step b) with at least 10 Gy, preferably at least 20 Gy, more preferably at least 40 Gy, with ozone, with elevated temperature or with UV radiation.

16. Preparation obtainable by a method according to any one of claims 13 or 15.

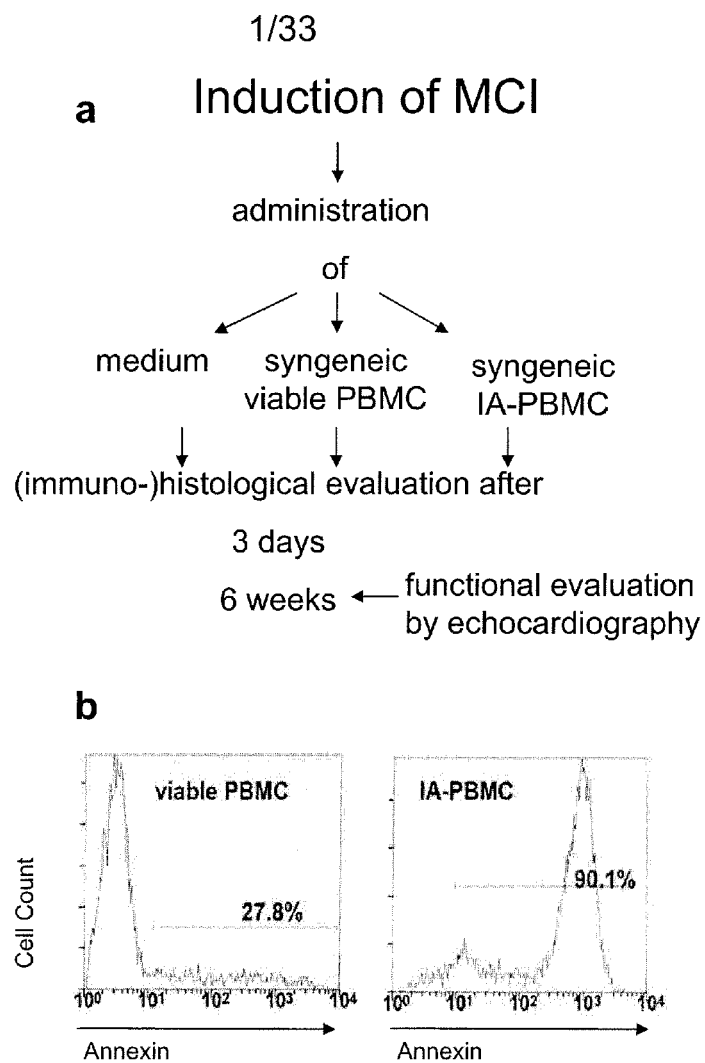


Fig. 1

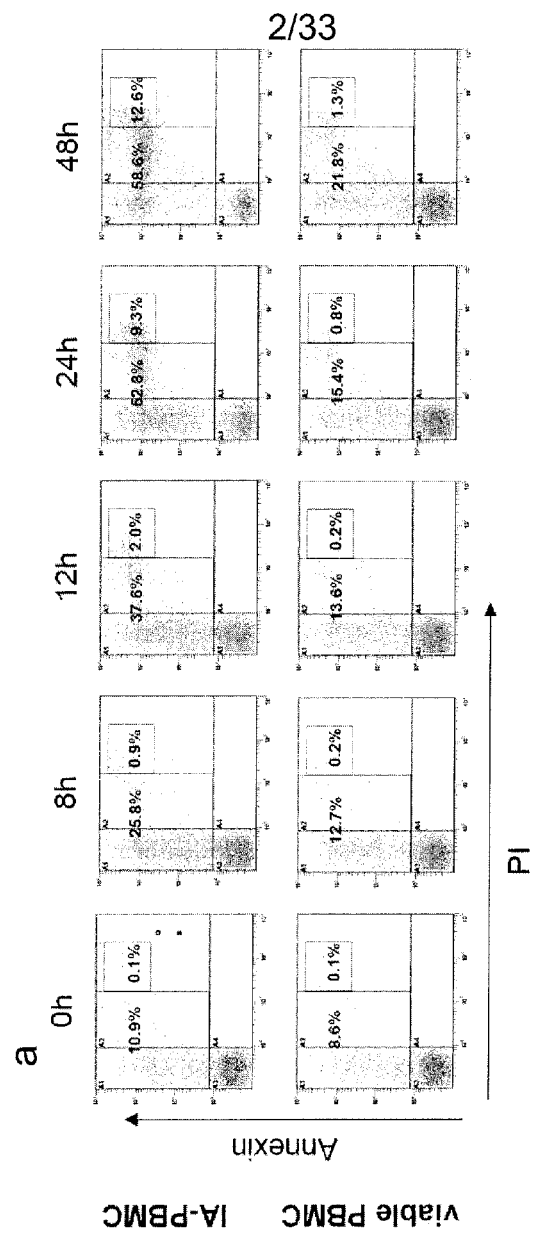


Fig. 2

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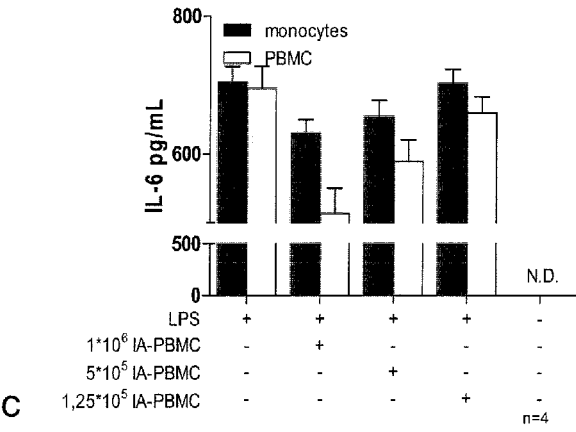
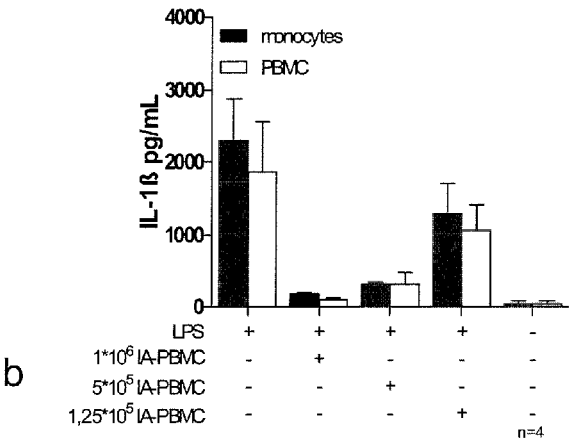


Fig. 2 cont

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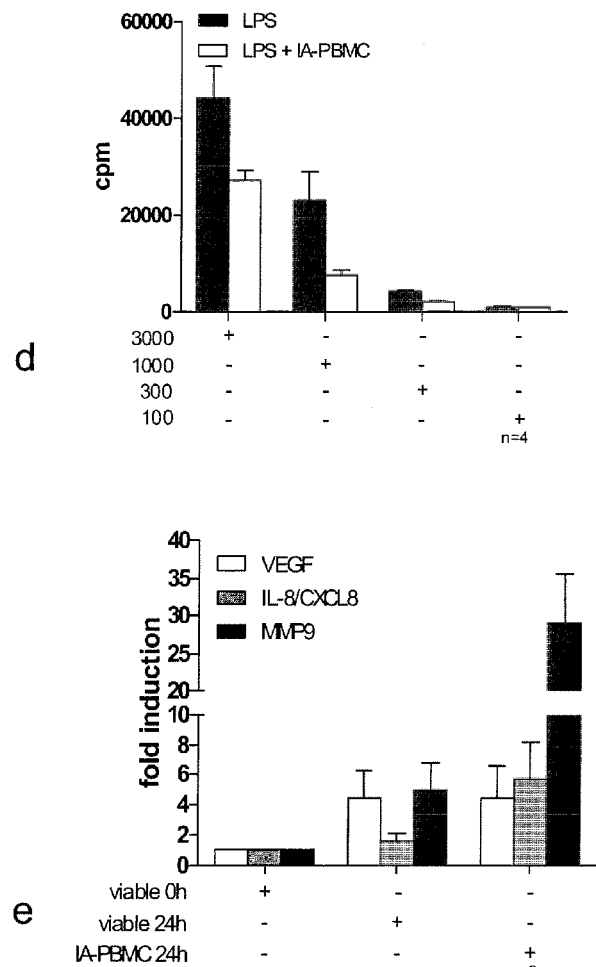


Fig. 2 cont

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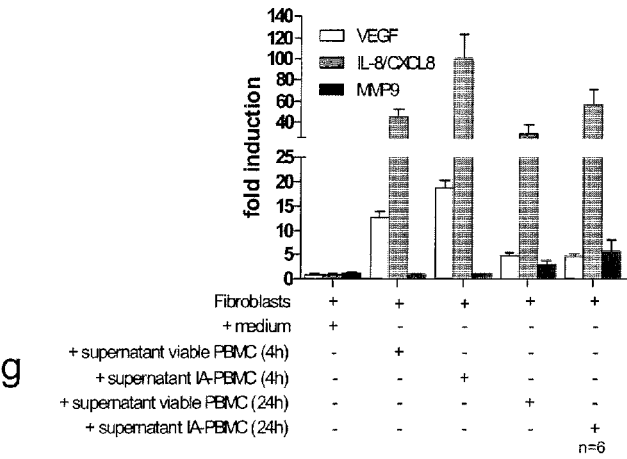
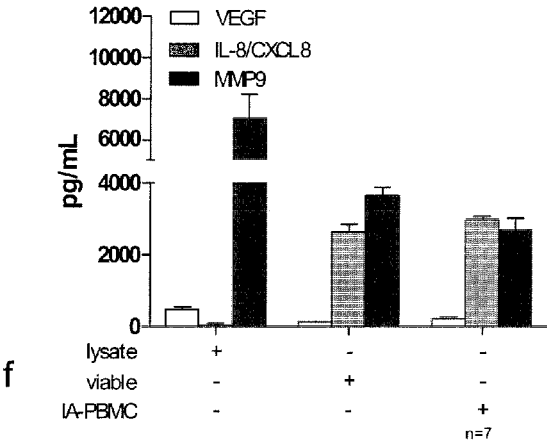


Fig. 2 cont

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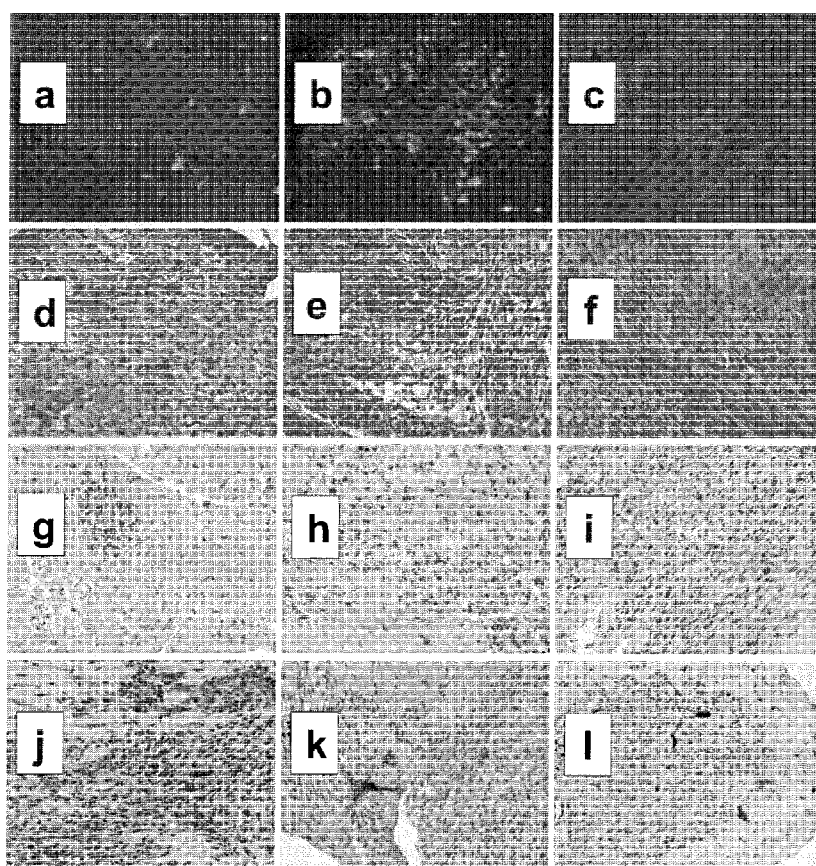


Fig. 3

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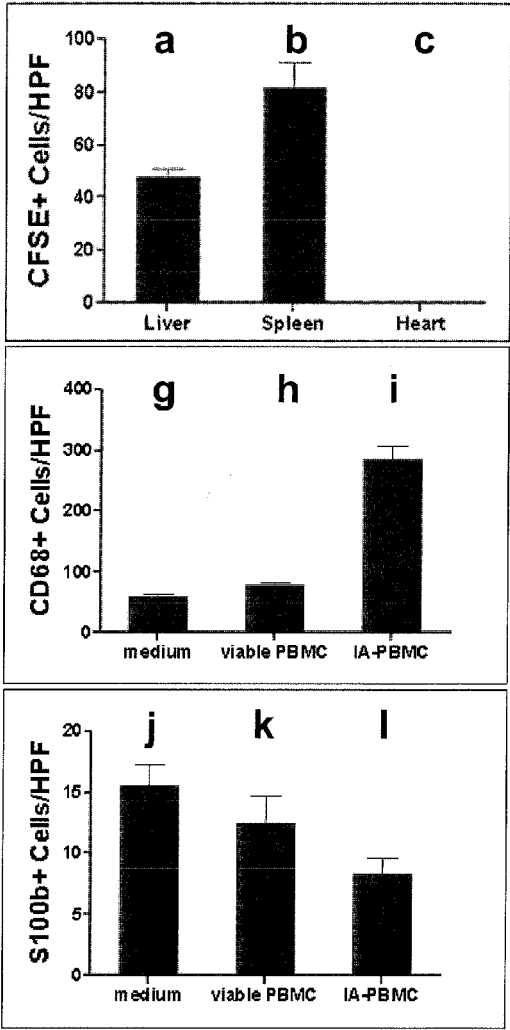


Fig. 3 cont.

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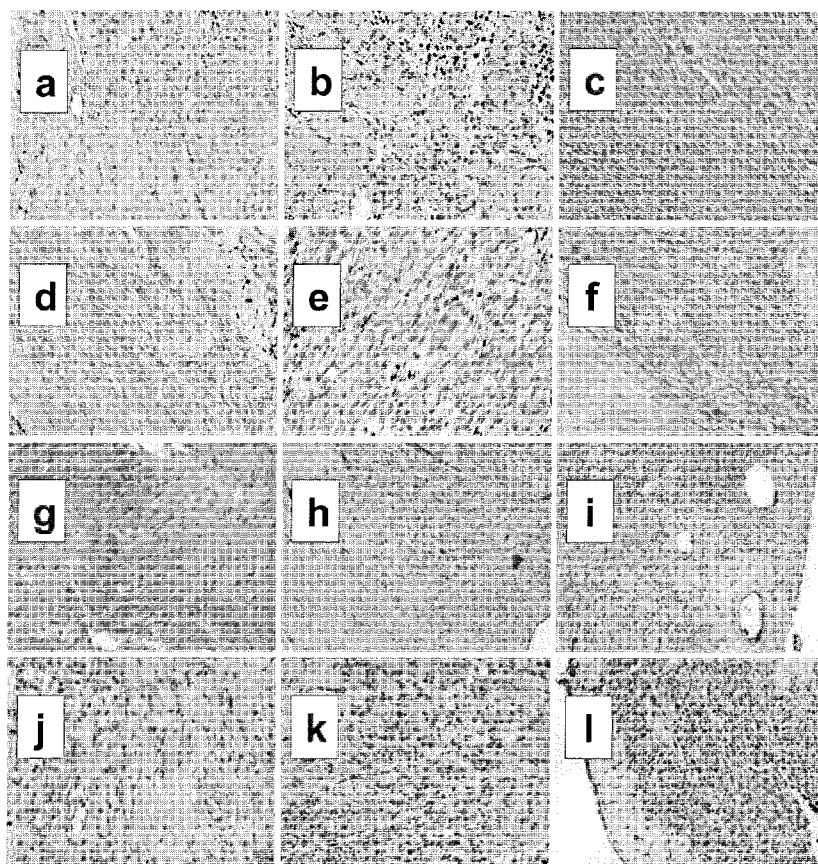


Fig. 4

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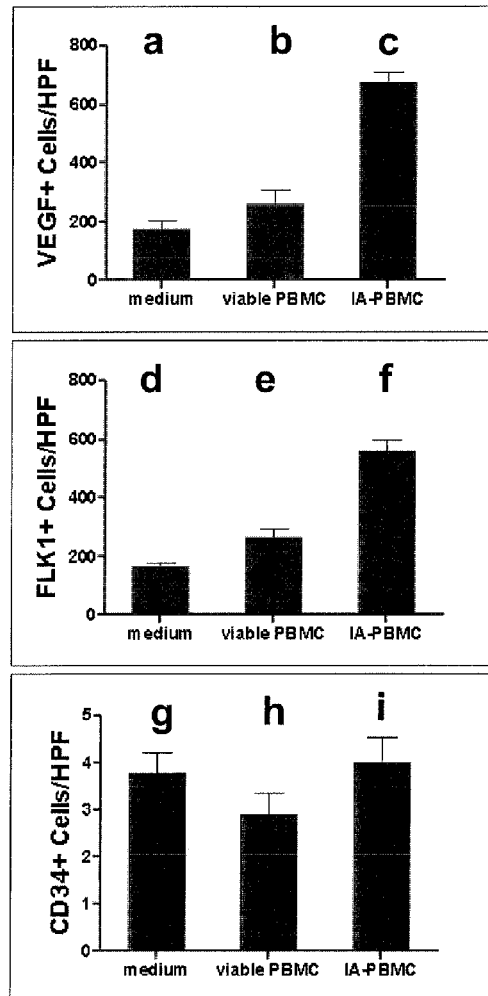


Fig. 4 cont.

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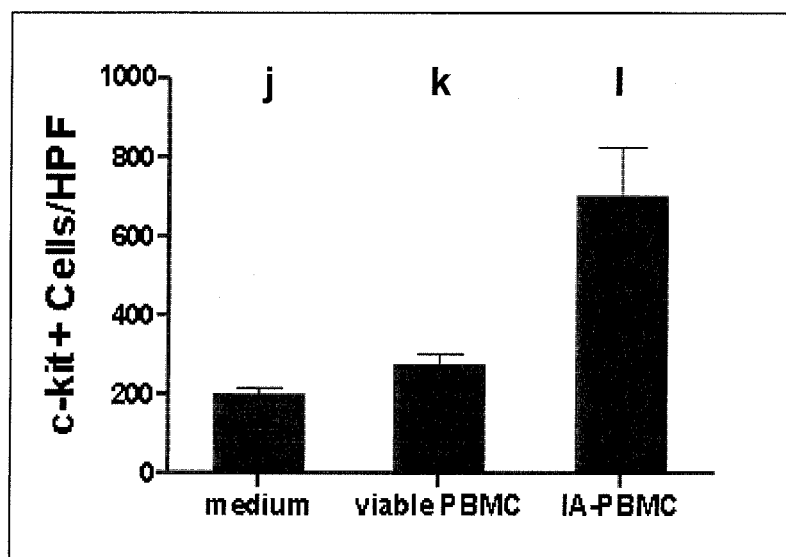


Fig. 4 cont.

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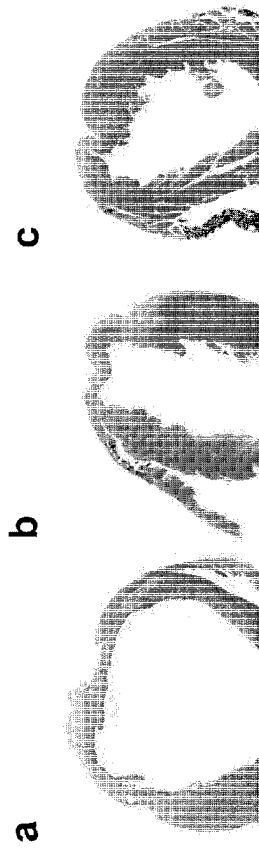


Fig. 5

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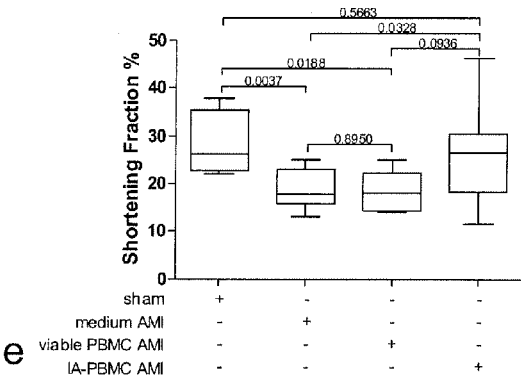
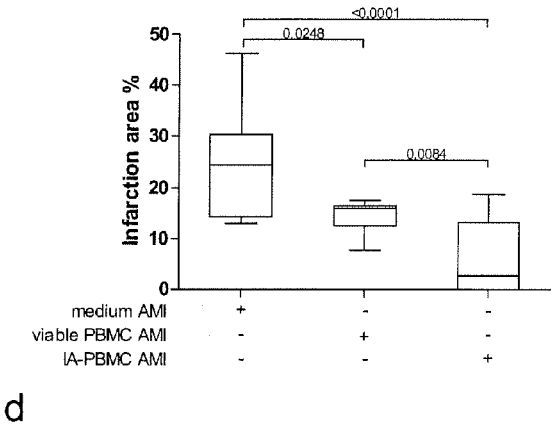


Fig. 5

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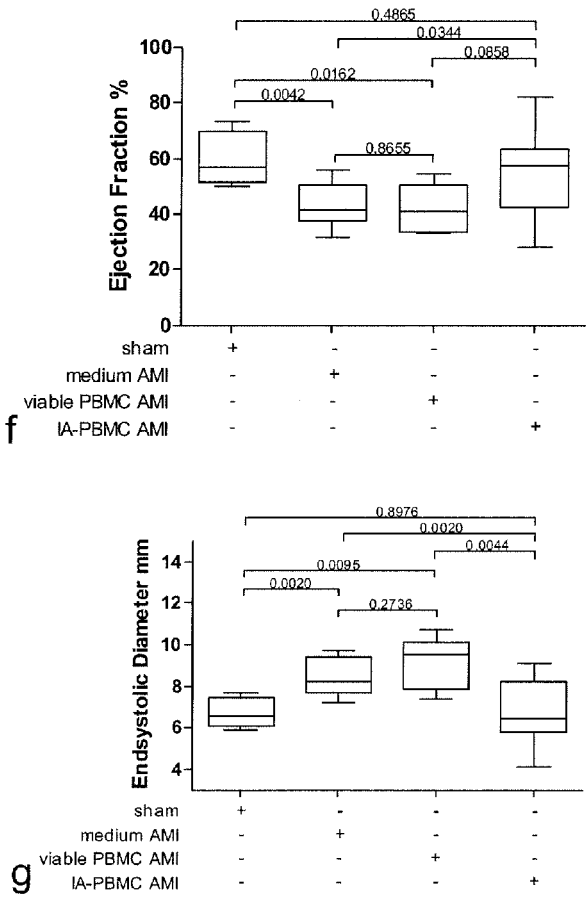


Fig. 5 cont

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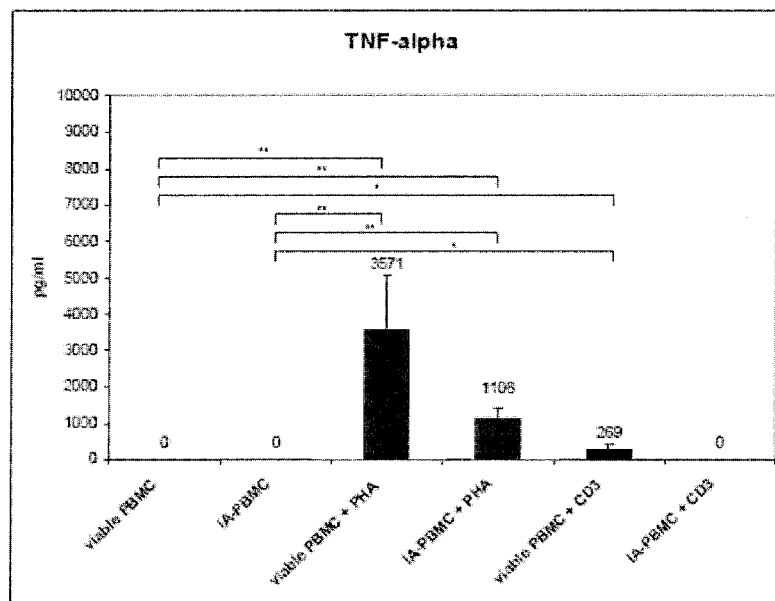


Fig. 6a

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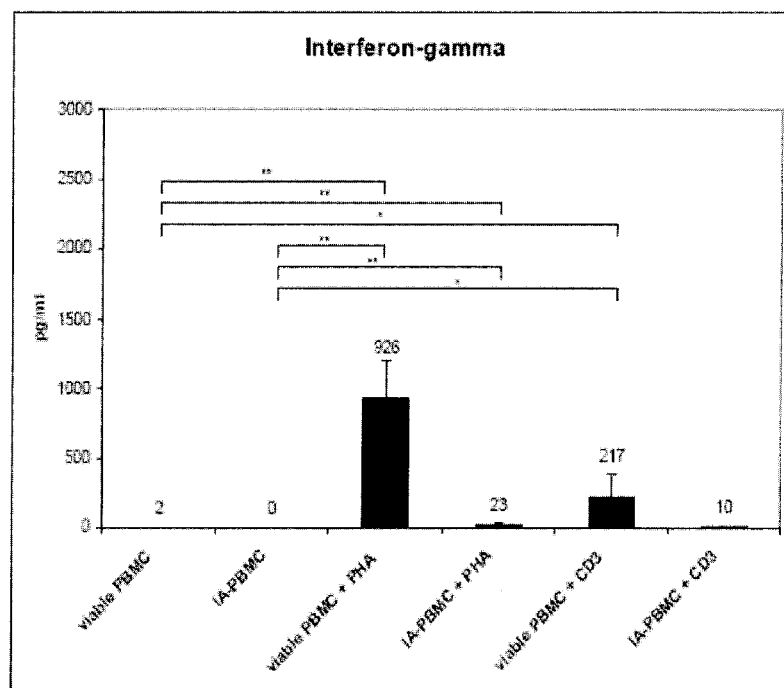


Fig. 6b

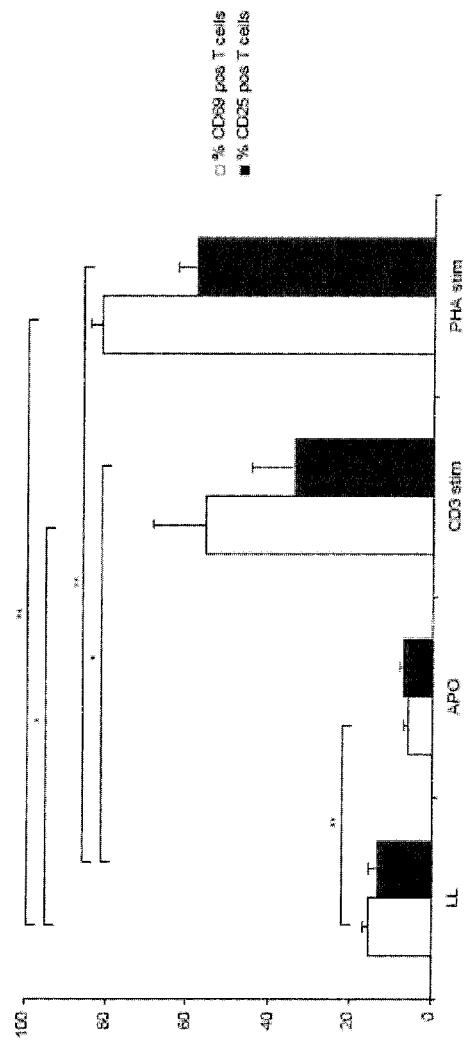


Fig. 7a

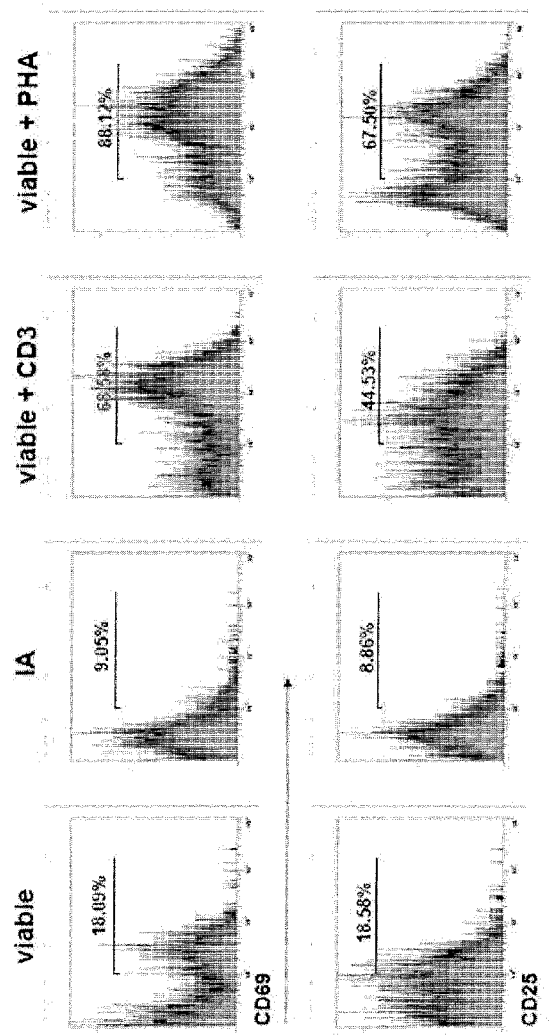


Fig. 7b

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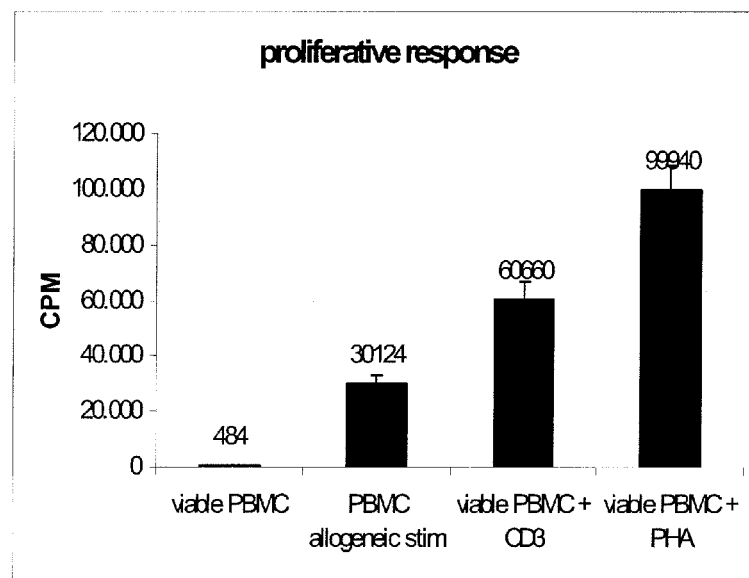


Fig. 8

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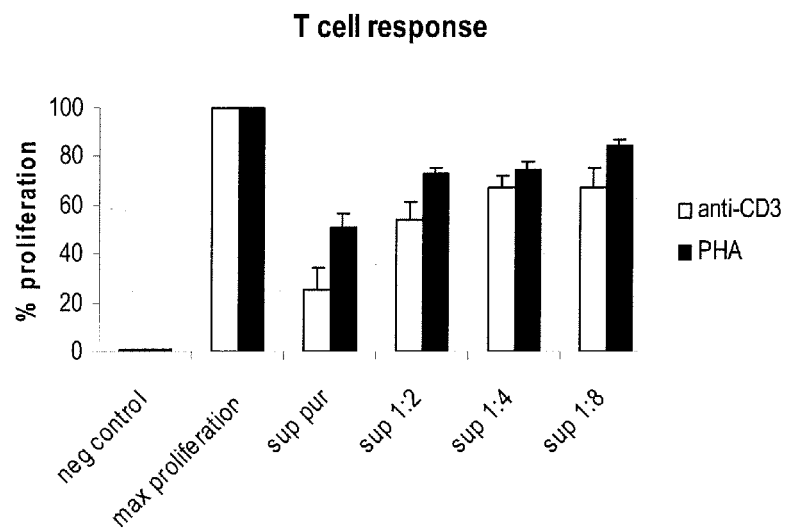


Fig. 9

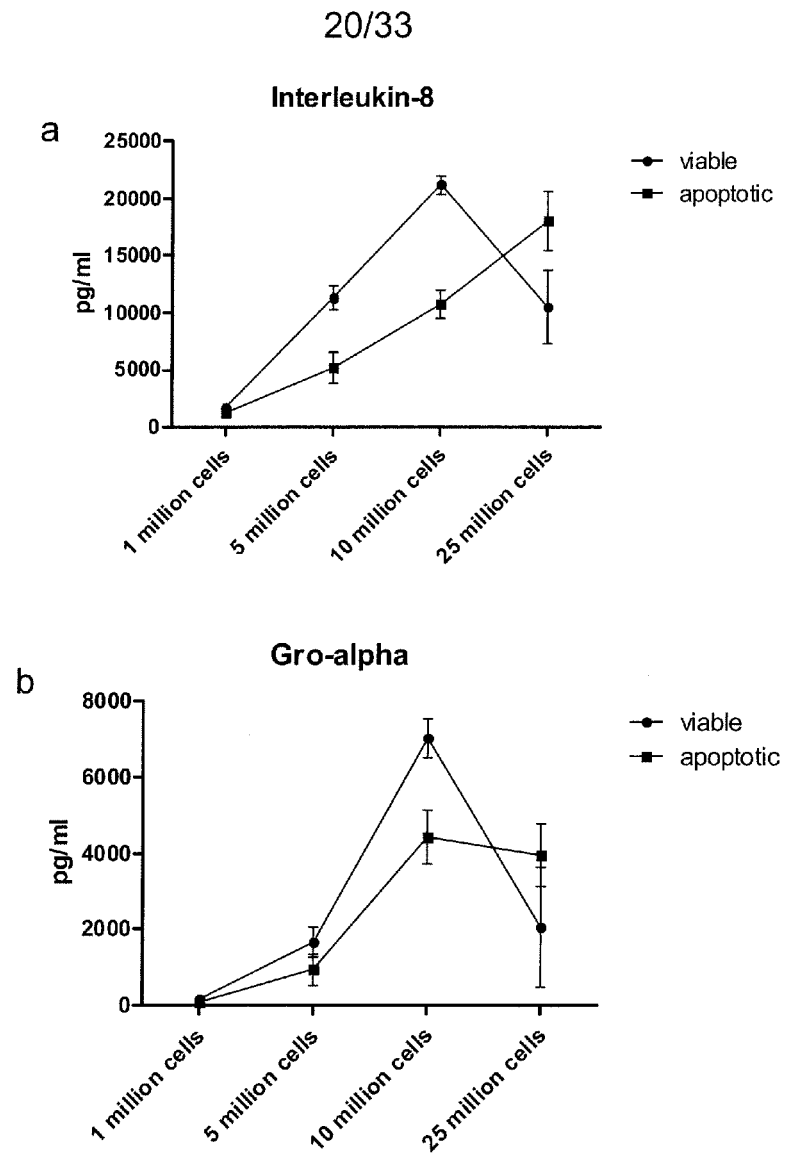


Fig. 10

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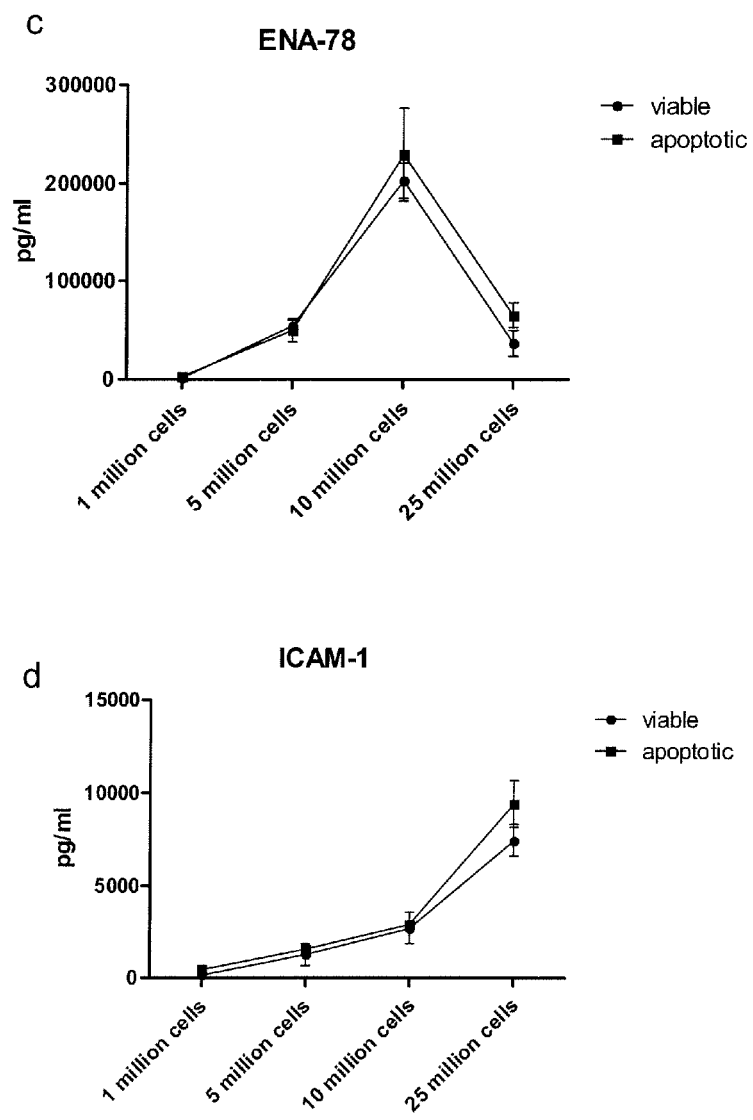


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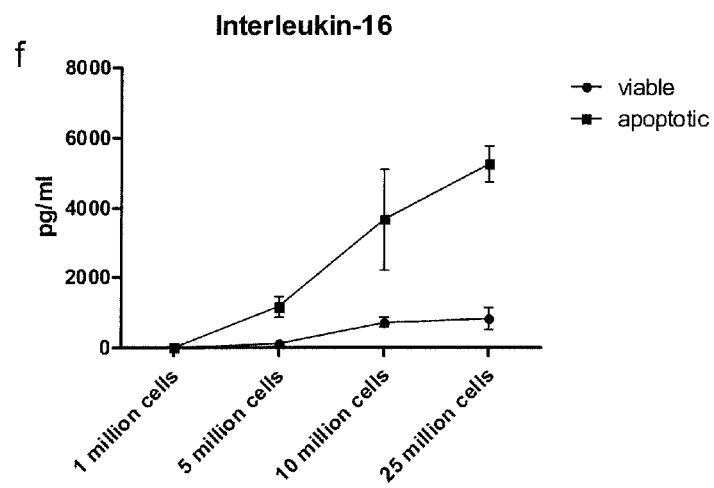
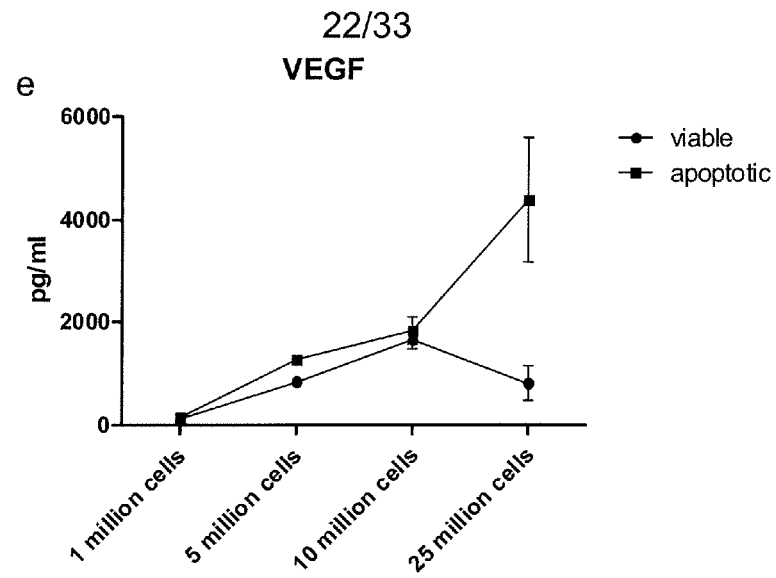


Fig. 10 cont.

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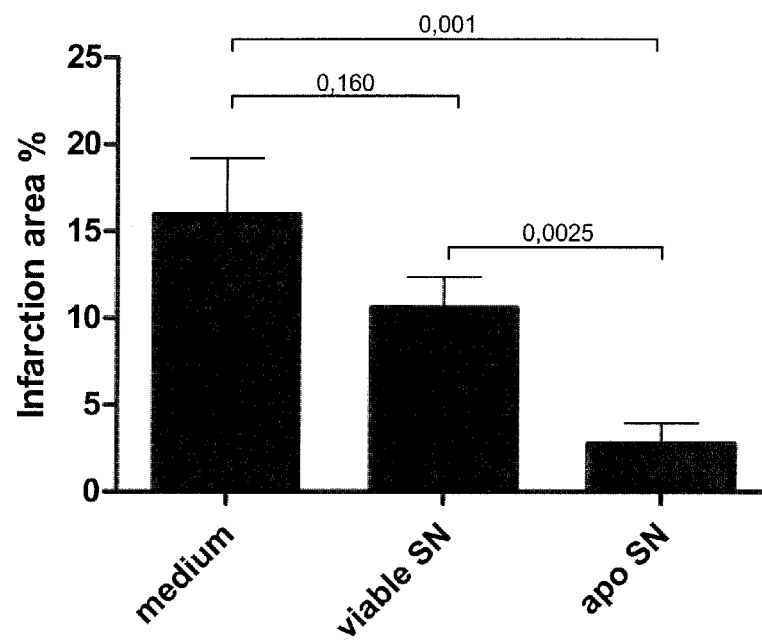
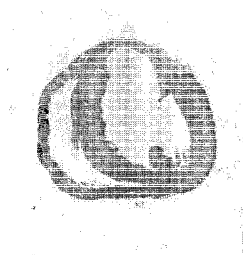


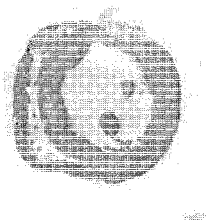
Fig. 11

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a



b



c



Fig. 12

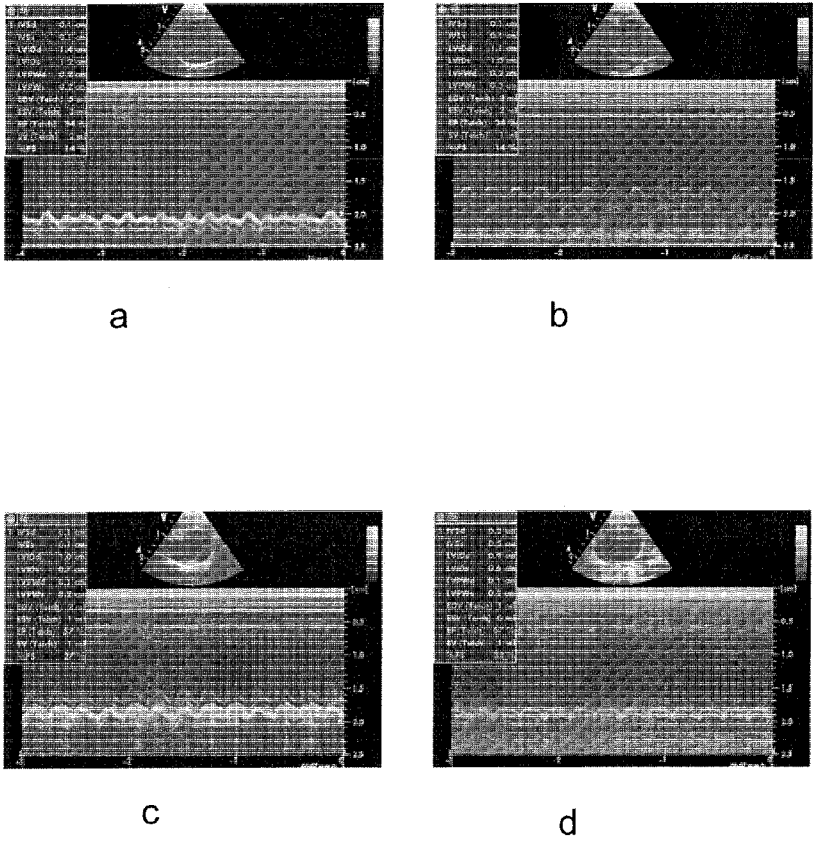


Fig. 13

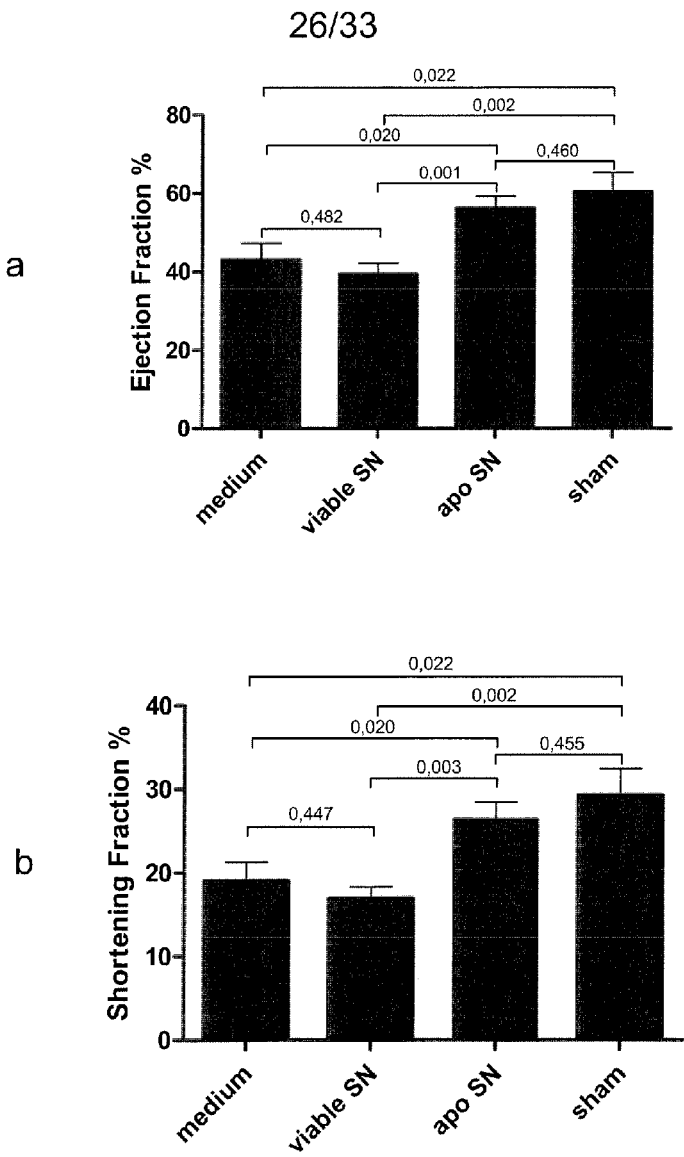


Fig. 14

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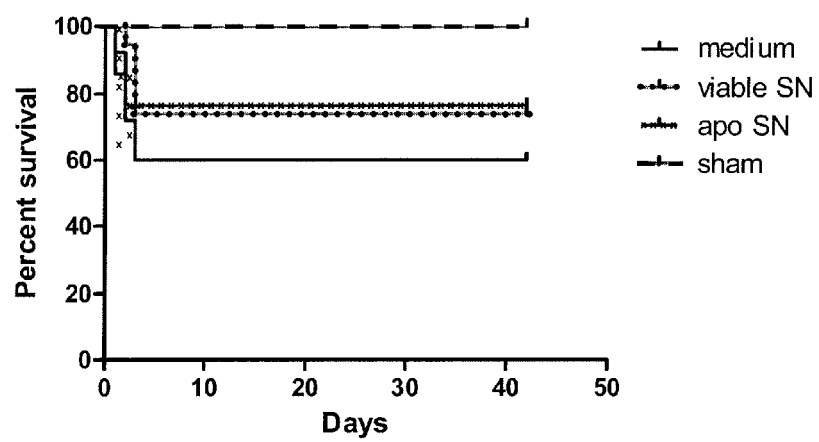


Fig. 15

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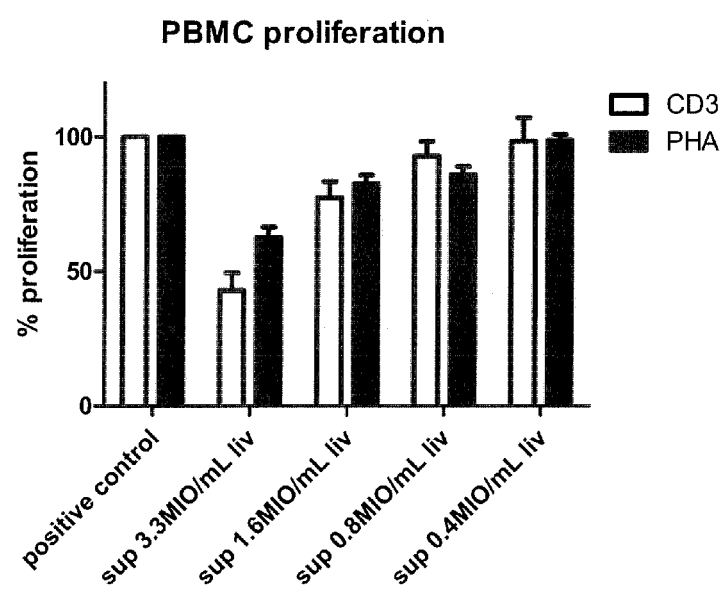


Fig. 16

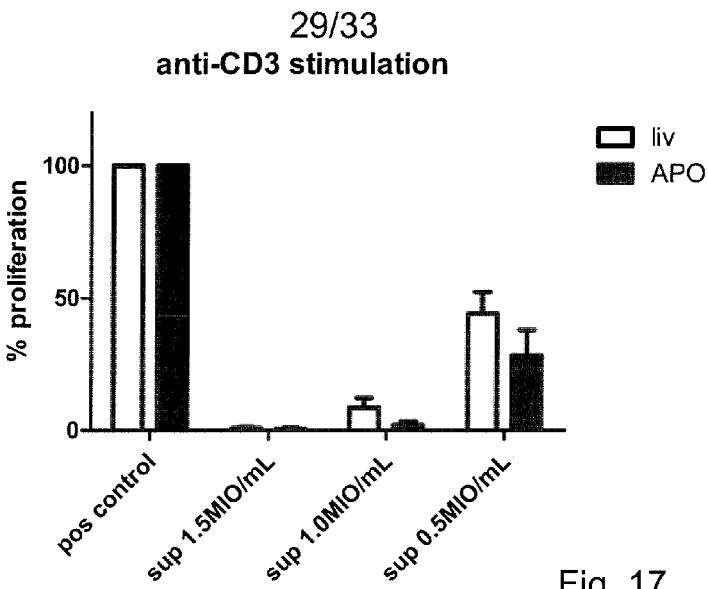
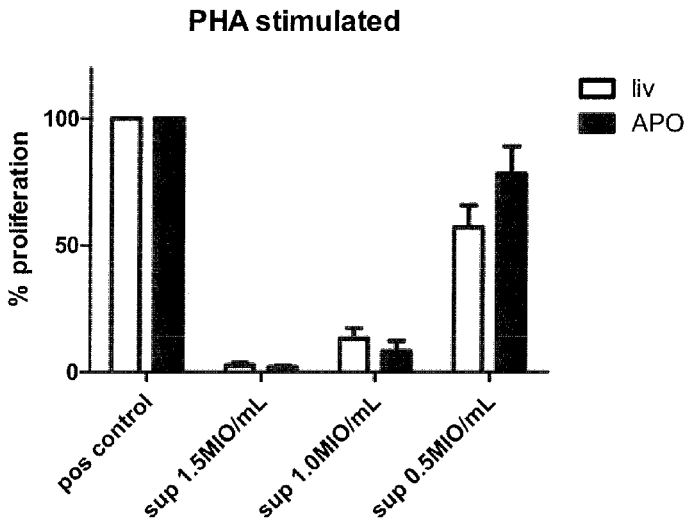


Fig. 17



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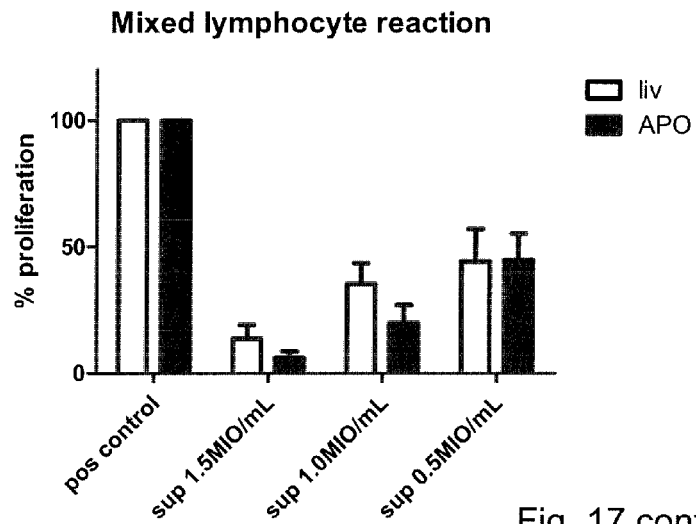
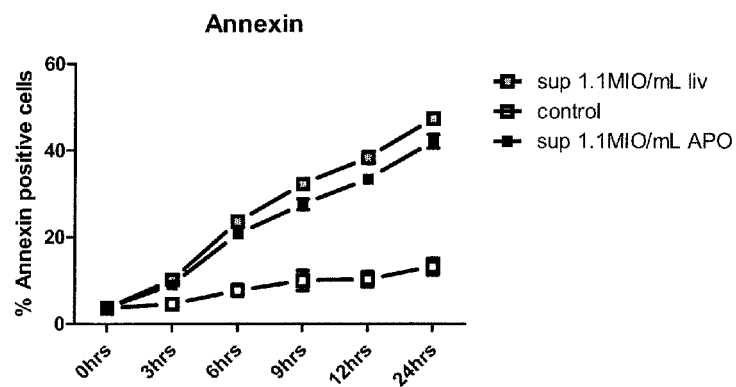


Fig. 17 cont.

Fig. 18



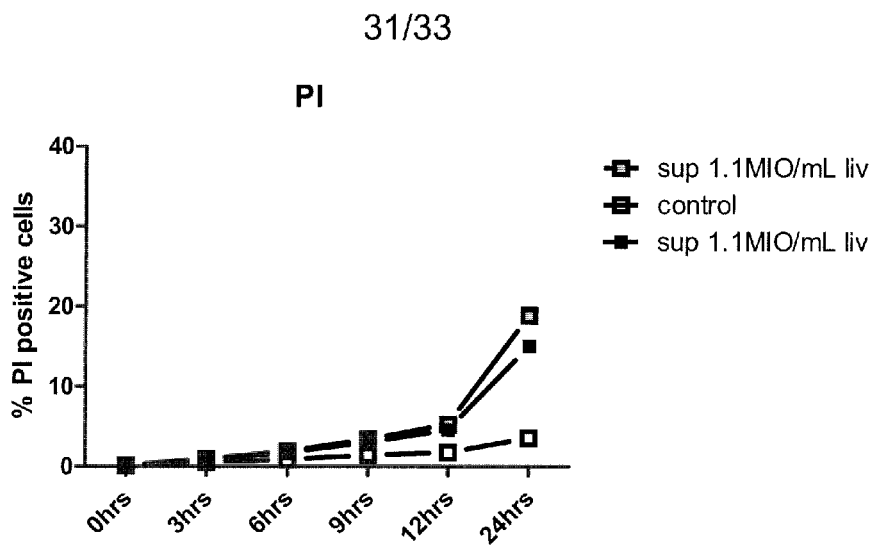
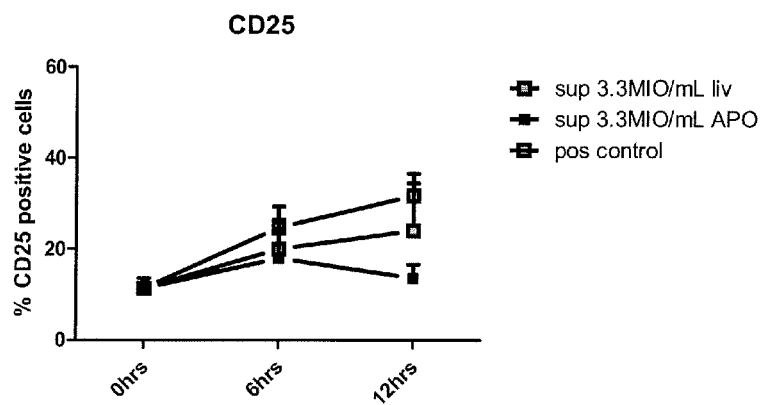


Fig. 18 cont.

Fig. 19



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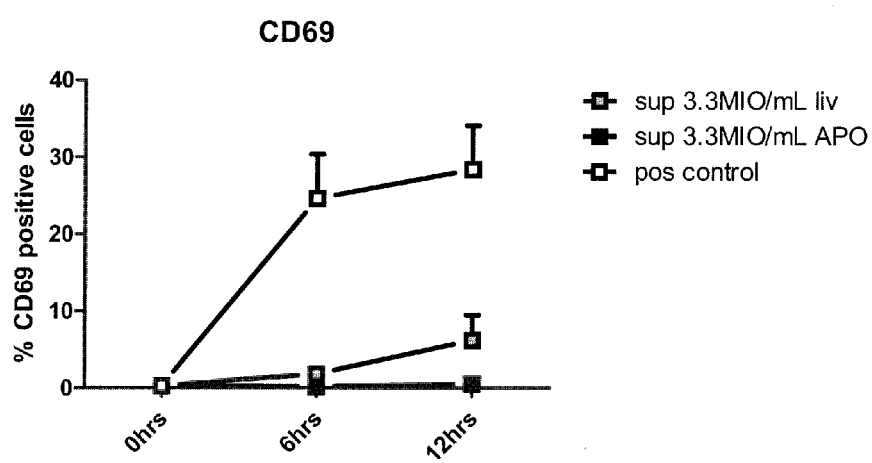


Fig. 19 cont.

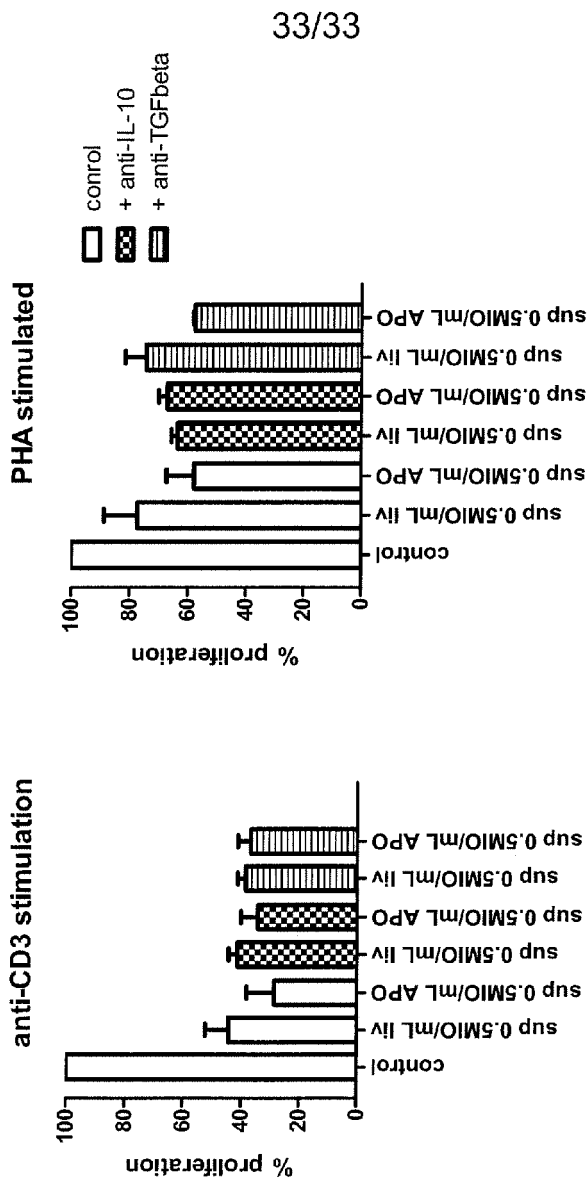


Fig. 20

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/067536

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K35/14 C12N5/078

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HOJO YUKIHIRO ET AL: "Expression of vascular endothelial growth factor in patients with acute myocardial infarction" 15 March 2000 (2000-03-15), JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, VOL. 35, NR. 4, PAGE(S) 968-973 , XP002559837 ISSN: 0735-1097	16
Y	page 969, column 2, paragraph isolation of PBMCs ----- -/--	1-16

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search

18 February 2010

Date of mailing of the international search report

02/03/2010

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Authorized officer

Mabit, Hélène

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/067536

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TATSUMI TETSUYA ET AL: "Intracoronary transplantation of non-expanded peripheral blood-derived mononuclear cells promotes improvement of cardiac function in patients with acute myocardial infarction" August 2007 (2007-08), CIRCULATION JOURNAL, VOL. 71, NR. 8, PAGE(S) 1199-1207, XP002559838 ISSN: 1346-9843 page 1200, column 2, paragraph	1-4, 9, 12, 16
Y	TUCHINDA CHANISADA ET AL: "Comparison of broadband UVB, narrowband UVB, broadband UVA and UVA1 on activation of apoptotic pathways in human peripheral blood mononuclear cells" PHOTODERMATOLOGY PHOTOIMMUNOLOGY & PHOTOMEDICINE, vol. 23, no. 1, February 2007 (2007-02), pages 2-9, XP002559839 ISSN: 0905-4383 page 3, column 2, paragraph Cell culture and isolation	1-16
Y	DOYLE BRENDAN ET AL: "Progenitor cell therapy in a porcine acute myocardial infarction model induces cardiac hypertrophy, mediated by paracrine secretion of cardiostrophic factors including TGFbeta1" STEM CELLS AND DEVELOPMENT,, vol. 17, no. 5, 1 October 2008 (2008-10-01), pages 941-951, XP009126888 ISSN: 1557-8534 page 942 page 947 page 949	1-16
Y	GOLPON HEIKO A ET AL: "Life after corpse engulfment: phagocytosis of apoptotic cells leads to VEGF secretion and cell growth" FASEB JOURNAL, vol. 18, no. 12, September 2004 (2004-09), XP002559840 ISSN: 0892-6638 page 2 page 8 page 949	1-16

-/--

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2009/067536

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	ANKERSMIT H J ET AL: "Irradiated cultured apoptotic peripheral blood mononuclear cells regenerate infarcted myocardium" June 2009 (2009-06), EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, VOL. 39, NR. 6, PAGE(S) 445-456 , XP002559841 ISSN: 0014-2972 -----	

MCTOX'CON

MC Toxicology Consulting GmbH

Overview of Toxicology Studies for APOSEC™

Prepared for Aposcience AG

Date: 23 March 2020

Confidential information

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List of Abbreviations

BrdU	5-Bromo-2-Deoxyuridine
CTA	Clinical Trial Application
ECG	Electrocardiography
FBS	Fetal Bovine Serum
GLP	Good Laboratory Practice
HED	Human Equivalent Dose
ICH	International Council for Harmonization
IMPD	Investigational Medicinal Product Dossier
i.p.	Intraperitoneal(ly)
i.v.	Intravenous(ly)
NOAEL	No Observable Adverse Effect Level
NOEL	No Observable Effect Level
p.a.	Post administration
s.c.	Subcutaneous(ly)
SD	Standard Deviation
SRB	Sulforhodamine B

1 Executive Summary

APOSEC™ was tested in a number of non-GLP and GLP studies performed in various species (mouse, rat, dog, minipig, cynomolgus monkey) with different routes of administration (subcutaneous (s.c.) and intravenous (i.v.)).

No signs of toxicity were observed when APOSEC™ was applied:

- as a single i.v. administration at dose levels of 50, 250 or 500 U/kg to CD® rats (NOEL defined as ≥ 500 U/kg under the experimental conditions of the study)
- as a single i.v. administration at a dose of 250 U/kg to beagle dogs
- three times weekly by s.c. administration for 2 weeks at dose levels 50, 250, or 500 U/kg to CD® rats
- three times weekly by s.c. administration for 2 weeks at a dose level of 33 U/kg to beagle dogs
- three times weekly by i.v. administration for 4 weeks at dose levels 50, 250 or 500 U/kg to mice (NOEL defined as ≥ 500 U/kg under the experimental conditions of the study)
- three times weekly by s.c. administration for 4 weeks at dose levels 3.3, 10.5 or 33.3 U/kg to Aachener minipigs (NOEL defined as ≥ 33.3 U/kg under the experimental conditions of the study)
- two times weekly by i.v. administration for 2 weeks at a dose level of 35 U/kg to Cynomolgus monkeys; exaggerated pharmacodynamic effect, i.e. vasodilation were observed at 110 and 200 U/kg under the experimental conditions of the study.

It is emphasized, that none of the study tested daily applications. Thus, an accumulation of effects due to more frequent dosing cannot be excluded.

The 2 week study in cynomolgus monkeys is considered as key study for potential i.v. application of Aposec™ in humans. In this study, APOSEC™ was infused at three dose levels over 30-40 minutes. The low dose of 35 U/kg induced no effects except for enlarged axillary lymph nodes observed in one male animal. No (exaggerated) pharmacodynamic effect attributed to vasodilation which is a postulated mode of action of the product was observed in animals treated at 35 U/kg. 35 U/kg translates to 2450 U per 70 kg person (dose between animals and humans scaled via body weight).

However, there is some uncertainty if for Aposec™ (containing the lyophilized secretome supernatant obtained from apoptotic PBMCs) extrapolation between animals and humans is better scaled via body weight or based on body surface scaling (Human Equivalent Dose; HED). If on basis of HED (HED conversion factors: 0.32 for cynomolgus monkey), 11 U/kg is the corresponding figure to 35 U/kg in cynomolgus. 11 U/kg translates to 770 U per 70 kg person (dose between animals and humans scaled via body surface area).

The mid dose of 110 U/kg induced clear effects considered as vasodilatory effects (reduced motility, asthenia, mydriasis, a lateral position and clonic convulsions).

At the high dose level (350/225/200 U/kg, see Table 2), effects in form of asthenia, somnolence, mydriasis, a lateral position, an increased respiratory rate, laboured breathing, a reduced motility, reduced reflexes, (clonic) convulsions, salivation and/or emesis were observed; all of these effects observed at mid and/or high dose can be monitored. In addition, at high dose, two of 5 male animals treated with 350 U/kg had to be sacrificed prematurely after the first administration.

The study did not test a dose level between 35 and 110 U/kg. Thus, the study data do not define in detail the lowest dose inducing biologic effects / vasodilation (> 35 U/kg and ≤ 110 U/kg scaled via body weight; > 11 U/kg and ≤ 35.5 U/kg scaled via body surface area).

2 Introduction

This document provides an overview of toxicology studies for APOSEC™ and includes the non-GLP and GLP studies performed in various species (mouse, rat, dog, minipig, cynomolgous monkey) with different routes of administration (subcutaneous (s.c.) and intravenous (i.v.)). For both routes of administration, APOSEC™ drug product was used as a solution in 0.9% saline. Doses of APOSEC™ are expressed as U/kg or U/mL. Safety pharmacology studies are also summarized in this document.

[Table 1](#) provides a tabular overview of all toxicology studies and the safety pharmacology study outlined in this document. [Section 2](#) provides the summary of studies already discussed in the Investigational Medicinal Product Dossier (IMPD) submitted for the Clinical Trial Application (CTA) for clinical study “MARSYAS II” (EudraCT no. 2018-001653-27). [Section 3](#) provides the summary of the repeat doses study in cynomolgous monkeys, which is the only toxicology study finished since submission of the above-mentioned CTA. Brief considerations on other aspects of toxicological profiling, likewise already discussed in the IMPD for EudraCT no. 2018-001653-27, are outlined in [Section 4](#). [Section 5](#) provides an aggregated summary and conclusion.

Acute and repeat dose toxicity studies included: a single dose study in rats (i.v. route of administration; GLP; [Section 2.2.1](#)); a single dose study in dogs (i.v. route; non-GLP; [Section 2.2.2](#)); repeat dose toxicity studies in rats (i.v. route; non-GLP; [Section 2.3.1](#)), dogs (s.c. route; non-GLP; [Section 2.3.2](#)), mice (i.v. route; GLP; [Section 2.3.3](#)), minipigs (s.c. route; GLP; [Section 2.3.4](#)) and cynomolgus monkey (i.v. infusion; GLP; [Section 3.1.1](#)). Effects on the CNS were investigated in a separate safety pharmacology study in rats (IRWIN screen; i.v. route of administration; GLP; [Section 2.1.1](#)). Selected cardiovascular and respiratory parameters were included in the pivotal GLP repeat dose toxicity study in minipigs ([Section 2.3.4](#)) and ECGs included in the GLP study in cynomolgus ([Section 3.1.1](#)). Further stand-alone *in vivo* safety pharmacology studies were not considered necessary. Local tolerance was assessed in a local lymph node assay (LLNA) in mice by the topical route of administration (GLP; [Section 2.4.1](#)).

This summary has been compiled from the individual study reports.

Table 1 Overview of Non-Clinical Toxicology Studies for APOSEC™

Study	Study No.	GLP Status	Test System / Groups and Group Size	Route of Administration / Treatment schedule / Observation period	Test Item / Dose	Highest Dose / Concentration [U/kg] or [U/mL]	Noteworthy Findings	Document Section
Safety Pharmacology								
Neuropharmacological screening in rats according to IRWIN following i.v. administration of APOSEC™	33202/1	GLP	Rat / Sprague Dawley (CD®) 5 groups of 6M+6F each	Single i.v. bolus (2 mL/kg) / Screening up to 72h	APOSEC™: 50, 250 or 500 U/kg positive control: Diazepam 0.8 mg/kg vehicle control: 0.9% NaCl	500 U/kg	Dose-dependent effect at mid and high dose at 1h (transient) on awareness, mood, motor activity, autonomic function, and reflexes at the highest dose	2.1.1
Single Dose Toxicity								
Acute Toxicity Study of APOSEC™ by single i.v. administration to CD® rats	33201/1	GLP	Rat / Sprague Dawley (CD®) 4 groups of 5M+5F each	Single i.v. bolus (2 mL/kg)	APOSEC™: 50, 250 and 500 U/kg vehicle control: 0.9% NaCl	500 U/kg	- No test item related effect on body weight, observations in-life, macroscopy - No toxicity observed - No observed effect level (NOEL) defined at ≥ 500 U/kg	2.2.1
Single Dose Toxicity Study with allogenic APOSEC™ after i.v. bolus injection to beagle dogs	33749	Non-GLP	Dog / Beagle 1M+1F	Single i.v. bolus (1 mL/kg)	APOSEC™: 250 U/kg vehicle control: 0.9% NaCl	250 U/kg	- No test item related effect on body weight, observations in-life, clinical pathology - No signs of local intolerance - No toxicity observed	2.2.2
Repeat Dose Toxicity								
2-week dose range finding	33647	Non-	Rat / Sprague	i.v. bolus (2 mL/kg) / 3 times	APOSEC™: 50,	500 U/kg	No test item related effect on body weight, observations in-	2.3.1

Study	Study No.	GLP Status	Test System / Groups and Group Size	Route of Administration / Treatment schedule / Observation period	Test Item / Dose	Highest Dose / Concentration [U/kg] or [U/mL]	Noteworthy Findings	Document Section
study of allogenic APOSEC™ by i.v. slow bolus administration 3 times weekly to CD® rats		GLP	Dawley (CD®) 4 groups of 3M+3F each Satellite animals for TK: 1 group of 6M+6F in total	weekly for 2 weeks (6 days for satellite group)	250 and 500 U/kg vehicle control: 0.9% NaCl		life, food and water consumption and macroscopy • Increase (114%) in eosinophilic granulocytes in males at day 14 in the high dose group • No toxicity observed	
Dose range-finding study with allogenic APOSEC™ by s.c. bolus injection to beagle dogs	33649	Non-GLP	Dog / Beagle 1 group of 1M+1F	s.c. bolus (1 mL/kg) / 3 times weekly for 2 weeks	APOSEC™: 33 U/kg vehicle control: 0.9% NaCl	33 U/kg	• No test item related effect on body weight, observations in-life, water consumption, clinical pathology and macroscopy • No signs of local intolerance • Decrease in food consumption (up to 51%) during the whole observation period • No toxicity observed	2.3.2
4-week toxicity study of allogenic APOSEC™ by i.v. slow bolus administration 3 times weekly to mice	34946	GLP	Mice 4 groups of 10M+10F each (main study); 2 groups of 5M+5F each (recovery)	i.v. bolus (2 mL/kg) / 3 times weekly for 4 weeks	APOSEC™: 50, 250 and 500 U/kg vehicle control: 0.9% NaCl	500 U/kg	• No test item related effect on body weight, observations in-life, food and water consumption, clinical pathology, ophthalmology, macroscopy and microscopic observations • No signs of local intolerance • No toxicity observed • NOEL defined at ≥ 500 U/kg	2.3.3
4-week toxicity study of allogenic APOSEC™ in	34873	GLP	Aachener Minipig 4 groups of 3M+3F each	s.c. / 3 times weekly for 4 weeks	APOSEC™: 3.3, 10.5 and 33.3 U/kg vehicle control:	33.3 U/kg	• No test item related effect on body weight, observations in-life, telemetry, food and water consumption, clinical	2.3.4

Study	Study No.	GLP Status	Test System / Groups and Group Size	Route of Administration / Treatment schedule / Observation period	Test Item / Dose	Highest Dose / Concentration [U/kg] or [U/mL]	Noteworthy Findings	Document Section
Aachener mini-pigs with s.c. administration 3 times weekly			(main study); 2 groups of 2M+2F each (recovery)		0.9% NaCl		pathology, macroscopy and microscopic observations - Slight signs of local intolerance in form of reddenings, swellings and/or thickenings of the s.c. injection sites, and of local intolerance reactions according to DRAIZE; both effects attributed to s.c. administration procedure - Ki67 staining of injection sites: no test item related influence on cell proliferation in the epidermis, corium and in the granulation tissue in the subcutis - No toxicity observed - NOEL defined at ≥ 33.3 U/kg	
2-week toxicity study of allogenic APOSEC™ by repeated twice weekly i.v. Infusion to cynomolgous monkeys followed by a 2-week treatment-free period	35015	GLP	Cynomolgous monkey 4 groups of 3M+3F each (main study); 2 groups of 2M+2F each (recovery); 2 replacement males in high dose group *	i.v. infusion 2 times a week for 2 weeks (4 dosing occasions)	APOSEC™: 35, 110 and 350/225/200 U/kg * vehicle control: 0.9% NaCl	350/225/200 U/kg *	- Preterm sacrifice of two males upon the first administration of high dose (350 U/kg) - Clinical signs at the high dose* and mid dose (110 U/kg; males): reduced motility, asthenia, mydriasis, a lateral position and clonic convulsions, somnolence, increased respiratory rate, laboured breathing, reduced reflexes, salivation and/or emesis - Enlargement of spleen in two males at high dose;	3.1.1

Study	Study No.	GLP Status	Test System / Groups and Group Size	Route of Administration / Treatment schedule / Observation period	Test Item / Dose	Highest Dose / Concentration [U/kg] or [U/mL]	Noteworthy Findings	Document Section
							microscopic correlate (follicular hyperplasia) in one animal - Enlarged axillary lymph nodes in one male treated at low dose (35 U/kg) and male at high dose; microscopic correlates (medullary hyperplasia) seen in both animals - NOAEL defined at 200 U/kg *	
Local Tolerance								
Skin sensitization: local lymph node assay: BrdU-ELISA of APOSEC™ in CBA/JN mice - according to OECD guideline 442B	33203/1	GLP	Mice / CBA/JN 6 groups of 5F each	Topical	APOSEC™: 0.625, 3.125 or 6.25 U per mouse (25, 125, or 250 U/mL, formulated in 0.9% NaCl, 25 µl applied per ear) Positive control: 25% solution (v/v) of α-hexyl cinnamic aldehyde in acetone / olive oil (4: 1 v/v) vehicle control: 0.9% NaCl	250 U/mL = 6.25 U per mouse	- Positive control increased BrdU index and caused irritation - BrdU index < positive control =>classified as non-sensitizing - No irritation properties noted - No systemic intolerance, no erythema, no effect on body weight	2.4.1

* For further explanation see [Section 3.1.1](#).

3 Studies Summarized in IMPD Submitted for EudraCT No. 2018-001653-27

3.1 Safety Pharmacology

3.1.1 Neuropharmacological Screening in Rats According to IRWIN Following Intravenous Administration of APOSEC™ (GLP, Study No. 33202/1)

Objective: The aim of this safety pharmacology study was to examine the effect of APOSEC™ on 40 neuropharmacological parameters of male and female rats following single i.v. administration in a neuropharmacological screening test according to IRWIN.

Study Design: Before and 1, 4, 7, 24, 48 and 72 hours after single i.v. bolus injection of APOSEC™ 50, 250 or 500 U/kg body weight into the tail vein of 6 CD® rats per sex and group, a neuropharmacological screening according to IRWIN was performed. Additionally, a placebo control group and positive control group (8 mg Diazepam/kg body weight given orally) were included.

Results: 17 neuropharmacological parameters were influenced in a dose-related way when assessed 1 hr after administration of 250 and 500 U/kg body weight, including a decrease in alertness, visual placing, grooming, reactivity, spontaneous activity, touch response, pain response, startle response, body posture, limb position, body tone, abdominal tone, pinna reflex and palpebral opening, and an increase in passivity, righting reflex and staggering gait. All parameters fully recovered by the 4 hr assessment time point. No effects were observed in animals treated with the low dose of 50 U/kg body weight. In comparison to that, the positive control Diazepam impacted on 19 of 40 parameters. The temporary impairments in the above-mentioned parameters observed at 1 hr after administration were considered to be an immediate consequence of the high i.v. doses, which may have particular impact on parameters of vitality. In all other animal studies performed in mice, rats, dogs and minipigs, these effects were not observed at that intensity. For clinical signs observed in cynomolgous monkeys, please refer in detail to [Section 3.1.1](#).

Conclusion: APOSEC™ in male and female rats at doses of 250 or 500 U/kg body weight i.v. influenced 17 of the 40 neuropharmacological parameters (incl. awareness, mood, motor activity, autonomic function and some reflexes) in the screening test according to IRWIN in a dose-related but transient manner.

3.2 Single Dose Toxicity

3.2.1 Acute Toxicity Study of APOSEC™ by Single Intravenous Administration to CD® Rats (Study No. 33201/1)

Objective: The aim of this study was to evaluate the toxicity of APOSEC™ following single i.v. administration to Sprague Dawley (CD®) rats.

Study Design: 5 CD® rats per group and sex were treated once with 50, 250 and 500 U/kg body weight or 0.9% NaCl as placebo via the i.v. route. Behaviour, clinical signs, body weight were investigated throughout the study. After a 2 weeks observation period, necropsy and macroscopic examinations were performed.

Results: Under the test conditions, single i.v. administration of 50, 250 or 500 U/kg body weight, respectively, did not reveal any signs of toxicity in 5 male and 5 female animals per group. No animal died prematurely. All animals gained the expected body weight throughout the whole study period. There were no macroscopic findings during necropsy and therefore, no microscopic examination was conducted.

Conclusion: No signs of toxicity were observed in this study. Therefore, the NOEL after single i.v. treatment was at or above the dose of 500 U/kg body weight, the highest tested dose.

3.2.2 Single Dose Toxicity Study with Allogenic APOSEC™ after Intravenous Bolus Injection to Beagle Dogs (Study No. 33749)

Objective: The aim of this study was to obtain initial toxicity and toxicokinetic data following single i.v. bolus injection to beagle dogs.

Study Design: 1 male and 1 female beagle dog were treated once with 250 U/kg body weight via the i.v. route. Behaviour, clinical signs, body weight, haematology, coagulation and clinical biochemistry parameters (incl. urinalysis), and cytokine concentration were investigated in this study.

Results: Under the test conditions, single i.v. administration of 250 U/kg body weight to beagle dogs did not reveal any signs of toxicity in the male and female animal. No animal died prematurely. No necropsy and macroscopic examination were conducted since no clinical findings were observed. No test-item related influence was noted on body weight as well as on haematology, coagulation, and clinical biochemistry or urinalysis parameters.

Conclusion: No signs of toxicity and no signs of local intolerance were observed in this study.

3.3 Repeat-Dose Toxicity

3.3.1 2-Week Dose-Range-Finding Study of Allogenic APOSEC™ by Intravenous Slow Bolus Administration Three Times Weekly to CD® Rats (Study No. 33647)

Objective: The aim of this dose-range-finding study was to select dose levels for a planned 4-week repeat dose toxicity study with i.v. administration of allogenic APOSEC™ three times a week in rats. The planned 4-week repeat dose toxicity study in rats was however not performed but replaced by a 4-week repeat dose toxicity study in mice ([Section 2.3.3](#)).

Study Design: 3 CD® rats per sex and group were assigned to the main study, and 6 males and 6 females for the satellite study for toxicokinetic evaluation. In the main study, 50, 250 or 500 U/per kg body weight were applied i.v. via slow bolus injection into the tail vein three times weekly for two weeks; in the satellite study, 500 U/kg body weight were applied three times weekly for one week. In this study, the following parameters were assessed: mortality, clinical signs, body weight, food and water consumption, haematology, coagulation, clinical biochemistry parameters, macroscopic post mortem findings, and assessment of selected lead cytokines by ELISA (IL-8, MMP-9, MIF and EGF) for the purpose of pharmacokinetic assessment, i.e. to investigate the kinetic profile of selected parameters (components) of APOSEC (results not discussed in this toxicology summary)

Results: None of the animals died during the course of the study. No test item-related findings in clinical signs, body weight, food and water consumption, coagulation, clinical biochemistry and macroscopic post mortem examinations were noted. Only in the hematologic parameters, the number of eosinophilic granulocytes was increased to approx. +113.6% in the high dose group (500 U/kg body weight) on test day 14 for the males ($p < 0.05$), and a slight increase of approx. + 17.3% was also noted for the female animals which was statistically not significant. Statistically significant decreases ($p \leq 0.05$) of calcium on test day 14 in male animals treated with 50 or 250 U/kg body weight, respectively, and a statistically significant increase ($p \leq 0.05$) of potassium on test day 14 in female animals treated with 50 U/kg body weight were regarded as spontaneous.

Conclusion: No adverse findings were noted in this study. Changes were limited to an increase in eosinophilic granulocytes in all 3 male animals (mean approx. +113.6%) and a slight increase in females (+17.3%) on test day 14 in the high dose group.

3.3.2 Dose-Range-Finding Study with Allogenic APOSEC™ by Subcutaneous Bolus Injection to Beagle Dogs (Study No. 33649)

Objective: This non-GLP dose-range-finding study aimed at selecting the dose levels for a planned 4-week toxicity study of allogenic APOSEC™ applied three times a week by s.c. bolus injection to beagle dogs. The planned 4-week repeat dose toxicity study in dogs was however not performed but replaced by a 4-week repeat dose toxicity study in minipigs ([Section 2.3.4](#)).

Study Design: After 4 weeks of acclimatization, 1 male and 1 female beagle dog received an s.c. bolus injection into the dorsal region on test days 1, 3 and 6. APOSEC™ was diluted to a final dose of 33 U/kg body weight in 0.9% NaCl solution. The dose level was selected considering the intended human dose (200 U for a 60 kg person = 3.3 U per kg). In this study, the following parameters were assessed: clinical signs, mortality and morbidity, body weight, food and water consumption, haematology, clinical chemistry, coagulation, urinalysis, macroscopic inspection.

Results: None of the animals died prematurely. No test item-related influence on local tolerance, clinical signs, body weight, water consumption, haematology and coagulation, clinical biochemistry, urinalysis and macroscopic post mortem findings were observed. No histopathological examination was carried out. The food consumption of both dogs was reduced by 51% from test day 1 to test day 2 and from test day 3 to test day 5 compared to the total amount offered to the animals. On test day 6, the food consumption was only slightly reduced by 24%.

Conclusion: No toxicities were observed after 3 s.c. bolus injections of APOSEC™ at 33 U/kg body weight.

3.3.3 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus Administration Three Times Weekly to Mice (GLP, Study no. 34946)

Objective: The aim of the study was to obtain information about the toxicity and local tolerance of APOSEC™ after repeated i.v. slow bolus administration (three times weekly) to C57BL/6N mice for 4 weeks and to assess the reversibility of any effect at the end of a 2-week recovery period.

Study Design: 10 C57BL/6N mice per sex and group were assigned to treatment groups of 50, 250 or 500 U/kg body weight, respectively, or to a control group of 0.9% NaCl solution. Recovery animals (5 males and 5 females per group) were additionally assigned to the control group and to the high-dose group, respectively. Animals were administered with test item (or control item) three times weekly for 4 weeks (in total 13 administrations) by i.v. slow bolus administration into the tail vein. The following parameters were assessed in this study: local tolerance, clinical signs, mortality and morbidity, body weight, food and water consumption, haematology, clinical chemistry, coagulation, urinalysis, ophthalmological and auditory examinations, macroscopic inspection, and histopathology including evaluation of the myeloid:erythroid ratio of 5 main study animals per sex and group and of all recovery animals.

Results: No signs of local intolerance reactions were observed in any dose group during the study. Neither the macroscopic inspection at necropsy nor the histopathological examination (restricted to the control and high-dose groups) revealed any test item related changes at the injection sites of the animals. None of the animals died or had to be sacrificed prematurely. No signs of systemic toxicity or behavioural effects were noted during the study. No test item related influence on body weight was noted. Neither haematological, coagulation, nor clinical chemistry or urinalysis parameters showed test item related alterations compared to the control group. Histopathological examinations of the main study animals, previously high-dose recovery animals, and control animals revealed no local intolerance or systemic morphological lesions that were considered to be test item related, nor changes in the myeloid:erythroid ratio.

Conclusion: No toxicities were observed in this study in which APOSEC™ was applied to mice three times weekly for 4 weeks (13 applications) by i.v. slow bolus injection. Under the test conditions of the study, the NOEL was therefore at or above the dose of 500 U/kg body weight, the highest tested dose.

3.3.4 4-Week Toxicity Study of Allogenic APOSEC™ in Aachener Minipigs with Subcutaneous Administration Three Times Weekly (GLP, Study no. 34873)

Objective: The aim of this study was to obtain information on the toxicity of APOSEC™ in Aachener minipigs administered with the product by s.c. bolus injection three times weekly for 4 weeks and to assess the reversibility of any effect after a 2-week recovery period. The minipig was selected as a suitable animal species because of the similarities of its skin to that of humans.

Study Design: 3 naïve Aachener minipigs per sex and group were assigned to treatment groups of APOSEC™ at

3.3, 10.5 or 33.3 U/kg body weight, respectively, or to a control group of 0.9% NaCl solution. Recovery animals (2 males and 2 females per group) were additionally assigned to the control group and to the high-dose group, respectively. APOSEC™ was administered by s.c. bolus injection under the skin in the inguinal region of the left and right sides (alternating) three times weekly for 4 weeks (a total of 13 administrations). The following parameters were assessed in this study: local tolerance, clinical signs, non-invasive telemetry for recording of ECG and blood pressure parameters, as well as skin temperature and respiratory and physical activity, mortality and morbidity, body weight, food and water consumption, haematology, clinical chemistry, coagulation, urinalysis, ophthalmological and auditory examinations, macroscopic inspection, and histopathology including Ki67 immunostaining of the injection sites.

Results: None of the animals treated with 3.3, 10.5 or 33.3 U/kg body weight revealed test item-related signs of local intolerance, neither during the 4-week treatment period nor during the 2-week treatment-free recovery period. However, slight signs of local intolerance in form of reddenings, swellings and/or thickenings of the s.c. injection sites were observed for a few male and female animals across all three dose groups. The changes were noted for 1 of 3 females of the low dose group, 1 of 3 males and 2 of 3 females of the intermediate dose group, and for 1 of 5 females of the high dose group on very few test days during the treatment period. These findings are regarded to be rather due to the s.c. administration procedure than to any irritating properties of the test item.

The assessment of local intolerance reactions according to DRAIZE (i.e. special emphasis on oedema, erythema or eschar formation) revealed the following changes in few animals during the treatment period: 1 of 3 males treated at low dose revealed slight to well-defined erythema on test days 29 and 30, and severe oedema on test day 30, and 1 of 5 females treated at high dose revealed well-defined erythema and moderate oedema on test day 30. The changes were likewise considered to be due to the s.c. administration procedure. The remaining male and female animals included in this study did not reveal any signs of local intolerance during the 4-week treatment period. No local intolerance reactions were noted for any of the recovery animals during the 2-week recovery period.

The macroscopic inspection at necropsy of the main study animals at the end of the treatment period on test day 30 (one day after the last administration on test day 29) revealed s.c. haemorrhagic and/or thickened injection sites for a few animals of all three dose groups. None of the recovery animals revealed any macroscopic changes at the injection sites at the end of the 2-week recovery period.

The histopathological examination of the tissue slides of the injection sites did not reveal microscopic changes related to treatment with the test item.

Ki67 staining of injection sites did not reveal test item related influence on cell proliferation in the epidermis, corium and in the granulation tissue in the subcutis. Positive reaction of some nuclei in the epidermis of the skin was considered to reflect normal cell proliferation. In summary, the skin in the area of the injection sites did not reveal any proliferative processes which were considered to be test item related. Both, the H&E stained sections and the Ki67 staining showed no morphological differences between the male and female animals of the control group and the animals of the high dose group. Low inflammatory reactions in the subcutis were considered to be due to the mechanical treatment procedure and were no longer detectable at the end of the recovery period.

Hence, all changes noted at the injection sites of male and female animals, either during the in-life phase of the study or at necropsy, were regarded to be rather due to the s.c. administration procedure than to any irritating properties of the test item.

None of the animals died prematurely or revealed any test item related signs of systemic intolerance. No test item related changes were observed in the external appearance of the animals or for behaviour, especially none related to the CNS. No test item related influence was noted on telemetry parameters, body weight, body weight gain, food and water consumption, haematological and biochemical parameters, urinary status, ophthalmologic and auditory functions, or relative and absolute organ weight.

The macroscopic inspection at necropsy and the histopathological examination revealed no morphological changes in male and female animals that were considered to be related to the administration of APOSEC™. All organ weights

recorded for the male and female animals were considered to be within the normal biological range of variation for minipigs. No test item related histopathological changes or morphological lesions or differences were noted for any of the organs examined.

Conclusion: No toxicities were observed in this study in which APOSEC™ was applied to Aachener minipigs three times weekly for 4 weeks (13 applications) by s.c. injection. Under the test conditions of the study, the NOEL was therefore defined at or above the dose of 33.3 U/kg body weight, the highest tested dose.

3.4 Local Tolerance

3.4.1 Skin Sensitization: Local Lymph Node Assay: BrdU-ELISA of APOSECTM in CBA/JN Mice - According to OECD Guideline 442B (GLP; Study No. 33203/1)

Objective: The aim of this study was to determine the skin sensitizing properties of APOSEC™ in the local lymph node assay in CBA/JN mice.

Study Design: Female CGA/JN mice (5 animals per group) were treated with APOSEC™ at 25, 125, or 250 U/mL (drug substance formulated in 0.9% NaCl, 25 µl per ear, corresponding to 0.625, 3.125 or 6.25 U per mouse) or negative control (0.9% NaCl solution), positive control (25% alpha-hexyl cinnamic aldehyde in acetone/olive oil 4:1 v/v) or placebo of positive control (acetone/olive oil 4:1 v/v) via open application to the dorsum of both ears. Application was performed on day 1, 2, and 3. On day 4, no treatment took place. On day 5, 5 mg/mouse of 5-bromo-2-deoxyuridine (BrdU) solution (10 mg/mL) was injected i.p. 24 h after injection of BrdU, necropsy was conducted, and draining auricular lymph nodes from each mouse ear were excised. Scoring of ear erythema and ear thickness as well as determination of cellular proliferation (= measurement of BrdU content in DNA of lymphocytes by ELISA) in single-cell suspension of lymph node cells (LNC) were performed afterwards.

In addition, clinical signs and body weight were assessed during the course of the study.

Results: The stimulation indices of the test item treated groups calculated for the BrdU labelling index did not exceed the threshold value of 1.6. Hence, APOSEC™ was classified as not skin sensitizing. The ear weight (punch biopsies) and the difference of ear thickness on test day 3 and test day 6 compared to the placebo control were not or only slightly increased, i.e. no skin irritating properties were noted. Treatment with the positive control item caused the expected increases in the BrdU labelling index. Therefore, the study was regarded as valid.

There were no deaths, and no signs of systemic intolerance were recorded. The animal body weight was not affected by the treatment.

Conclusion: APOSEC™ up to a concentration level of 250 U/mL (corresponding to 6.25 U per mouse) did not reveal any skin sensitizing properties in the LLNA in CBA/JN mice.

4 New Studies

4.1.1 2-Week Toxicity Study of Allogenic APOSEC™ by Repeated Twice Weekly Intravenous Infusion to Cynomolgous Monkeys Followed by a 2-Week Treatment-Free Period (GLP, Study no. 35015)

Objective: The aim of the study was to obtain information on the potential toxicity, including the local tolerance of allogenic APOSEC™ given twice weekly by i.v. infusion to cynomolgus monkeys for 2 weeks and to assess the reversibility of any effect after a 2-week recovery period.

Study Design: Per the original study design, 3 male and 3 female cynomolgous monkeys per group were assigned to treatment groups of APOSEC™ at 35, 110 or 350 U/kg body weight, respectively, or to a control group of 0.9% NaCl solution. Recovery animals (2 males and 2 females per group) were additionally assigned to the control group and to the high-dose group, respectively. APOSEC™ was administered by i.v. infusion two times weekly for 2 weeks on days 1, 4, 8 and 11. However, upon the need for preterm termination of two males after the first dose of 350 U/kg (high dose; discussed in the [results](#) section below) and guided by further considerations on potential exaggerated pharmacodynamic effects (see [results](#) below), the dosing conditions (dose level, infusion volume, infusion speed) were modified throughout the study as detailed in [Table 2](#). Moreover, two replacement animals were added to the study for replacing the two prematurely terminated males.

Table 2 Dosing Conditions in 2-Week Toxicity Study in Cynomolgous Monkey

Dose level	Sex	# of animals	Dosing condition	Dose 1 (Day 1)	Dose 2 (Day 4)	Dose 3 (Day 8)	Dose 4 (Day 11)
Control	male	3 + 2 recovery	Dose given	--			
			Infusion volume	5 mL/kg	15 mL/kg		
			Infusion time	30 min			40 min
	female	3 + 2 recovery	Dose given	--			
			Infusion volume	15 mL/kg			
			Infusion time	30 min	40 min		
Low dose (35 U/kg)	male	3	Dose given	35 U/kg			
			Infusion volume	5 mL/kg	15 mL/kg		
			Infusion time	30 min			40 min
	female	3	Dose given	35 U/kg			
			Infusion volume	15 mL/kg			
			Infusion time	30 min	40 min		
Mid dose (110 U/kg)	male	3	Dose given	110 U/kg			
			Infusion volume	5 mL/kg	15 mL/kg		
			Infusion time	30 min			40 min
	female	3	Dose given	110 U/kg			
			Infusion volume	15 mL/kg			
			Infusion time	30 min			40 min
High dose (350/225/ 200 U/kg)	male	3 *	Dose given	350 U/kg		225 U/kg	200 U/kg
			Infusion volume	5 mL/kg	15 mL/kg		
			Infusion time	30 min			40 min
	male replacements	2 (continuing to recovery)	Dose given	225 U/kg	200 U/kg		
			Infusion volume	15 mL/kg			
			Infusion time	30 min	40 min		
	female	3 + 2 recovery	Dose given	225 U/kg	200 U/kg		
			Infusion volume	15 mL/kg			
			Infusion time	30 min	40 min		

* 2 additional males in this group, originally assigned to continue to recovery, had to be terminated after the first

dose of 350 U/kg (see discussion in [results](#))

The following parameters were assessed in this study: local tolerance, clinical signs, mortality, body weight, food and drinking water consumption, ECG and blood pressure parameters, haematology, clinical chemistry, coagulation, urinalysis, ophthalmological and auditory examinations, macroscopic inspection, and histopathology and bone marrow examination (myeloid:erythroid ratio).

Results: Two of 5 male animals treated with 350 U/kg (two of them assigned for recovery period at start of the study) had to be sacrificed prematurely after the first administration on test day 1. For both animals, changes in form of increased body temperature (within 20 minutes post administration (p.a.)), reduced motility (within 60 minutes p.a.), lateral position (within 2 hours p.a.), reduced reflexes (within 2 hours p.a.), convulsions (within 2 hours p.a.) and reduced body temperature (within 1 to 2 hours p.a.) were noted before sacrifice. Enlarged axillary lymph nodes were observed for both males for which no microscopic correlate was noted. Emphysematous lungs were observed for one male that could not be associated with microscopy. This was also the case for enlarged cervical lymph node and adrenal glands in the other male. However, haemorrhagic and oedematous subcutaneous tissue in the thighs and lower legs of this animal were associated with slight diffuse phlegmonous inflammation, consisting of acute inflammation with interstitial oedema and minimal haemorrhage as observed at microscopy. These macroscopic changes were related to the administration of the test item. It was assumed that the death of these animals was caused by an exaggerated vasodilation, which is a pharmacodynamic effect of the test item.

As a result of premature termination of the two males at high dose and of further clinical signs discussed below, the dosing conditions were modified according to the scheme presented in [Table 2](#). In particular, the initial high dose of 350 U/kg to males was reduced to 225 U/kg and further to 200 U/kg in the course of the study. Females entered into the study with a time lag of one week and received an initial high dose of 225 U/kg only, which was further reduced in the course of the study to 200 U/kg according to [Table 2](#). Two males added as replacement animals to the study were treated according to the same dosing conditions as females, i.e. received in initial high dose of 225 U/kg only, further reduced in the course of the study to 200 U/kg. The two replacement animals in the high dose group continued to the end of the recovery period.

None of the animals treated i.v. with 35 or 110 U/kg (low and mid dose, respectively) twice weekly for 2 weeks (males and females) and no females treated at high dose died or had to be sacrificed prematurely. Low and mid dose levels were not changed during the course of the study; however, further dosing conditions (infusion volume, infusion time) were modified according to [Table 2](#).

Reduced motility was noted for 2 of 3 males treated intravenously with 110 U/kg twice weekly for 2 weeks after the 3rd administration. In addition, 1 of 3 male animals revealed asthenia, mydriasis, a lateral position and clonic convulsions on after the 3rd administration (according to dosing conditions in [Table 2](#)). At the high dose level (350/225/200 U/kg, see [Table 2](#)), changes in form of asthenia, somnolence, mydriasis, a lateral position, an increased respiratory rate, laboured breathing, a reduced motility, reduced reflexes, (clonic) convulsions, salivation and/or emesis on the administration days and up to 1 day thereafter.

No test item-related signs of local intolerance reactions were noted during clinical observations and at macroscopic inspection at necropsy. The histopathological examination of the infusion sites did not reveal any test item-related findings.

No test item-related influence was further noted on: body weight and body weight gain, food and drinking water consumption, electrocardiography, blood pressure, haematology and coagulation, clinical chemistry, urinalysis, and ophthalmological and auditory examinations.

Upon macroscopic inspection, in the males treated intravenously with 350/225/200 U/kg (high dose) for 2 weeks, spleens were enlarged in two males at scheduled sacrifice, for which a microscopic correlate (follicular hyperplasia) was made for one animal only. Enlarged axillary lymph nodes were observed for one male treated with 35 U/kg and for one male of the high dose at scheduled sacrifice, for which microscopic correlates were seen in both animals (medullary hyperplasia).

No test item-related influence was noted on organ weights and bone marrow examination at any dose level.

Microscopic findings correlated to macroscopic results were already discussed in the paragraph above. No further test item-related changes were noted at histopathological examination.

Throughout the recovery period, none of the animals revealed any late test item-related local intolerance reactions. No premature deaths occurred, and no clinical signs of systemic toxicity were noted. No test item-related changes were noted for body weight and body weight gain, food and drinking water consumption, electrocardiography, blood pressure, hematological, clinical chemistry and urinary parameters, at ophthalmological and auditory examinations, at necropsy, and for organ weights and bone marrow evaluation during or at the end of the 2-week treatment-free recovery period.

Conclusion: Effects observed in this study were considered to be related to the vasodilating effects of APOSEC™. Intravenous treatment with APOSEC™ twice weekly for 2 weeks was determined to result in an experimental NOAEL of 200 U/kg under the experimental conditions of the study.

5 Further Aspects of Toxicology

Genotoxicity studies for APOSEC™ were not performed. According to the ICH S6 (R1) guideline, the range and type of genotoxicity studies routinely conducted for pharmaceuticals is not applicable to biotechnology-derived pharmaceuticals and therefore not needed. Moreover, ICH S6 also states that the administration of large quantities of peptides/proteins may yield uninterpretable results.

Carcinogenicity studies were not performed so far. According to the ICH S6 (R1) guideline, standard carcinogenicity bioassays are generally inappropriate for products falling under the scope of this guidance. However, the effect of APOSEC™ on human cancer cell lines was investigated (Section 4.1.1), showing that APOSEC™ had no significant impact on *in vitro* tumour cell growth. Moreover, Ki67 staining of injection sites in the 4-week toxicity study of APOSEC™ in minipigs (Section 2.3.4) did not reveal test item related influence on cell proliferation in the epidermis, corium and in the granulation tissue in the subcutis.

No developmental and reproductive toxicity studies were performed so far. It is noted that there were no signs of toxicity on male or female reproductive organs in repeated dose toxicology studies in mice, rats, dogs, minipigs and cynomolgous monkey.

With regard to assessment of immunogenicity, the administration of the human clinical product to an immune competent animal represents a xenogeneic setting, and any generated immunogenic response would not reflect the clinical situation. Specific assessment of immunogenicity was therefore not done.

The potential for immunotoxicity was assessed as part of the pivotal GLP repeat dose toxicity studies, in which potential changes in haematology and clinical chemistry parameters, as well as potential alterations in gross pathology, immune system organ weights and histopathology, and potential increased incidence of infections were investigated (with no findings).

5.1.1 Investigation of the Effect of APOSECTM on Human Cancer Cell Lines

Objective: The aim of the study is to evaluate the effect of APOSEC™ on the *in vitro* growth of human lung cancer, melanoma, breast cancer and sarcoma cells.

Study Design: The impact of APOSEC™ on the growth of human non-small cell lung cancer (A549, H358, H1650, and HCC15), small cell lung cancer (Crl2066), melanoma (A375), breast cancer (MDA-MB-231) and sarcoma (HTB-92, HT-1080) cell lines was investigated. For the short-term viability assay, 2.5×10^3 cells were seeded in 96 well plates and incubated overnight. On the next day, cells were treated with APOSEC™ and solvent control (0.9% saline) in medium containing 2% fetal bovine serum (FBS). After 72 hours, the medium was removed and the cells were fixed, stained with sulforhodamine B (SRB) and air dried. SRB was dissolved in Tris buffer, and the absorbance was measured at 570 nm. Viability (compared to solvent control) was calculated.

The effect of APOSEC™ on the clone forming capacity of tumour cells was evaluated by a clonogenicity assay. Depending on the cell type, 1 or 2×10^3 /well cells were seeded in 6 well plates and incubated overnight, followed by treatment with APOSEC™ or control medium for 2 weeks. Colonies were then stained with crystal violet, destained with 2% sodium dodecyl sulphate, and the absorbance was measured at 562 nm by a plate reader.

Results: APOSEC™ had no significant effect on the growth of human tumour cell lines in short-term viability assays (Figure 1). When the tumour cells were exposed to APOSEC™ for two weeks, there was a tendency to reduced clonogenicity in three lung cancer cell lines (H358, H1650, Crl2066), one breast cancer cell line (MDA-MB-231) and one sarcoma cell line (HTB-92). However, this effect did not reach statistical significance (Figure 2).

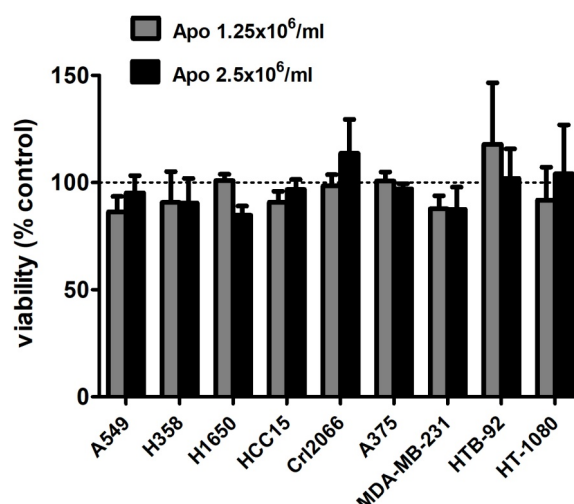


Figure 1 Short-Term Effect of APOSEC™ on the Growth of Human Tumour Cell Lines

Tumour cells were incubated with different concentrations of APOSEC™ or solvent control for three days. SRB assay was performed and viabilities were calculated as percent of the respective solvent control. Data (mean ± SD) from three independent experiments are shown.

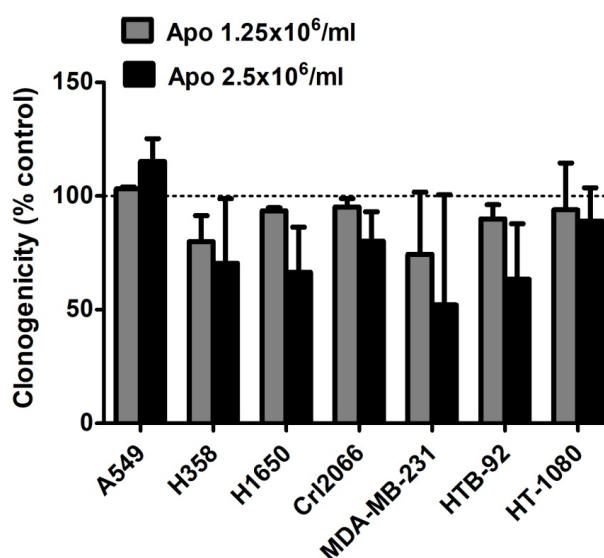


Figure 2 Effect of APOSEC on Clonogenic Growth

Tumour cells were seeded at low densities and exposed to APOSEC™ or solvent control for two weeks. Tumour clones were quantified using crystal violet staining and clonogenicity was calculated as percent of the respective control. Mean ± SD are shown.

Conclusion: APOSEC™ had no significant impact on *in vitro* tumour cell growth.

6 Summary and Conclusion

No signs of toxicity were observed when APOSEC™ was applied:

- as a single i.v. administration at dose levels of 50, 250 or 500 U/kg to CD® rats (NOEL defined as ≥ 500 U/kg under the experimental conditions of the study)
- as a single i.v. administration at a dose of 250 U/kg to beagle dogs
- three times weekly by s.c. administration for 2 weeks at dose levels 50, 250, or 500 U/kg to CD® rats
- three times weekly by s.c. administration for 2 weeks at a dose level of 33 U/kg to beagle dogs
- three times weekly by i.v. administration for 4 weeks at dose levels 50, 250 or 500 U/kg to mice (NOEL defined as ≥ 500 U/kg under the experimental conditions of the study)
- three times weekly by s.c. administration for 4 weeks at dose levels 3.3, 10.5 or 33.3 U/kg to Aachener minipigs (NOEL defined as ≥ 33.3 U/kg under the experimental conditions of the study)

However, application of APOSEC™ to cynomolgous monkey at the high dose level in this study (350 U/kg) resulted in preterm sacrifice of two males upon the first dose. A number of clinical signs were noted at high dose, even when the dose was reduced to 225 and 200 U/kg during the course of the study. Clinical signs were also noted in males at the mid dose level of 110 U/kg. Signs at mid and high dose included: reduced motility, asthenia, mydriasis, a lateral position and clonic convulsions, somnolence, increased respiratory rate, laboured breathing, reduced reflexes, salivation and/or emesis on the administration days and up to 1 day thereafter. Macroscopic inspection at scheduled termination revealed enlargement of spleen in two males at high dose; in one animal, there was a microscopic correlate (follicular hyperplasia). Enlarged axillary lymph nodes were observed for one male treated at low dose (35 U/kg) and for one male of the high dose at scheduled sacrifice, for which microscopic correlates were seen in both animals (medullary hyperplasia). All effects observed in this study were considered to be related to the vasodilating effects of APOSEC™.

In the local lymph node assay in CBA/JN mice, APOSEC™ up to a concentration level of 250 U/mL (corresponding to 6.25 U per animal) did not reveal any skin sensitizing properties.

To conclude on safety and toxicology studies for APOSEC™, Table 3 summarizes the NOEL / NOAEL derived from single dose and repeat dose toxicology studies from all routes of administration in all species. Regardless of applicability of the concept of HED to this product (see discussion in Section 1 – Executive Summary), the HED corresponding to the respective NOEL / NOAEL is also shown in Table 3.

Table 3 Summary of NOEL and NOAEL From Single Does and Repeat Dose Toxicology Studies with APOSEC™

Study	Study No.	Route of Administration	NOEL / NOAEL / Animal dose level (U/kg)	HED corresponding to NOEL / NOAEL (U/kg) *
Single dose toxicity				
Acute Toxicity Study of APOSEC™ by single i.v. administration to CD® rats	33201/1	i.v. bolus	NOEL: ≥ 500 U/kg	≥ 80 U/kg
Single Dose Toxicity Study with allogenic APOSEC™ after i.v. bolus injection to beagle dogs	33749	i.v. bolus	Not defined in this non-GLP study; highest tested dose: 250 U/kg	--
Repeat dose toxicity				
2-week dose range finding study of allogenic APOSEC™ by i.v. slow	33647	i.v. bolus	Not defined in this non-GLP study;	--

Study	Study No.	Route of Administration	NOEL / NOAEL / Animal dose level (U/kg)	HED corresponding to NOEL / NOAEL (U/kg) *
bolus administration 3 times weekly to CD® rats			highest tested dose: 500 U/kg	
Dose range-finding study with allogenic APOSEC™ by s.c. bolus injection to beagle dogs	33649	s.c. bolus	Not defined in this non-GLP study; highest tested dose: 33 U/kg	--
4-week toxicity study of allogenic APOSEC™ by i.v. slow bolus administration 3 times weekly to mice	34946	i.v. bolus	NOEL: ≥ 500 U/kg	≥ 40 U/kg
4-week toxicity study of allogenic APOSEC™ in Aachener minipigs with s.c. administration 3 times weekly	34873	s.c.	NOEL: ≥ 33.3 U/kg	≥ 31 U/kg
2-week toxicity study of allogenic APOSEC™ by repeated twice weekly i.v. Infusion to cynomolgous monkeys followed by a 2-week treatment-free period	35015	i.v. infusion	NOAEL: 200 U/kg Low dose tested in study: 35 U/kg **	65 U/kg 11 U/kg **

* HED conversion factors: 0.08 for mice, 0.16 for rats, 0.95 for minipig, 0.32 for cynomolgus monkey (FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers; FDA/CDER, July 2005)

** The low dose level (35 U/kg) was the only dose at which no clinical signs attributed to exaggerated pharmacodynamic effect, i.e. vasodilation, were reported. A finding of enlarged axillary lymph nodes in one male treated with at this dose level was still reported, though, with the microscopic correlate of medullary hyperplasia.

Concluding from the 2-week toxicity study of allogenic APOSEC™ by repeated twice weekly i.v. Infusion to cynomolgus monkeys followed by a 2-week treatment-free period:

The test item was applied 2 times a week for 2 weeks (4 dosing occasions). There is currently no study testing daily applications.

The study director defined the NOAEL upon repeated (4 times) i.v. administration to cynomolgus monkey at 200 U/kg (HED = 65 U/kg). This dose induced vasodilation, which is an expected effect of the test item and thus, these effects were not defined as adverse by the study director.

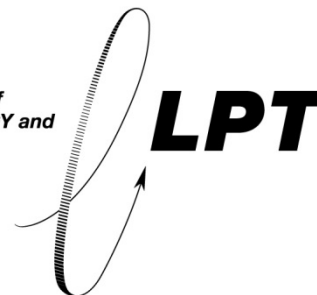
The mid dose of 110 U/kg (35,5 U/kg) also induced vasodilatory effects.

Only the low dose tested in the same study, 35 U/kg, induced no effect (except for the enlarged axillary lymph nodes in one male). The HED corresponding to this dose is calculated at 11 U/kg (770 U per patient assuming a body weight of 70 kg). There is no tested dose between 35 and 110 U/kg.

Finally, it is mentioned, that there is no clear regulatory guidance on the need to apply the HED (conversion of animal dose to human dose based on body surface scaling) for Aposec™ containing the lyophilized secretome supernatant obtained from apoptotic peripheral blood mononuclear cells (PBMCs). The HED is usually calculated for small molecules and some biologics, but for Aposec scaling based on body weight might be more appropriate.

APOSCIENCE AG
Mariannengasse 14/9
1090 Wien
Österreich

LABORATORY of
PHARMACOLOGY and
TOXICOLOGY



Contact Person: [REDACTED]

January 28, 2016 / Ba

LPT COST PROPOSAL No. 32937 - Version 2

All studies are carried out according to EC/ICH GLP

Study	Costs [EUR]	Reporting time ¹
Acute Toxicity		
1. Acute toxicity in rats, i.v. bolus injection LPT Study No. 33201	4,400.00	6 weeks
1.1. optional dose group (for 1 group)	1,100.00	
Safety Pharmacology		
2. Irwin test in rats, i.v. bolus injection LPT Study No. 33202		8 weeks
Sensitising Properties		
3. Local Lymph Node Assay (LLNA): BrdU-ELISA LPT Study No. 33203		8 weeks

Payment schedule: 100% at draft report

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Signature

¹ Approx. time from start of study (first dosing) until draft report.

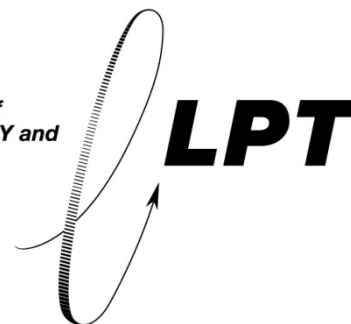
These prices are valid for a period of 6 months from the date of this offer.

The prices **do not** include the VAT.

APOSCIENCE AG
Mariannengasse 14/9
1090 Wien
Austria

Contact person: XXXXXXXXXX

LABORATORY of
PHARMACOLOGY and
TOXICOLOGY



May 9, 2017 / göt

COST PROPOSAL NO. 34946 - VERSION 1

All studies are carried out according to EC/ICH GLP.

Study	Costs [EUR]	Reporting time ¹
1. Subchronic Toxicity in Rodents		
1.1. 4-week repeated dose toxicity study in mice, with recovery period (2 weeks) i.v. slow bolus injection 3 times weekly 4 study groups incl. histopathology	115,000.00	10-12 weeks

Payment
schedule:

< EUR 10,000.00	EUR 10,000.00 to 100,000.00	> EUR 100,000.00
100% at draft report	50% upon start of study 50% at draft report	40% upon start of study 30% upon main dissection 30% at draft report

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Place, Date

Name, Position, Signature

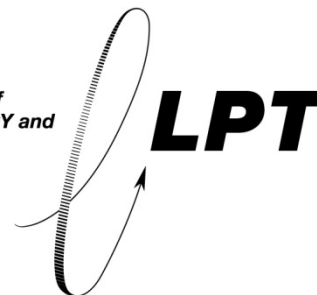
¹ Approx. time from start of study (first dosing) until draft report.

These prices are valid for a period of 6 months from the date of this offer.
The prices **do not** include the VAT, however, no VAT will be charged for NON-German clients.

The costs also include the archiving of one copy of the final report, all specimen and raw data for 15 years.

APOSCIENCE AG
Mariannengasse 14/9
1090 Wien
Austria

LABORATORY of
PHARMACOLOGY and
TOXICOLOGY



Contact Person: [REDACTED]

November 02, 2018 / BB

COST PROPOSAL NO. 35015 - VERSION 3

Study	Costs ¹ [EUR]	Reporting time ²
1. Subchronic Toxicity in Cynomolgus Monkeys by Intravenous 30-min Infusion		
1.1. 2-week repeated dose study in non-human primates (cynomolgus monkeys) <u>with</u> recovery period	299,500.00	12 weeks
1.2. ECG and blood pressure: <u>All study animals</u> Test days 1, 14 and end of recovery One time-point per day Riva Rocci procedure ("snap-shot" recording)	10,500.00	
TOTAL COSTS	310,000.00	

¹ The costs **do not** include analytical determination for stability, homogeneity and concentration of the test item-vehicle mixture.

² Approx. time from start of study (first dosing) until draft report.

Payment schedule:	< EUR 10,000.00	EUR 10,000.00 to 100,000.00	> EUR 100,000.00
	100% at draft report	50% upon start of study 50% at draft report	40% upon start of study 30% upon main dissection 30% at draft report

These prices are valid for a period of 6 months from the date of this offer.
The prices **do not** include the VAT, however, no VAT will be charged for NON-German clients.

The costs also include the archiving of one copy of the final report, all specimen and raw data for 15 years.

For order placement please sign below and return this page to us by telefax or e-mail.

Terms accepted by APOSCIENCE AG:

Place, Date

Name, Position, Signature

Place, Date

Name, Position, Signature



Aposcience AG

Dresdner Straße 87/A 21
A-1200 Wien

P: +43 / (0) 664 2120557

E: info(at)aposcience.com

Vienna, 23 July 2026

Cost of Aposec for Toxicology Studies

The following table resumes the costs for Aposec for 3 toxicology studies:

1. Acute Toxicity Study of Aposec by Single Intravenous Administration to CD Rats – LPT Report No. 33201-1;
2. 4-Week Toxicity Study of Allogeneic Aposec by Intravenous Slow Bolus Administration Three Times Weekly to Mice – LPT Report No. 34946
3. 2-Week Toxicity Study of Allogeneic Aposec by Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys Followed by a 2-Week Treatment-Free Period – LPT Report No. 35015

	EUR	Vials à 500 U	Units/MPS
Aposec for Toxicity Study in CD Rats	2.109,58	6	3.000
Aposec 4-Week Toxicity Study in Mice	14.185,08	39	19.500
Aposec for 2-Week Toxicity Study in Cynomolgus Monkeys	82.224,40	190	95.000
SUM	98.519,06	235	117.500



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Vienna, 21 July 2026

Costs of Aposcience Tox Studies:

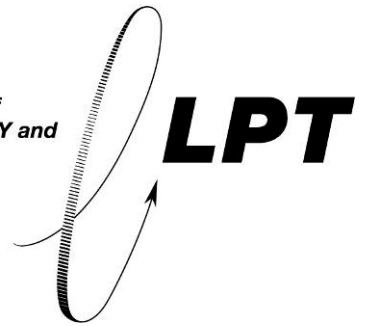
Acute Tox & Dose Escalation in Rats (iv) and Repeated Dose Toxicology Study in Cynomolgus monkeys (iv)

	EUR	Vials	Units/MPS
Acute tox + dose escalation in rats	4.400		
Repeated dose in cynomolgus monkeys	319.586,80		
Aposec for acute tox in rats	3.273,48	9	4.500
Aposec for tox in cynomolgus monkey	82.224,40	190	95.000
SUM	409.484,68	199	99.500

The studies were performed in 2016 (acute tox in rats) and in 2019 (repeated dose in cynomolgus monkeys).

Mit freundlichen Grüßen

Univ.-Prof. Dr. Hendrik Ankersmit (CEO)



**4-WEEK TOXICITY STUDY OF
ALLOGENIC APOSEC™
BY INTRAVENOUS SLOW BOLUS ADMINISTRATION
THREE TIMES WEEKLY
TO MICE
- Multi-Site Study -**

Sponsor:

APOSCIENCE AG
Mariannengasse 14/9
1090 Vienna
Austria

Study conducted by:

LPT Laboratory of Pharmacology
and Toxicology GmbH & Co. KG
Redderweg 8
21147 Hamburg
Germany

Contact person:

Dr. Silvio Wuschko

Contact person:

Dr. Jost Leuschner

December 01, 2017

This report consists of 541 pages.

- Page 1 -

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STATEMENT OF COMPLIANCE

**4-WEEK TOXICITY STUDY OF
ALLOGENIC APOSEC™
BY INTRAVENOUS SLOW BOLUS ADMINISTRATION
THREE TIMES WEEKLY
TO MICE
- Multi-Site Study -**

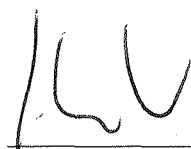
The study was performed in compliance with:

- 'Good Laboratory Practice' Regulations of the EC enacted in Germany in the 'Chemikaliengesetz' [Chemicals Act], current edition;
- 'OECD Principles of Good Laboratory Practice' Document Nos. 1, 8 and 13 ENV/MC/CHEM (98) 17, ENV/JM/MONO (99) 24, and ENV/JM/MONO (2002) 9, respectively.

These principles are compatible with 'Good Laboratory Practice' regulations specified by regulatory authorities throughout the European Community, the United States of America (EPA and FDA) and Japan (MHLW, MAFF and METI).

There were no deviations from the 'Good Laboratory Practice' regulations. Raw data obtained during the performance of the study are accurately reflected.

The Principal Investigator (PI) was responsible for compliance with his national GLP regulations for any work performed at his Test Site (TS) and for data provided to **LPT** for inclusion in the Study Report (**LPT**).



Dr. phil. J. Leuschner
Study Director

12.12.2017
Date

QUALITY ASSURANCE STATEMENT

Based on a quality assurance review, it was concluded that this report accurately reflects the data for the study. Methods, procedures and observations are correctly and completely described in the report.

**4-WEEK TOXICITY STUDY OF
ALLOGENIC APOSEC™
BY INTRAVENOUS SLOW BOLUS ADMINISTRATION
THREE TIMES WEEKLY
TO MICE
- Multi-Site Study -**

Study Plan dated June 23, 2017 and 1 Study Plan amendment.

Date of inspection	Criteria	Date of report to the Study Director and the Management
23 Jun 2017	Study Plan.	23 Jun 2017
26 Jun 2017	Identification of the test item, test item preparation, administration, animal behaviour, documentation.	26 Jun 2017
24 Jul 2017	Administration of water bolus, urine sampling, documentation.	24 Jul 2017
25 Jul 2017	Anaesthesia, blood withdrawals, sacrifice of animals, body weights, removal of organs, macroscopic inspection, organ weights, fixation of organs, withdrawal of bone marrow, preparation of bone marrow smears, documentation.	25 Jul 2017
28 Jul 2017	Body weights, administration, documentation.	28 Jul 2017
01 Dec 2017	Final Report.	01 Dec 2017

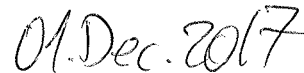
In addition to the detailed study-based inspections series of routine facility inspections were also conducted and reported to the Management.

For further QAU audits at the Principal Investigator's Test Site please refer to the respective appendix.

Approved and
submitted by:



Dr. med. vet. habil. K. R. Sultan
Director of Leading Quality
Assurance Unit (LQAU)



Date

EXPLANATIONS AND ABBREVIATIONS USED IN THIS REPORT**Symbols**

-	not examined / no data
0	no pathological findings / normal
1 - n	reference to footnotes in the text
#	reference to footnotes in the tables
**	statistically significant at $p \leq 0.01$
*	statistically significant at $p \leq 0.05$
()	animal number (in the tables)

Letters / Acronyms

%Diff	% difference compared to the control group
a.m.	ante meridiem
approx.	approximately
b.w.	body weight
EC	European Community
EDTA	ethylene diamino tetraacetic acid
EPA/USA	Environmental Protection Agency/United States of America
EU	European Union
f	female
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
GPS	Global Pathology Support
HTS	Head of Test Site
i.e.	it est
i.v.	intravenous administration
LPT	Laboratory of Pharmacology and Toxicology
LQAU	Leading Quality Assurance Unit (LPT)
LUFA-ITL	Landwirtschaftliche Untersuchungs- und Forschungsanstalt, Institut für Tiergesundheit und Lebensmittelqualität
m	male
MAFF	Ministry of Agriculture, Forestry and Fisheries
Mean	mean value
METI	Ministry of Economy, Trade and Industry
MHLW	Ministry of Health, Labour and Welfare
MS	main study
N/A	not applicable
no.	number
NOEL	no-observed-effect level
ns	not significant at $p \leq 0.01$
OECD	Organization for Economic Co-Operation and Development
p.a.	post application
p.m.	post meridiem
PBMC	peripheral blood mononuclear cell
PI	Principal Investigator
QAU	Quality Assurance Unit
RP	recovery period

Letters / Acronyms (continued)

RS	recovery sacrifice
SD	standard deviation
SOP	Standard Operating Procedure
TD	test day
TD -5	pre-drug examination
TS	terminal sacrifice (necropsy context)
TS	Test Site (multi-site context)
TSQAU	Test Site Quality Assurance Unit
TW	test week

Weights and Measures

%	percent
°C	degree Celsius
μL	microlitre
μmol	micromol
cm	centimetre
fL	femtolitre
fmol	femtomol
g	gram
h	hour
kg	kilogram
L	litre
mg	milligram
min	minute
mL	millilitre
mmol	millimol
sec	second
U	unit

Haematology

aPTT	activated partial thromboplastin time
Baso	basophilic granulocytes
Eos	eosinophilic granulocytes
HCT	haematocrit
HGB	haemoglobin
LUC	large unstained cells
Lym	lymphocytes
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
Mono	monocytes
Neut	neutrophilic granulocytes
PLT	platelets
RBC	erythrocytes (red blood cells)
Reti	reticulocytes

Haematology (continued)

TPT	thromboplastin time
TT	thrombin time
WBC	leucocytes (white blood cells)

Clinical chemistry

ALAT	alanine aminotransferase
Alb.	albumin
aP	alkaline phosphatase
ASAT	aspartate aminotransferase
BUN	blood urea
CK	creatine phosphokinase
Creat.	creatinine
Glob.	globulin
LDH	lactate dehydrogenase

Urinalysis

A	crystalluria
B	organisms (i.e. worm eggs, bacteria)
C	further constituents (i.e. sperm, casts)
E	epithelial cells
ery	erythrocytes count
L	leucocytes
LC	lemon-coloured
R	erythrocytes
SC	straw-coloured

neg.	negative/none found in any field examined
norm.	normal
pos.	positive

+	'small amount' of analyte/few in some fields examined
++	'moderate amount' of analyte/few in all fields examined
+++	'large amount' of analyte/many in all fields examined

Organ weights

Adren.	adrenal
--------	---------

Measuring units

body weight in g
food intake in g/kg b.w./day
absolute urine volume in mL/cage/6 h
relative urine volume in mL/kg b.w./24 h
absolute organ weights in g
relative organ weights in g/kg b.w.

Histopathology

for explanations see the '[Phase Report on Histopathology](#)'

1. SUMMARY

1.1 Conduct of study

Test item	Allogenic APOSEC™
Charge nos./ number of bottles/vials received	399049/ 9 vials 399050/ 7 vials 399051/ 8 vials 399053/ 7 vials (not used) 399057/ 8 vials (not used)
Test species / Strain / Nomenclature	Mouse / BL/6N / C57BL/6NCrL
Breeder	Charles River Laboratories Germany GmbH Sandhofer Weg 7 97633 Sulzfeld Germany
Number and sex of animals	100 animals (50 male and 50 female animals). <u>Main study animals</u> 80 animals (40 males and 40 females); 10 animals/sex/group. <u>Recovery animals</u> 20 animals (10 males and 10 females); 5 animals/sex/group for groups 1 and 4. For details see Section 3.7 .
Dose levels	Group 1 Control (vehicle) Group 2 50 Units APOSEC™/kg b.w. Group 3 250 Units APOSEC™/kg b.w. Group 4 500 Units APOSEC™/kg b.w.
Route of administration	Intravenous slow bolus administration into a tail vein.
Frequency of administration	Three times weekly for 4 weeks; in total 13 administrations.
Injection speed	Dose/approx. 15 sec
Vehicle	Sterile 0.9% NaCl solution
Administration volume	2 mL/kg b.w./administration

Duration of study

- 5 adaptation days
- 4 test weeks
- 14 additional test days for the animals
scheduled for the recovery period

1.2 Findings

Treatment period

Local tolerance

No signs of local intolerance reactions were observed in any of the male and female animals treated with **50, 250 or 500 Units allogenic APOSEC™/kg b.w.** three times weekly by intravenous slow bolus injection for 4 weeks during the course of the study.

Neither the macroscopic inspection at necropsy nor the histopathological examination (restricted to the control and high dose group) did reveal any test item-related changes at the injection sites of the animals.

Systemic tolerance

Mortality

None of the animals died or had to be sacrificed prematurely.

Clinical signs

No signs of systemic toxicity were noted for the animals treated with **50, 250 or 500 Units allogenic APOSEC™/kg b.w.** three times weekly by intravenous slow bolus injection during the course of the study.

Body weight and body weight gain

No test item-related influence was noted.

Food and drinking water consumption

No test item-related influence was noted.

The visual appraisal of the drinking water consumption revealed no differences between the control and the test item-treated animals.

Haematology and coagulation

No test item-related influence was noted.

Clinical chemistry

No test item-related influence was noted.

Urinalysis

No test item-related influence was noted.

Ophthalmological and auditory examination

No test item-related changes were noted.

Macroscopic post
mortem findings

No test item-related systemic changes were noted.

Organ weights

No test item-related changes were noted.

Bone marrow

No test item-related changes were noted.

Histopathology
(restricted to groups 1
(control) and 4 (high dose))

The histopathological examination did not reveal any systemic or local morphological lesions which are considered to be related to the administration of the test item.

Recovery period

No premature deaths occurred and no signs of local intolerance or systemic toxicity were noted. No test item-related changes were noted at the body weight, body weight gain and body weight at autopsy, food and drinking water consumption, the haematological, clinical chemistry and urinary parameters, at ophthalmological and auditory examinations, at necropsy as well as for organ weights and the myeloid:erythroid ratio at the end of the 14-day recovery period.

Histopathology of the previously high dosed recovery animals did not reveal any test item-related changes.

1.3 Conclusion

The aim of the study was to obtain information on the toxicity and local tolerance of **allogenic APOSEC™** after repeated intravenous slow bolus administration (three times weekly) to C57BL/6 mice for 4 weeks and to assess the reversibility of any effect at the end of a 2-week recovery period. The mice were treated with **50, 250 or 500 Units allogenic APOSEC™/kg b.w.** The control animals received the vehicle (sterile 0.9% NaCl solution).

No signs of local intolerance reactions were observed in any group.

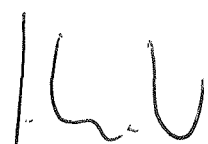
None of the animals died or had to be sacrificed prematurely.

No changes in behaviour, external appearance or faeces were noted. No test item-related influence was noted on the body weight, body weight gain and body weight at autopsy, the food and drinking water consumption, the haematological, clinical chemistry and urinary parameters, the eyes or optic region, the auditory acuity, the relative and absolute organ weights, and the myeloid:erythroid at any of the dose levels. The macroscopic inspection at necropsy did not reveal any morphological changes which are considered related to the administration of the test item.

The histopathological examination did not reveal any local intolerance and systemic morphological lesions which are considered to be related to the administration of the test item.

No test item-related changes were noted during or at the end of the 14-day recovery period, and no toxicologically relevant microscopic changes were noted for the previously high dosed recovery group animals of both sexes.

Under the present test conditions of this study, the no-observed-effect level (NOEL) was **above 500 Units allogenic APOSEC™/kg b.w.** three times weekly for four weeks (13 applications) by intravenous slow bolus injection.


Dr. phil. J. Leuschner
Study Director
Date

2. GENERAL INFORMATION

2.1 Aim of experiment The aim of this study was to obtain information on the toxicity and local tolerance of allogenic APOSEC™ after repeated intravenous slow bolus administration (three times weekly) to C57BL/6 mice for 4 weeks and to assess the reversibility of any effect at the end of a 2-week recovery period.

2.2 Duration of study

- 5 adaptation days
- 4 test weeks
- 14 additional test days for the animals scheduled for the recovery period

2.3 Test item

Designation Allogenic APOSEC™

Charge nos./
number of bottles/vials received

- a) 399049/ 9 vials
- b) 399050/ 7 vials
- c) 399051/ 8 vials
- d) 399053/ 7 vials (not used)
- e) 399057/ 8 vials (not used)

LPT receipt nos.

- a) 63321
- b) 63322
- c) 63323
- d) 63324
- e) 63325

Date of receipt at LPT June 14, 2017

Characteristics Lyophilisate

Dates of lyophilisation

- a) June 29, 2016
- b) July 1, 2016
- c) June 15, 2016
- d) July 15, 2016
- e) June 29, 2016

Storage conditions At $\leq -80^{\circ}\text{C}$

Stability / Retest date Stability at -80°C at least 3 month after lyophilisation.

Content Each of the 100 mL glass bottles contained 20 mL lyophilised APOSEC™.

Further information on the test item is given in [Appendix 1](#) 'Certificates of Analysis'.

Retention sample
of the test item
(charge no. 399049)

Stored in **LPT**'s archives.

2.4 Identification of the test item

After receipt at **LPT**, the test item was inspected. Batch number, amount and characteristics (colour, consistency and form) were determined and compared with information given by the Sponsor. An identification sheet was filed with the raw data.

Test item	Parameter	LPT identification	Sponsor identification
Allogenic APOSEC™	colour consistency form	N/A [#] solid lyophilisate	not specified not specified lyophilisate

[#]: The test item was delivered in brown glass bottles; hence, the colour of the test item could not be determined.

No further identification was carried out at **LPT**.

2.5 Sponsor / Test Facility / Responsible personnel

Sponsor	APOSCIENCE AG Mariannengasse 14/9 1090 Vienna Austria
Study Monitor	Dr. Silvio Wuschko Phone: +43 664 885 893 54 E-mail: acc_safety.research@gmx.at
Test Facility	LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG Redderweg 8 21147 Hamburg Germany Phone: +49 40 70 20 20 Fax: +49 40 70 20 22 60 E-mail: LPT@LPT-Hamburg.de
Study Director	Dr. phil. J. Leuschner LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG Redderweg 8 21147 Hamburg Germany
Deputy study director	Dr. rer. nat. J. Haferkorn
Test Facility Management	Dr. rer. nat. A. Winkler
Conduct of study / Animal husbandry	Dipl. Ing. Biotech. F. Kunst
Haematology / coagulation / Clinical chemistry	Dr. rer. nat. J. Stien
Veterinarian / Macropathology	Dr. med. vet. M. Wölm / Dipl. vet. med. A. Byk
Statistics	Dipl. Biol. J. Köpcke
Leading Quality Assurance Unit (LQAU)	Dr. med. vet. habil. K. R. Sultan

2.6 Test Site for Histopathology

Test Site (TS)	Global Pathology Support Benoordenhoutseweg 23 2596 BA The Hague The Netherlands Phone: +31 70 3142 404
Principal Investigator (PI)	Dr. R.J.M.M. Thoolen Toxicologic Pathologist E-mail: bob.thoolen@gpstoxpath.com
Head of Test Site (HTS)	Dr. R.J.M.M. Thoolen Toxicologic Pathologist E-mail: bob.thoolen@gpstoxpath.com
Test Site Quality Assurance Unit (TSQAU)	N. Tirtodikromo Phone: +31 70 3142 404 E-mail: suzy.tirtodikromo@gpstoxpath.com
Test Site reference number	457

2.7 Multi-Site regulations

The Test Site followed its own SOPs and provided a Phase Report that was integrated into the main report.

As details regarding the histopathological examination were standardized and already summarized in the Study Plan and in Study Plan Amendment No. 1, a separate Phase Plan issued by Global Pathology Support (GPS) was not required.

The histopathology phase of the Study Plan, histopathology study procedures and the histopathology phase of the study report were inspected by the GPS Quality Assurance Unit. The Principal Investigator informed the Test Site QAU when the histopathology was performed. In case Leading Quality Assurance Unit requested to perform a study audit, GPS would have cooperated.

The Principal Investigator was responsible for compliance with his national GLP regulations for any work performed at his Test Site as well as for all data sent to **LPT** for inclusion in the study report. Any Phase Report provided by the PI included a statement of GLP Compliance signed by the PI and a Quality Assurance Statement signed by an authorized representative of the Test Site QAU. Archiving procedures for all work performed at the Test Site were described in the Phase Report. The Phase Report is given in [Appendix 3](#) 'Histopathological Phase Report'.

The PI would have informed his TSQAU and contacted the study director in case of unexpected findings or occurrences at his Test Site. The TSQAU would have reported these findings to the LQAU. However, no unexpected findings were communicated from the Test Site.

The Test Site QAU inspected the work at its Test Site as well as the Phase Report according to its SOPs. The TSQAU reported any inspection results in writing to the PI, Test Site Management, Study Director, Test Facility Management and Leading QAU. Critical findings were reported immediately, other non-critical findings were communicated in due time.

2.8 Rules and regulations

The study was performed in compliance with the 'Good Laboratory Practice' Regulations (see the [Statement of Compliance](#) on page 5 and the enclosed GLP Certificate of the Test Facility **LPT** in [Appendix 4](#)).

2.9 Archiving and storage, Standard Operating Procedures, staff safety

Archives of data
and specimens

During the study:

In the depot

LPT, Redderweg 8
21147 Hamburg, Germany

After reporting:

The final report will be archived by the Sponsor.

A copy of the final report as well as all specimens, written raw data, and other study-related documents listed in the Study Plan Section 'Study Materials to be Archived' will be stored in the **LPT** archives.

Duration of storage

The duration of storage (15 years) will be in compliance with the GLP regulations as stated in the German Chemicals Act ('Chemikaliengesetz').

All archived study materials will be destroyed after the 15-year GLP storage period unless the Sponsor requests otherwise.

Three months after the issuance of the Final Study Report, any samples or aliquots not listed in the Study Plan Section 'Study Materials to be Archived' and still remaining at **LPT** will be destroyed unless the Sponsor requests otherwise.

**Archiving at Test Site
for histopathology**

All slides and/or specimens were transferred to the Test Facility after completion of the histopathology phase of the study. All raw data and relevant documentation and the original Phase Report generated at the Test Site for histopathology evaluation are archived by the Test Site under the study number 457 for 3 years. Thereafter, the data will be returned to the Test Facility for storage for the remainder of the legal archiving period required by the local authorities (15 years). The Principal Investigator informed the Study Director of the time when the documentation was archived.

**Standard Operating
Procedures (SOPs)**

All work was carried out according to Standard Operating Procedures which were followed for all stages of the study. They may be inspected in those divisions which were engaged in the study and in the Quality Assurance Unit (QAU).

Staff safety

The standard safety precautions operating within the department were applied to this study.

2.10 Study dates**Code number of the study
in the raw data**

34946

Start of Study**Study Plan**

June 23, 2017

Study Plan amendment

No. 1, dated June 28, 2017

1st administration

Males: June 26, 2017
Females: July 03, 2017

**Termination of the in-life period
- Main dissections**

Males: July 25, 2017
Females: August 01, 2017

- Recovery period

Males: August 08, 2017
Females: August 15, 2017

Date of final report

December 01, 2017

2.11 Deviations from Study Plan

The study was conducted in accordance with the Study Plan agreed upon and 1 Study Plan amendment. There were no major deviations from the Study Plan and the Study Plan amendment. However, the following minor deviations were noted:

- Ophthalmological and auditory examinations

The examinations were performed at study initiation and at the end of the treatment period from all main study and recovery animals as a standard routine and not from the main study animals only as stated in the Study Plan. This change was caused by a copy and paste error in the Study Plan.

- Animals

The correct description of the mice used in this study is

Test species / Strain / Nomenclature: Mouse / BL/6N / C57BL/6NCrL and not Test species / Strain / Stock:Mouse / BL6 / C57BL/6NCrL as stated in the Study Plan due to a typing error.

These minor deviations that were not reflected by a Study Plan amendment did not affect the validity and integrity of the scientific results obtained during the study.

3. METHODS

3.1 Animals

Mice supplied by Charles River Laboratories Germany GmbH were used in this experiment. The body weight range did not exceed 10% of the mean weight for each sex at the time of selection.

An initial health check was performed upon delivery of the animals. Only animals free of signs of illness were selected for the study.

The animals were allocated to the 4 test groups based on body weight by means of a computerized randomization program. Animals with a body weight at the extremes of the weight distribution were excluded and replaced by healthy spare animals. Animal replacement after the first dosing was not planned nor did it occur.

Test species / Strain /
Nomenclature

Mouse / BL/6N / C57BL/6NCrL

Breeder

Charles River Laboratories Germany GmbH
Sandhofer Weg 7
97633 Sulzfeld
Germany

Number and sex of animals

100 animals (50 male and 50 female animals).

Main study animals

80 animals (40 males and 40 females);
10 animals/sex/group.

Recovery animals

20 animals (10 males and 10 females);
5 animals/sex/group for groups 1 and 4.

For details see [Section 3.7](#).

Additionally, 10 (5 male and 5 female) spare animals were available for possible replacement during the adaptation period.

Body weight
(at 1st dosing)

Males: 23.1 g - 26.3 g
Females: 18.8 g - 22.2 g

Age of animals
(at 1st dosing)

Males: 54 days
Females: 61 days

Selection of species	The mouse is a commonly used rodent species for toxicity studies.
Identification of animals	Each mouse received a continuous number. Points were set on paws and/or tail by tattoo. Additionally, the animal cages were labelled with the study number, animal number, sex and treatment group.
Adaptation period	5 days.

3.2 Housing and feeding

Diet

Commercial diet ssniff®-R/M-H V1534 (ssniff® Spezialdiäten GmbH, 59494 Soest, Germany) served as food (see [Appendix 2](#) 'Composition of the Diet'). This food was offered *ad libitum*. Food residue was removed and weighed weekly.

Periodic analysis of the food for contaminants based on EPA/USA¹ is conducted at least twice a year by LUFA-ITL² (see [Appendix 2](#) 'Limitation for Contaminants in the Diet'). Certificates of analysis of the composition and for contaminants were provided by the manufacturer and are included in the raw data.

Housing

The animals were kept singly in MAKROLON cages (type II) with a basal surface of approx. 22 cm x 16 cm and a height of approx. 14 cm at a room temperature of 22°C ± 3°C (maximum range) and a relative humidity of 55% ± 10% (maximum range). Deviations from the maximum range caused for example during cleaning procedures are dealt with in SOPs. The rooms were lit (about 150 lux at approx. 1.50 m room height) and darkened for periods of 12 hours each. The air change rate was 15 - 20 exchanges/hour.

¹ EPA/USA, Proposed Health Effects Test Standards for Toxic Substances Control Act Test Rules, Federal Register 44, 27334 - 27375, May 1979.

² Landwirtschaftliche Untersuchungs- und Forschungsanstalt, Institut für Tiergesundheit und Lebensmittelqualität GmbH, 24107 Kiel, Germany.

Granulated textured wood (Granulat A2, J. Brandenburg, 49424 Goldenstedt, Germany) was used as bedding material for the cages. The cages were changed and cleaned once a week. Periodic analysis of the bedding material for contaminants based on EPA/USA is conducted at least once a year by LUFA-ITL (see [Appendix 2](#) 'Limitation for Contaminants in the Bedding Material').

Drinking water

Drinking water was offered *ad libitum*.

Drinking water is examined according to the 'Deutsche Trinkwasserverordnung 2001' [German Regulations on Drinking Water 2001]³ by the Hamburger Wasserwerke, 20539 Hamburg, Germany, at least four times a year (see [Appendix 2](#) 'Limitation for Contaminants in the Drinking Water').

In addition, drinking water samples taken at **LPT** are analysed by LUFA-ITL once a year for means of bacteriological investigations according to the 'Deutsche Trinkwasserverordnung 2001, Anlage 1' [German Regulations on Drinking Water 2001, Addendum 1].

³ Version from August 02, 2013, revised on November 18, 2015.

3.3 Preparation of the item-vehicle mixtures

The allogenic APOSEC™ was reconstituted with sterile 0.9% aqueous NaCl solution to the appropriate concentration as described in the table below. For each dose level separate bottles/vials were reconstituted.

The APOSEC™ drug substance was produced from the supernatant of standardised cultures of PBMCs with a cell density of 25 Mio PBMCs/mL. The lyophilisate of 1 mL supernatant contained the secretome of 25 Mio PMBCs, which is referred to as 25 Units hereafter.

Dose level [Units/kg]	Content per test item vial [Units]	Vial filled to a final volume of [mL]	Achieved concentration of the administration solution [Units/mL]
50	500	20	25
250	500	4	125
500	500	2	250

The administration solutions were freshly prepared on each administration day before initiation of the administration.

Remainders of the administration solutions were stored at +2°C to +8°C for up to 14 days. These remainders were used for administration, if usage was within the stability period and under sterile conditions.

3.4 Administration

Route of administration	Intravenous slow bolus administration into a tail vein.
Frequency of administration	Three times weekly for 4 weeks; in total 13 administrations.
Injection speed	Dose/approx. 15 sec
Vehicle	Sterile 0.9% NaCl solution ⁴
Administration volume	2 mL/kg b.w./administration

⁴ Batch no. 16507451, B.Braun Medical SA, 08191 Rubí, Barcelona, Spain.

Selection of route
of administration

According to clinical use and recommendation.
The intravenous route is an anticipated route for
human exposure to the test item.

The test item formulations were administered intravenously at a constant relative administration volume.

The control animals receive the vehicle at the same administration volume in the same way as the high dose group.

The amount of the test item was adjusted to each animal's current body weight on each administration day (see [Section 4.3](#)).

3.5 Test item formulation analysis

No test item formulation analysis was carried out.

3.6 Dose selection

The dose levels for this study were selected by the Sponsor.

3.7 Group size / Dose levels

The animals were allocated to the 4 test groups based on body weight by means of a computer generated randomization program.

Group	APOSEC™ dose, i.v. [Units/kg b.w.]	Concentration of the administration solutions [Units/mL]	No. and sex of animals MS + RP	Animal number	
				MS	RP
1	0 (0.9% NaCl solution)	0	10 + 5 m 10 + 5 f	1 - 10 16 - 25	11 - 15 26 - 30
2	50 (low dose)	25	10 m 10 f	31 - 40 41 - 50	none
3	250 (intermediate dose)	125	10 m 10 f	51 - 60 61 - 70	none
4	500 (high dose)	250	10 + 5 m 10 + 5 f	71 - 80 86 - 95	81 - 85 96 - 100

b.w.; body weight

i.v.: intravenous

MS: main study

RP: recovery period

m: male

f: female

4. OBSERVATIONS

Dated and signed records of all activities relating to the day by day running and maintenance of the study within the animal unit as well as to the group observations and examinations outlined in the Study Plan were recorded in the appropriate documentation. In addition, observations related to individual animals made throughout the study were recorded.

The following observations were made during the course of the study:

4.1 Clinical signs

The animals were observed individually before and after dosing at each time of dosing for any signs of behavioural changes, reaction to treatment or illness.

In addition, the animals were checked regularly throughout the working day from 7.30 a.m. to 4.30 p.m. by cage-side observations. On Saturdays and Sundays, the animals were checked regularly from 8.00 a.m. to 12.00 noon with a final check performed at approximately 4.00 p.m.

Cage-side observations included skin/fur, eyes, mucous membranes, respiratory and circulatory systems, somatomotor activity and behaviour patterns. The onset, intensity and duration of any signs observed were recorded.

Dated and signed records of appearance, change and disappearance of clinical signs were maintained on clinical history sheets for individual animals.

Special attention was paid to the local tolerance of the test item at the injection sites.

4.2 Mortality

Further checks were made early in the morning and again in the afternoon of each working day to look for dead or moribund animals. This would have allowed post mortem examinations to be carried out during the working period of that day. On Saturday and Sundays a similar procedure was followed with a final check at approximately 4.00 p.m.

However, none of the animals died or had to be sacrificed prematurely.

4.3 Body weight

The weight of each mouse was recorded

- at delivery and at the time of group allocation
- during the treatment period: before each treatment (three times weekly)
- during the recovery period: three times weekly
- on the day of necropsy.

Weekly values are stated in the report.

4.4 Food and drinking water consumption

The quantity of food left by individual animals was recorded on a weekly basis throughout the experimental period. Food intake per mouse (g/mouse/week) was calculated using the total amount of food given to and left by each mouse in each group upon completion of a treatment week. From these data the food consumption (in g/kg b.w./day) was determined using the following formula:

$$\text{Relative food consumption (g/kg b.w./day)} = \frac{\text{Total food given (g)} - \text{Total food left (g)}}{\text{Number of animal days}^{\#} \times \text{Body weight (kg)}}$$

[#] The term 'animal days' counts one animal day for each animal alive for a whole day; it is assumed that on the day of death an animal does not eat.

Drinking water consumption was monitored by daily visual appraisal throughout the study.

4.5 Laboratory examinations

Blood samples were taken from the retrobulbar venous plexus under isoflurane anaesthesia from animals fasted overnight. The blood samples collected were divided into tubes as follows:

EDTA anticoagulant (whole blood)for haematological investigations
Citrate anticoagulant (plasma).....for coagulation tests
Li-Heparin anticoagulant (plasma) for clinical chemical tests

4.5.1 Haematology

The parameters listed below were determined at the following times:

- On test day 25 All main study animals.
- On test day 39 All recovery animals.

Parameter	Unit	Instrument
Haemoglobin content (HGB)	mmol/L	ADVIA™ 120 Siemens Diagnostics GmbH 35463 Fernwald, Germany
Erythrocytes (RBC)	$10^6/\mu\text{L}$	
Leucocytes (WBC)	$10^3/\mu\text{L}$	
Reticulocytes (Reti)	% of the erythrocytes	
Platelets (PLT)	$10^3/\mu\text{L}$	
Haematocrit value (HCT)	%	
Differential blood count (relative) ⁵	%	
Differential blood count (absolute) ⁵	$10^3/\mu\text{L}$	
Mean corpuscular volume (MCV)	fL	
Mean corpuscular haemoglobin (MCH)	fmol	
Mean corpuscular haemoglobin concentration (MCHC)	mmol/L	

Following the haematological examinations using the ADVIA system, blood smears were prepared from all samples, dried and stained for possible histopathological examinations in case of pathological findings (see Section 5.1).

⁵ Neutrophilic, eosinophilic and basophilic granulocytes, lymphocytes, and monocytes. Large unstained cells were simultaneously quantified during measurement of the differential blood count.

4.5.2 Coagulation parameters

The parameters listed below were determined at the following times:

- On test day 30 All main study animals.
- On test day 44 All recovery animals.

Parameter	Unit	Instrument
Thromboplastin time (TPT)	sec	Amax Destiny Plus™ TCoag Deutschland GmbH 32657 Lemgo, Germany
Activated partial thromboplastin time (aPTT)	sec	
Thrombin time (TT)	sec	

4.5.3 Clinical chemistry

- On test day 30 All main study animals.
- On test day 44 All recovery animals.

Parameter	Unit	Instrument / Method
Albumin	g/L plasma	KONELAB 30i Thermo Fisher Scientific, 63303 Dreieich, Germany
Globulin	g/L plasma	by subtraction
Albumin/globulin ratio	(non-dimensional)	by calculation
Bilirubin (total)	μmol/L plasma	KONELAB 30i Thermo Fisher Scientific, 63303 Dreieich, Germany
Cholesterol (total)	mmol/L plasma	
Creatinine	μmol/L plasma	
BUN/creatinine ratio	(non-dimensional)	by calculation
Glucose	mmol/L plasma	KONELAB 30i Thermo Fisher Scientific, 63303 Dreieich, German
Protein (total)	g/L plasma	
Urea (in blood, BUN)	mmol/L plasma	

- continued -

Parameter	Unit	Instrument / Method
Calcium	mmol/L plasma	KONELAB 30i Thermo Fisher Scientific, 63303 Dreieich, German
Chloride	mmol/L plasma	
Potassium	mmol/L plasma	
Sodium	mmol/L plasma	
Alanine amino-transferase (ALAT)	U/L plasma	
Alkaline phosphatase (aP)	U/L plasma	
Aspartate aminotransferase (ASAT)	U/L plasma	
Lactate dehydrogenase (LDH)	U/L plasma	
Creatine phosphokinase (CK)	U/L plasma	

4.6 Urinalysis

Urine samples were collected from animals fasted overnight at the following times and the parameters listed below were determined:

- On test day 29 All main study animals.
- On test day 43 All recovery animals.

Due to the low excretion volume of urine per animal, mice were placed in URIMAX funnel cages in groups of 5 animals per sex. After the mice have received 30 mL tap water/kg body weight by gavage, urine was collected for 6 hours.

The following parameters were measured using the methods given below:

Parameter	Instrument / Method	Units
Volume	graduated vial	mL
pH	using a digital pH meter type WTW InoLab pH 720	(non-dimensional)
Specific gravity	using an Atago refractometer, type Uricon sample compared with water (nominal value of 1.000)	g/mL

The following tests were also performed using qualitative indicators (Combur 9® Test, Roche Diagnostics GmbH, 68305 Mannheim, Germany) of analyte concentration:

Parameter	Reporting convention					
	Units	Semi-quantitative determination level				
Protein	g/L	neg	0.3	1	5	
Glucose	mmol/L	normal	2.8	5.5	17	55
Bilirubin	-	neg	+	++	+++	
Urobilinogen	$\mu\text{mol/L}$	normal	17	70	140	200
Ketones	-	neg	+	++	+++	
Haemoglobin (Hb) (approx. values)	ery/ μL	neg	10	25	50	250
Nitrite	-	neg	pos			

neg = negative

+ = 'small amount' of analyte

pos = positive

++ = 'moderate amount' of analyte

ery = erythrocytes count

+++ = 'large amount' of analyte

Microscopic examinations of urine samples were carried out by centrifuging samples and spreading the resulting deposit on a microscopic slide. The deposits were examined for the presence of the following parameters:

- Epithelial cells (E)
- Leucocytes (L)
- Erythrocytes (R)
- Organisms (B)
- Further constituents (i.e. sperm, casts) (C)
- Crystalluria (A)

The frequency of the above parameters in the centrifugal deposits was recorded as follows:

- 0 None found in any field examined
- + Few found in some fields examined
- ++ Few in all fields examined
- +++ Many in all fields examined

The colour and turbidity of the urine were examined visually.

4.7 Ophthalmological and auditory examinations

Examinations were performed at the following times:

- Predose (before the first administration) All main study and recovery animals.
- On test day 29
(at the end of the treatment period) All main study and recovery animals.
- On test day 43
(at the end of the recovery period) All recovery animals.

The eyes were examined with a HEINE ophthalmoscope.

After examination of the pupillary reflex, mydriasis was produced by instillation of STULLN^{®6} eye drops onto the cornea. The following ocular structures were then examined:

- Adnexa oculi (i.e. lids, lacrimal apparatus), conjunctiva
- Cornea, anterior chamber
- Lens, vitreous body, fundus (retina, optic disc)

The auditory acuity was checked with a simple noise test.

⁶ ankerpharm GmbH, 07407 Rudolstadt, Germany.

5. PATHOLOGY AND HISTOPATHOLOGY

5.1 Necropsy

On test day 30 (approximately 24 hours after the last administration), the main study animals were dissected following a randomisation scheme. Necropsy of all animals assigned for the recovery period was carried out on test days 44.

Immediately after blood withdrawal for laboratory examinations, the animals were sacrificed under inhalation anaesthesia (isoflurane), weighed, dissected and inspected macroscopically under the direction of a pathologist.

All superficial tissues were examined visually and by palpation and the cranial roof was removed to allow observation of the brain, pituitary gland and cranial nerves. After ventral midline incision and skin reflection, all subcutaneous tissues were examined. The condition of the thoracic viscera was noted with due attention to the thymus, lymph nodes and heart.

The abdominal viscera were examined before and after removal, the urinary bladder was examined externally and by palpation. The gastro-intestinal tract was examined as a whole and the stomach and caecum were incised and examined. The lungs were removed and all pleural surfaces examined under suitable illumination. The liver and the kidneys were examined. Any abnormalities in the appearance and size of the gonads, adrenal glands, uterus, intra-abdominal lymph nodes and accessory reproductive organs were recorded.

The weights of the following organs of all animals were determined before fixation:

Adrenal gland (2)	Ovary (2)
Brain	Spleen
Epidymides	Testicle (2)
Heart	Thymus
Kidney (2)	Uterus (including cervix)
Liver	

Paired organs were weighed individually and identified as left or right.

The following organs or parts of organs with the exception of the eyes and testicles of all animals were fixed in 7% buffered formalin. The eyes were preserved in Davidson's solution and the testicles in modified Davidson's solution for optimum fixation.

Adrenal gland (2)	Oesophagus
Aorta abdominalis	Ovary (2)
Bone (os femoris with joint)	Pancreas
Bone marrow (os femoris/sternum)	Pituitary
Brain (cerebrum, cerebellum, brain stem)	Prostate
Epididymis (2)	Salivary glands (mandibular, parotid, sublingual)
Eye with optic nerve and Harderian gland (2)	Seminal vesicle
Gall bladder	Skin (left flank)
Gross lesions	Spinal cord (3 sections)
Heart (left and right ventricle, septum)	Spleen
Injection site(s)	Stomach
Intestine, large (caecum, colon, rectum)	Testicle (2)
Intestine, small (duodenum, jejunum, ileum, Swiss roll method)	Thymus
Kidney and ureter (2)	Thyroid (2) (incl. parathyroids)
Liver 2 (lobes)	Tissue masses or tumours (including regional lymph nodes)
Lungs (with mainstem bronchi and bronchioles)	Tongue (incl. base)
Lymph node (1, cervical)	Trachea (incl. larynx)
Lymph node (1, mesenteric)	Urinary bladder
Mammary gland (inguinal)	Uterus (incl. cervix and oviducts)
Muscle (skeletal, leg)	Vagina
Nerve (sciatic)	

5.2 Histopathology

The afore-listed organs of all main study and all recovery animals of groups 1 and 4 were examined histopathologically after preparation of haematoxylin-eosin stained paraffin sections.

In addition, frozen sections of the heart, liver and one kidney were prepared, stained with Oil Red-O and examined histopathologically.

Parathyroids cannot always be identified macroscopically. They were examined microscopically in the plane of section and in all cases where they were noted as grossly enlarged.

The blood smears prepared during the haematological examinations (see [Section 4.5.1 'Haematology'](#)) were available for possible examination of pathological changes but will be examined and evaluated only depending on necropsy findings and upon agreement of the Sponsor. So far, no evaluation has been carried out.

The histotechnique was performed by **LPT**. The slides (labelled with study number, test species, animal number, and block number) were dispatched to Global Pathology Support (GPS) on September 01 and September 08, 2017.

The transport of slides for the histopathology work to the Test Site of GPS was arranged by **LPT**, whereas the return transport to the Test Facility will be arranged by GPS.

Histopathology was performed by Global Pathology Support (GPS), Dr. R.J.M.M. Thoolen, Benoordenhoutseweg 23, 2596 BA The Hague, The Netherlands under Test Site Reference No. 457 according to all relevant GPS SOPs.

All observations upon final assessment were reported per animal and the findings considered relevant for the treatment in an incidence and occurrence table. All microscopic findings were recorded, reported and archived with the Provantis system.

The report of this phase of the study comprises a description of objective, materials and methods, results (including results of macroscopic and microscopic changes), and conclusions. The unaudited Draft Phase Report was presented electronically to the Study Director for comments/review. Comments were addressed and the Final Draft Phase Report of the study was presented to the TSQAU for auditing.

The audited Final Draft Phase Report of the histopathology phase of the study was sent electronically to the Study Director who provided documented approval on the contents of the Phase Report by e-mail to the Principle Investigator. An original of the final, signed Phase Report was sent (on paper and electronically) to the Study Director. A copy will be archived by Global Pathology Support.

The 'Phase Report on Histopathology' prepared by GPS is given in [Appendix 3](#).

5.3 Bone marrow evaluation

During dissection fresh bone marrow was obtained from the os femoris (3 air-dried smears/animal) of 5 main study animals per sex and group and of all recovery animals, and stained according to PAPPENHEIM. The myeloid : erythroid ratio was determined by cell differentiation (counting of 200 nuclei-containing cells).

6. STATISTICS

Data for toxicology and pathology were captured, as far as possible, using the departmental computerised systems (Provantis® Integrated preclinical software, version 9.4.0, Instem LSS Ltd., Stone, Staffordshire ST15 0SD, United Kingdom). Raw data not fully compatible with the computerised systems were maintained on paper according to appropriate SOPs.

The test item groups 2 to 4 were compared to the control group 1.

The following statistical methods were used:

Multiple t-test based on DUNNETT, C. W. New tables for multiple comparisons with a control. Biometrics, 482-491 (September 1964)	Body weight / Food consumption / Haematology / Coagulation / Clinical chemistry / Relative and absolute organ weights ($p \leq 0.05$ and $p \leq 0.01$)
---	---

chi ² test	Bone marrow ($p \leq 0.01$)
-----------------------	----------------------------------

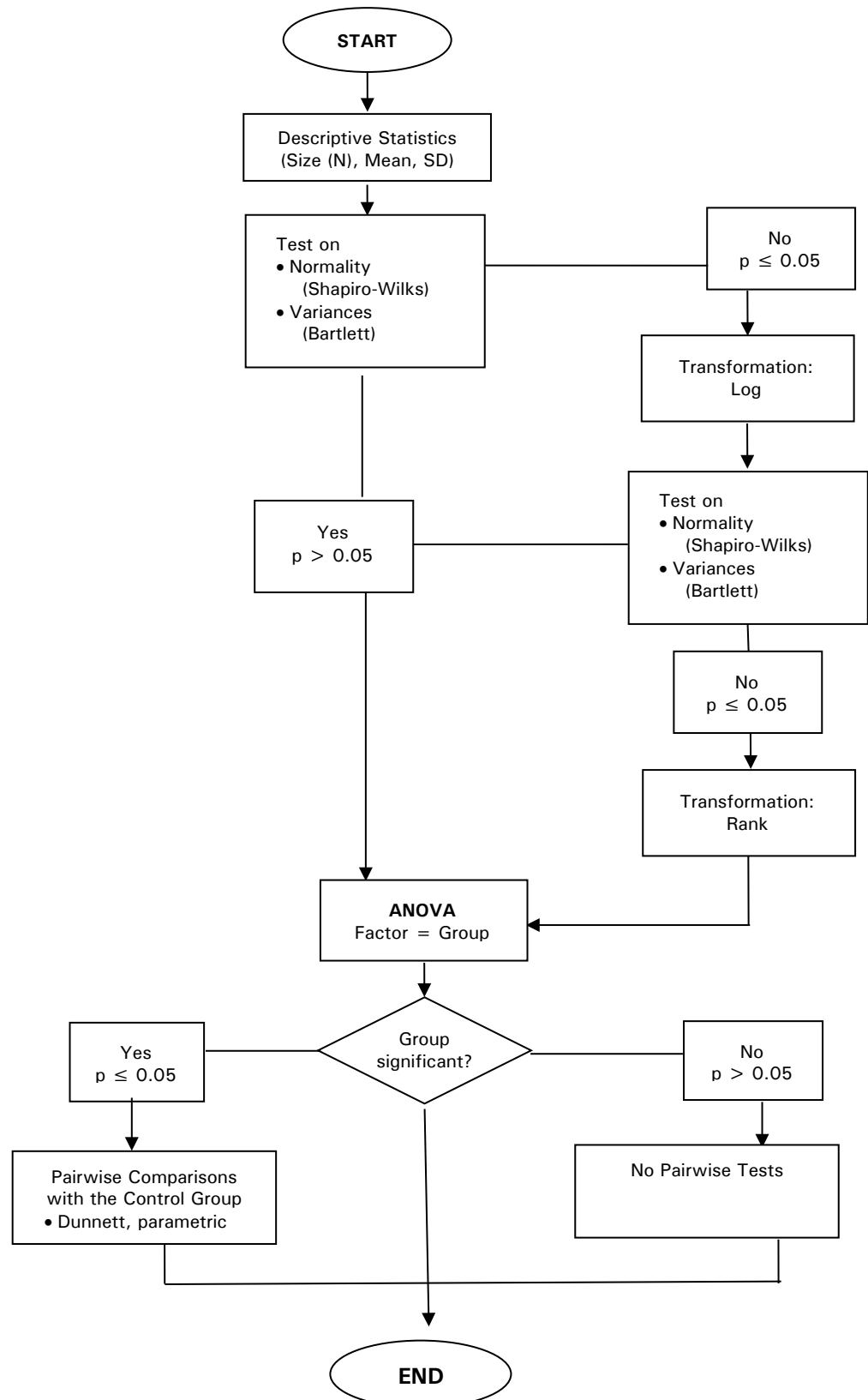
Exact test of R. A. FISHER (if applicable)	Histopathology ($p \leq 0.05$)
---	-------------------------------------

The following settings were used for the statistical evaluation of the parametrical values captured by Provantis (see flow chart of decision tree on the next page):

Homogeneity of variances and normality of distribution were tested using the BARTLETT's and SHAPIRO-WILKS test. In case of heterogeneity and/or non-normality of distribution, stepwise transformation of the values into logarithmic or rank values was performed prior to ANOVA. If the ANOVA yielded a significant effect ($p \leq 0.05$), intergroup comparisons with the control group was made by the DUNNETT's test ($p \leq 0.01$ and $p \leq 0.05$).

These statistical procedures were used for all data. Significantly different data are indicated in the tables.

Flow chart of Decision Tree for ANOVA and Dunnett's Test calculation



7. RESULTS

7.1 Local tolerance

Treatment period and recovery period (restricted to groups 1 and 4)

No signs of local intolerance reactions were observed in any of the male and female animals treated with **50, 250 or 500 Units allogenic APOSEC™/kg b.w.** three times weekly by intravenous slow bolus injection, neither during the 4-week treatment period nor during the 14-day treatment-free recovery period.

The macroscopic inspection at the end of the treatment and recovery period did not reveal any changes at the injection sites for any group.

The histopathological examination (restricted to the control and high dose group) did not reveal any test item-related changes at the injection sites of the animals. All microscopic findings observed at the injection sites are considered to be a result of the mode of application (intravenous administration).

See [Table 1-1](#) (Clinical Signs - Local and Systemic Tolerance - Summary), [Table 1-2](#) (Clinical Signs - Local and Systemic Tolerance - Individual Data), [Table 9](#) (Macroscopic Post Mortem Findings) and the Phase Report 'Histopathology' in [Appendix 3](#) for details.

7.2 Systemic tolerance

7.2.1 Mortality

Treatment period and recovery period (restricted to groups 1 and 4)

None of the male and female animals treated with **50, 250 or 500 Units allogenic APOSEC™/kg b.w.** three times weekly by intravenous slow bolus injection for 4 weeks died or had to be sacrificed prematurely during the 4-week treatment period or during the 14-day treatment-free recovery period.

7.2.2 Behaviour, external appearance and faeces

Treatment period and recovery period (restricted to groups 1 and 4)

None of the male and female mice treated with **50, 250 or 500 Units allogenic APOSEC™/kg b.w.** three times weekly by intravenous slow bolus injection revealed any changes in behaviour, external appearance, or consistency of faeces, neither during the 4-week treatment period nor during the 14-day treatment-free recovery period.

See [Table 1-1](#) (Clinical Signs - Local and Systemic Tolerance - Summary) and [Table 1-2](#) (Clinical Signs - Local and Systemic Tolerance - Individual Data) for details.

7.2.3 Body weight and body weight gain

Treatment period and recovery period (restricted to groups 1 and 4)

No test item-related influence was noted on the body weight, the body weight gain and the body weight at autopsy of the male and female animals treated with **50, 250 or 500 Units allogenic APOSEC™/kg b.w.** three times weekly by intravenous slow bolus injection compared to the control group, neither during the 4-week treatment period nor during the 14-day treatment-free recovery period.

Statistically significant differences in body weight compared to the control animals which are not considered to be test item-related are given in the table below:

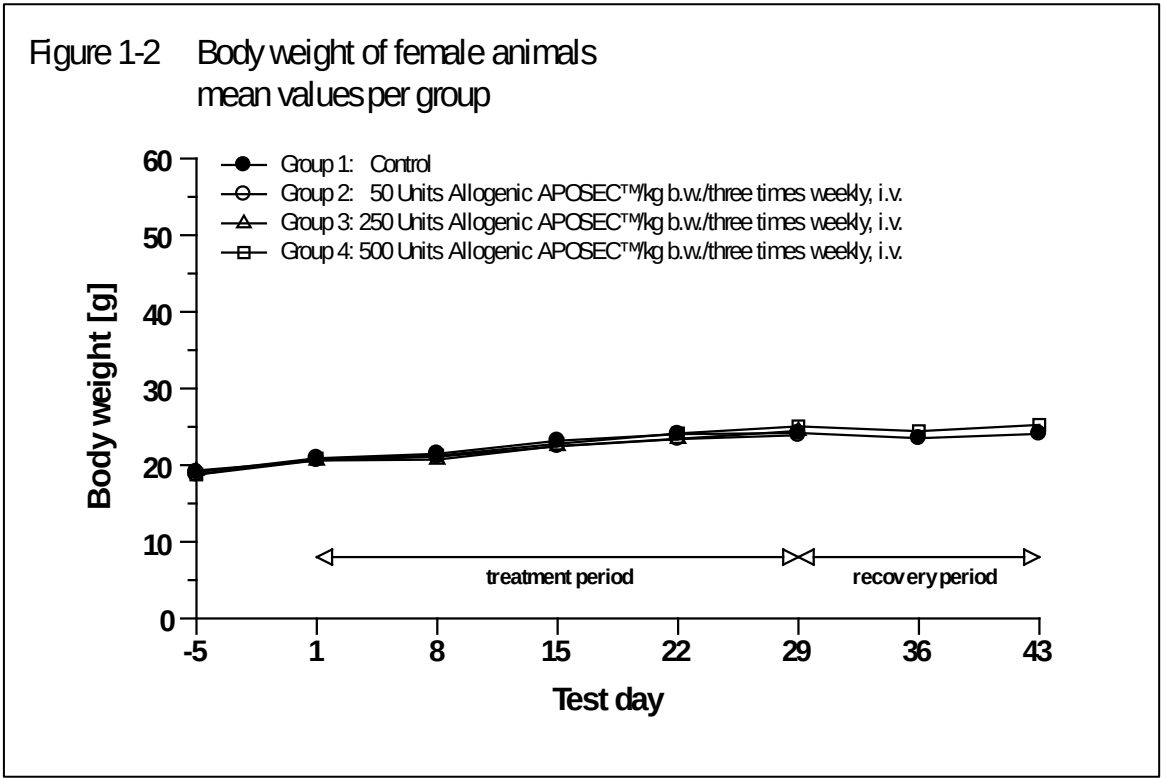
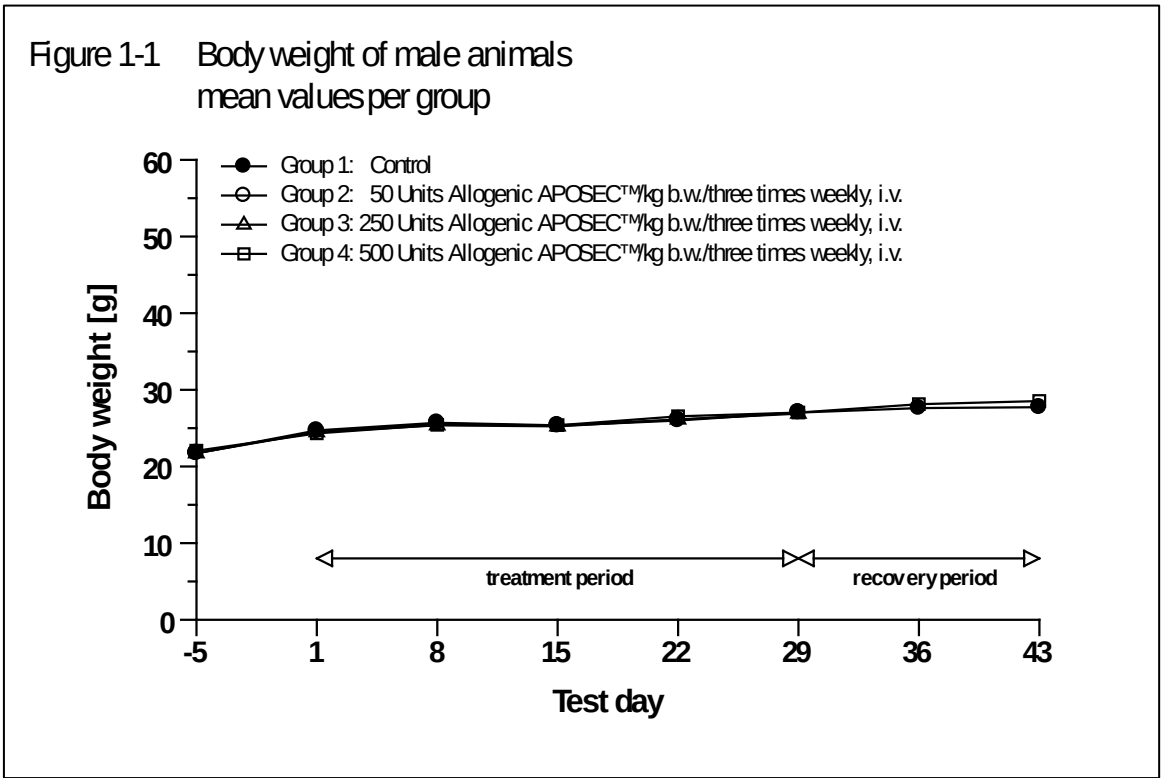
Parameter	Ref. table no.	Group / Sex	Increase ↑ Decrease ↓	Test day	Statistical significance	Reason
Body weight	2-1	4 f	↑	43	$p \leq 0.01$	A

f: female

A: the slight alteration in comparison to control animals is without any biological relevance

See [Table 2-1](#) (Body Weight - Summary) and [Table 2-2](#) (Body Weight - Individual Data) for the mean and individual body weight data, [Table 2-3](#) (Body Weight Gain - Summary) and [Table 2-4](#) (Body Weight Gain - Individual Data) for the mean and individual body weight gain. Body weight at autopsy is given in [Table 2-5](#).

The weekly mean body weight is shown graphically in [Figure 1-1](#) (males) and [Figure 1-2](#) (females) on the next page.



7.2.4 Food and drinking water consumption

Treatment period and recovery period (restricted to groups 1 and 4)

No test item-related influence on the food consumption was noted for any of the animals treated with **50, 250 or 500 Units allogenic APOSEC™/kg b.w.** three times weekly by intravenous slow bolus injection compared to the control group, neither during the 4-week treatment period nor during the 14-day treatment-free recovery period.

The visual appraisal of the drinking water consumption revealed no differences between the control and the test item-treated animals.

Statistically significant differences in relative food consumption compared to the control animals which are not considered to be test item-related are given in the table below:

Parameter	Ref. table no.	Group / Sex	Increase ↑ Decrease ↓	Test week	Statistical significance	Reason
Food consumption	3-1	4 m	↑	1	$p \leq 0.01$	A

m: male

A: the slight alteration in comparison to control animals is without any biological relevance

See [Table 3-1](#) (Food Consumption - Summary) and [Table 3-2](#) (Food Consumption - Individual Data) for details on food intake.

The weekly mean food consumption (in g/kg b.w./day) is shown graphically in [Figure 2-1](#) (males) and [Figure 2-2](#) (females) on the next page.

Figure 2-1 Food consumption of male animals
mean values per group

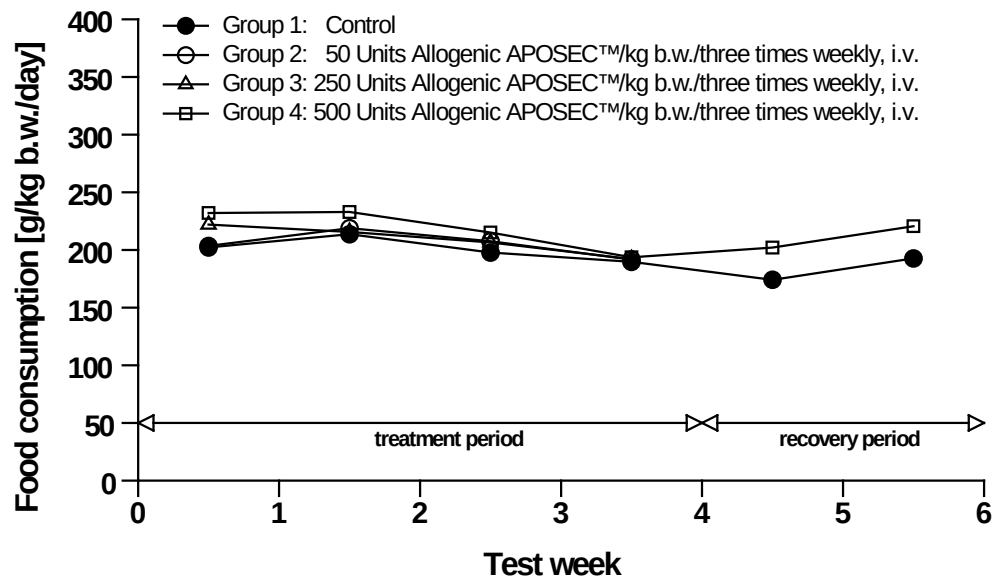
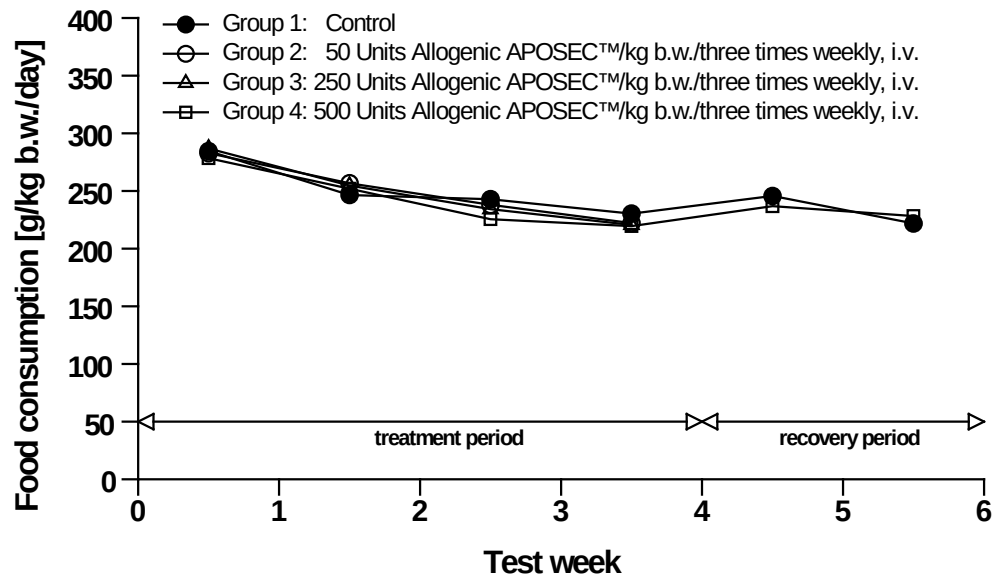


Figure 2-2 Food consumption of female animals
mean values per group



7.2.5 Haematology and coagulation

Treatment period and recovery period (restricted to groups 1 and 4)

No test item-related changes were noted for the haematological parameters of the male and female animals treated with **50, 250 or 500 Units allogenic APOSEC™/kg b.w.** three times weekly by intravenous slow bolus injection compared to the control group animals, neither at the end of the 4-week treatment period nor at the end of the 14-day treatment-free recovery period.

Statistically significant differences in haematological parameters compared to the control animals which are not considered to be test item-related are given in the table below:

Parameter	Ref. table no.	Group / Sex	Increase ↑ Decrease ↓	Test day	Statistical significance	Reason
Reticulocytes	4-1	4 f	↑	25	$p \leq 0.01$	A
Platelets		4 m	↓	25	$p \leq 0.01$	A
Eosinophilic granulocytes (absolute)		4 f	↑	39	$p \leq 0.05$	A
Thrombin time		4 m	↑	44	$p \leq 0.05$	A

m: male

f: female

A: the slight alteration in comparison to control animals is without any biological relevance

No test item-related influence was observed for the haemoglobin content (HGB), the number of erythrocytes (RBC), leucocytes (WBC) and platelets (PLT), the percentage of reticulocytes (Reti), the haematocrit value (HCT), the relative and absolute count of neutrophilic granulocytes (Neut), lymphocytes (Lym), monocytes (Mono), eosinophilic granulocytes (Eos), large unstained cells (LUC) and basophilic granulocytes (Baso), the thromboplastin time (TPT), the activated partial thromboplastin time (aPTT), the thrombin time (TT), the mean corpuscular volume (MCV), the mean corpuscular haemoglobin (MCH) and the mean corpuscular haemoglobin concentration (MCHC).

Haematological values are listed in [Table 4-1](#) (Haematological Parameters - Summary) and in [Table 4-2](#) (Haematological Parameters - Individual Data).

7.2.6 Clinical chemistry

Treatment period and recovery period (restricted to groups 1 and 4)

No test item-related changes were noted for the clinical chemistry parameters of the male and female animals treated with **50, 250 or 500 Units allogenic APOSEC™/kg b.w.** three times weekly by intravenous slow bolus injection compared to the control group animals, neither at the end of the 4-week treatment period nor at the end of the 14-day treatment-free recovery period.

Statistically significant differences in clinical chemistry parameters compared to the control animals which are not considered to be test item-related are given in the table below:

Parameter	Ref. table no.	Group / Sex	Increase ↑ Decrease ↓	Test day	Statistical significance	Reason
ALAT	5-1	4 m	↑	44	$p \leq 0.05$	A
ASAT		4 m	↑	44	$p \leq 0.05$	A

m: male

A: the slight alteration in comparison to control animals is without any biological relevance

No test item-related influence was noted for the plasma levels of albumin and globulin, the albumin/globulin ratio, the plasma levels of bilirubin (total), cholesterol (total), creatinine, glucose, protein (total), urea, calcium, chloride, potassium and sodium, and on the urea/creatinine ratio. Further, the plasma activities of alanine aminotransferase (ALAT), alkaline phosphatase (aP), aspartate aminotransferase (ASAT), lactate dehydrogenase (LDH) and creatine phosphokinase (CK) were not test item-relatedly influenced.

Biochemical parameters are listed in [Table 5-1](#) (Biochemical Parameters - Summary) and in [Table 5-2](#) (Biochemical Parameters - Individual Data).

7.2.7 Urinalysis

Treatment period and recovery period (restricted to groups 1 and 4)

No test item-related influence was noted on any of the urinary parameters examined in the male and female animals treated with **50, 250 or 500 Units allogenic APOSEC™/kg b.w.** three times weekly by intravenous slow bolus injection, neither at the end of the 4-week treatment period nor at the end of the 14-day treatment-free recovery period.

No test item-related changes were noted for the specific gravity and the pH value of the urine and the urine volume. The analyte concentrations of nitrite, protein, glucose, ketones, urobilinogen, bilirubin and haemoglobin were not influenced in male and female animals. No test item-related changes were observed in the urine colour and the microscopically analysed urine sediments.

Mean and individual values for urinalysis are listed in [Table 6-1](#) (Urinalysis - Summary), [Table 6-2](#) (Urinalysis - Individual Data) and [Table 6-3](#) (Urine Volume - Individual Data).

7.2.8 Ophthalmological and auditory examinations

Treatment period and recovery period (restricted to groups 1 and 4)

Ophthalmological examination did not reveal any test item-related changes of the eyes and the optic region in the male and female animals treated with **50, 250 or 500 Units allogenic APOSEC™/kg b.w.** three times weekly by intravenous slow bolus injection during the course of the study.

The changes noted in the right eye of 1 of 10 female animals treated with **50 Units allogenic APOSEC™/kg b.w.** (moderate clouding of the lens), in the right eyes of 2 of 10 female animals treated with **250 Units allogenic APOSEC™/kg b.w.** (complete opacity of the cornea, obscuring underlying structures), and in the right eye of 1 of 10 female animals treated with **500 Units allogenic APOSEC™/kg b.w.** (slight clouding of the lens) at the end of the treatment period are considered to be incidental findings due to the low number of animals affected.

No test item-related pathological changes were noted on the adnexa oculi, conjunctiva, cornea, anterior chamber, lens, vitreous body and fundus.

There was no indication of any impairment to auditory acuity.

See [Table 7](#) (Ophthalmological Examination) and [Table 8](#) (Auditory Examination) for details.

7.3 Final examinations

7.3.1 Macroscopic post mortem findings

Treatment period

Macroscopic inspection at necropsy did not revealed any test item-related systemic changes in the organs or tissues of the animals treated with **50, 250 or 500 Units allogenic APOSEC™/kg b.w.** three times weekly by intravenous slow bolus injection for 4 weeks at terminal sacrifice on test day 30.

One of 10 male animals of the low dose group revealed a brain of soft consistency. This change is considered an incidental finding due to the low number of animals affected.

Recovery period (restricted to groups 1 and 4)

Macroscopic inspection at necropsy did not revealed any changes in the organs or tissues of the animals previously treated with **500 Units allogenic APOSEC™/kg b.w.** three times weekly at recovery sacrifice on test day 44.

See [Table 9](#) (Macroscopic Post Mortem Findings) for details.

7.3.2 Organ weights

Treatment period and recovery period (restricted to groups 1 and 4)

No test item-related influence was noted on the relative or absolute organ weights of male and female animals treated with **50, 250 or 500 Units allogenic APOSEC™/kg b.w.** three times weekly by intravenous slow bolus injection, neither at the end of the 4-week treatment period nor at the end of the 14-day treatment-free recovery period.

Statistically significant differences in absolute or relative organ weights compared to the control animals which are not considered to be test item-related are given in the table below:

Organ	Ref. table no.	Group / Sex	Increase ↑ Decrease ↓	Test day	Statistical significance	Reason
Epididymis, right (relative)	10-1	3 m	↓	30	$p \leq 0.05$	B C
Epididymis, left (absolute)	11-1	2 m	↓	30	$p \leq 0.05$	B
Epididymis, right (absolute)	11-1	2 m 3 m	↓ ↓	30 30	$p \leq 0.05$ $p \leq 0.05$	B B
Testis, left (relative)	10-1	4 m	↓	44	$p \leq 0.01$	A
Testis, right (relative)	10-1	4 m	↓	44	$p \leq 0.05$	A
Testis, right (absolute)	11-1	4 m	↓	44	$p \leq 0.05$	A
Spleen (relative)	10-1	2 m 4 m	↑ ↑	30 30	$p \leq 0.01$ $p \leq 0.01$	A A
Spleen (absolute)	11-1	2 m 4 m	↑ ↑	30 30	$p \leq 0.05$ $p \leq 0.01$	A A
Thymus (relative)	10-1	2 m	↓	30	$p \leq 0.05$	B
Thymus (absolute)	11-1	2 m	↓	30	$p \leq 0.05$	B

m: male

A: the slight alteration in comparison to control animals is without any biological relevance

B: lacking dose dependence

C: effect is due to the relative low or high value observed for the control group

Relative organ weights are listed in [Table 10-1](#) (Relative Organ Weights - Summary) and [Table 10-2](#) (Relative Organ Weights - Individual Data). Absolute organ weights are listed in [Table 11-1](#) (Absolute Organ Weights - Summary) and [Table 11-2](#) (Absolute Organ Weights - Individual Data). The body weight at autopsy is given in [Table 2-5](#).

7.3.3 Bone marrow examination

Treatment period

The myeloid:erythroid ratio of the male and female animals treated with **50, 250 or 500 Units allogenic APOSEC™/kg b.w.** three times weekly by intravenous slow bolus injection was not test item-relatedly influenced compared to the control group at the end of the 4-week treatment period.

Recovery period (restricted to groups 1 and 4)

The myeloid:erythroid ratio of the male and female animals previously treated with **500 Units allogenic APOSEC™/kg b.w.** three times weekly by intravenous slow bolus injection was not test item-relatedly influenced compared to the control group at the end of the 14-day treatment-free recovery period.

See [Table 12-1](#) (Bone Marrow - Summary) and [Table 12-2](#) (Bone Marrow - Individual Data) for details.

7.3.4 Microscopic examinations

Treatment period and recovery period (both restricted to groups 1 and 4)

The histological examination of a variety of organs and tissues was restricted to the control group 1 and the high dose group 4 treated with **500 Units allogenic APOSEC™/kg b.w.** three times weekly (main study and recovery animals).

All animals survived until scheduled necropsy and occasional macroscopic findings did not reveal any test item-related changes.

After histopathological assessment of all group 1 and 4 animals in both sexes, no significant and toxicologically relevant test item-related effects could be observed.

Both macroscopic and/or microscopic changes observed were all considered to be normal background alterations which may be seen in untreated mice of this age and strain.

For details see the Phase Report 'Histopathology' in [Appendix 3](#).

8. T A B L E S

Allogenic APOSEC™

TABLE 1-1 Clinical Signs - Local and Systemic Tolerance Mouse
- Summary -

Observation Type: All Types From Day 1 (Start Date) to 30 (Start Date)	Male			
	Group 1: Control	Group 2: 50 Units/kg	Group 3: 250 Units/kg	Group 4: 500 Units/kg
Normal				
Number of Animals Affected	15	10	10	15
First to Last seen	1 - 30	1 - 29	1 - 29	1 - 30
% of Affected Animals	100	100	100	100
Number of Times Recorded	440	290	290	440
Scheduled Removal (Terminal)				
Number of Animals Affected	10	10	10	10
First to Last seen	30	30	30	30
% of Affected Animals	67	100	100	67
Number of Times Recorded	10	10	10	10

Allogenic APOSEC™

TABLE 1-1 Clinical Signs - Local and Systemic Tolerance
- Summary - Mouse

Observation Type: All Types From Day 31 (Start Date) to 44 (Start Date)	Male	
	Group 1: Control	Group 4: 500 Units/kg
Normal		
Number of Animals Affected	5	5
First to Last seen	31 - 43	31 - 43
% of Affected Animals	100	100
Number of Times Recorded	65	65
Scheduled Removal (Terminal)		
Number of Animals Affected	5	5
First to Last seen	44	44
% of Affected Animals	100	100
Number of Times Recorded	5	5

Allogenic APOSEC™

TABLE 1-1 Clinical Signs - Local and Systemic Tolerance Mouse
- Summary -

Observation Type: All Types From Day 1 (Start Date) to 30 (Start Date)	Female			
	Group 1: Control	Group 2: 50 Units/kg	Group 3: 250 Units/kg	Group 4: 500 Units/kg
Normal				
Number of Animals Affected	15	10	10	15
First to Last seen	1 - 30	1 - 29	1 - 29	1 - 30
% of Affected Animals	100	100	100	100
Number of Times Recorded	440	290	290	440
Scheduled Removal (Terminal)				
Number of Animals Affected	10	10	10	10
First to Last seen	30	30	30	30
% of Affected Animals	67	100	100	67
Number of Times Recorded	10	10	10	10

Allogenic APOSEC™

TABLE 1-1 Clinical Signs - Local and Systemic Tolerance
- Summary - Mouse

Observation Type: All Types From Day 31 (Start Date) to 44 (Start Date)	Female	
	Group 1: Control	Group 4: 500 Units/kg
Normal		
Number of Animals Affected	5	5
First to Last seen	31 - 43	31 - 43
% of Affected Animals	100	100
Number of Times Recorded	65	65
Scheduled Removal (Terminal)		
Number of Animals Affected	5	5
First to Last seen	44	44
% of Affected Animals	100	100
Number of Times Recorded	5	5

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 1: Control Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date																				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
2	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
3	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
4	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
5	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
6	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
7	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
8	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
9	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
10	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
11	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
12	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
13	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
14	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

N=Normal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 1: Control Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date																				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
14	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
15	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 1: Control Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date																				
		22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
1	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
2	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
3	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
4	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
5	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
6	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
7	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
8	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
9	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
10	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
11	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
12	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
13	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
14	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal; K=Scheduled Removal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 1: Control Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date																				
		22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
14	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
15	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 1: Control Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date															
		43	44														
1	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
2	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
3	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
4	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
5	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
6	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
7	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
8	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
9	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
10	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
11	Normal	N	.														
	Scheduled Removal (Terminal)	.	K														
12	Normal	N	.														
	Scheduled Removal (Terminal)	.	K														
13	Normal	N	.														
	Scheduled Removal (Terminal)	.	K														
14	Normal	N	.														

N=Normal; K=Scheduled Removal

K=Scheduled Removal; N=Normal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 2: 50 Units/kg Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date																				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
31	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
32	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
33	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
34	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
35	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
36	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
37	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
38	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
39	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
40	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 2: 50 Units/kg Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date																				
		22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
31	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
32	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
33	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
34	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
35	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
36	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
37	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
38	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
39	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
40	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal; K=Scheduled Removal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 3: 250 Units/kg Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date																				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
51	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
52	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
53	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
54	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
55	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
56	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
57	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
58	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
59	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
60	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 3: 250 Units/kg Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date																				
		22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
51	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
52	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
53	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
54	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
55	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
56	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
57	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
58	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
59	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
60	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal; K=Scheduled Removal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 4: 500 Units/kg Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date																				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
71	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
72	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
73	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
74	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
75	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
76	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
77	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
78	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
79	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
80	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
81	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
82	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
83	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 4: 500 Units/kg Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date																				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
84	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
85	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 4: 500 Units/kg Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date																					
		22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	
71	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.	
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.	
72	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.	
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.	
73	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.	
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.	
74	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.	
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.	
75	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.	
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.	
76	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.	
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.	
77	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.	
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.	
78	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.	
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.	
79	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.	
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.	
80	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.	
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.	
81	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
82	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
83	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	

N=Normal; K=Scheduled Removal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 4: 500 Units/kg Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date																				
		22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
84	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
85	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 4: 500 Units/kg Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date															
		43	44														
71	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
72	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
73	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
74	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
75	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
76	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
77	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
78	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
79	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
80	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
81	Normal	N	.														
	Scheduled Removal (Terminal)	.	K														
82	Normal	N	.														
	Scheduled Removal (Terminal)	.	K														
83	Normal	N	.														
	Scheduled Removal (Terminal)	.	K														

N=Normal; K=Scheduled Removal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 4: 500 Units/kg Sex: Male	Observation Type: All Types	Day(s) Relative to Start Date															
		43	44														
84	Normal	N	.														
	Scheduled Removal (Terminal)	.	K														
85	Normal	N	.														
	Scheduled Removal (Terminal)	.	K														

N=Normal; K=Scheduled Removal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 1: Control Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date																				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
16	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
17	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
18	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
19	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
20	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
21	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
22	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
23	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
24	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
25	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
26	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
27	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
28	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
29	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

N=Normal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 1: Control Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date																				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
29	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
30	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 1: Control Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date																				
		22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
16	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
17	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
18	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
19	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
20	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
21	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
22	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
23	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
24	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
25	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
26	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
27	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
28	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
29	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

N=Normal; K=Scheduled Removal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 1: Control Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date																				
		22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
29	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
30	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 1: Control Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date															
		43	44														
16	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
17	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
18	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
19	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
20	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
21	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
22	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
23	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
24	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
25	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
26	Normal	N	.														
	Scheduled Removal (Terminal)	.	K														
27	Normal	N	.														
	Scheduled Removal (Terminal)	.	K														
28	Normal	N	.														
	Scheduled Removal (Terminal)	.	K														
29	Normal	N	.														

N=Normal; K=Scheduled Removal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 2: 50 Units/kg Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date																				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
41	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
42	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
43	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
44	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
45	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
46	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
47	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
48	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
49	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
50	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 2: 50 Units/kg Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date																				
		22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
41	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
42	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
43	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
44	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
45	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
46	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
47	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
48	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
49	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
50	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal; K=Scheduled Removal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 3: 250 Units/kg Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date																				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
61	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
62	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
63	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
64	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
65	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
66	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
67	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
68	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
69	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
70	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 3: 250 Units/kg Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date																				
		22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
61	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
62	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
63	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
64	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
65	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
66	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
67	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
68	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
69	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
70	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal; K=Scheduled Removal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 4: 500 Units/kg Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date																				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
86	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
87	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
88	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
89	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
90	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
91	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
92	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
93	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
94	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
95	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
96	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
97	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
98	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 4: 500 Units/kg Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date																				
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
99	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
100	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 4: 500 Units/kg Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date																				
		22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
86	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
87	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
88	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
89	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
90	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
91	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
92	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
93	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
94	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
95	Normal	N	N	N	N	N	N	N	N	.	.	.	.	.	.	.	.	.	.	.	.	.
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	K	.	.	.	.	.	.	.	.	.	.	.	.
96	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
97	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
98	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal; K=Scheduled Removal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 4: 500 Units/kg Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date																				
		22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
99	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
100	Normal	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Scheduled Removal (Terminal)	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.

N=Normal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 4: 500 Units/kg Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date															
		43	44														
86	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
87	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
88	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
89	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
90	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
91	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
92	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
93	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
94	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
95	Normal	.	.														
	Scheduled Removal (Terminal)	.	.														
96	Normal	N	.														
	Scheduled Removal (Terminal)	.	K														
97	Normal	N	.														
	Scheduled Removal (Terminal)	.	K														
98	Normal	N	.														
	Scheduled Removal (Terminal)	.	K														

N=Normal; K=Scheduled Removal

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local and Systemic Tolerance Mouse
- Individual Data -

Group 4: 500 Units/kg Sex: Female	Observation Type: All Types	Day(s) Relative to Start Date															
		43	44														
99	Normal	N	.														
	Scheduled Removal (Terminal)	.	K														
	Normal	N	.														
	Scheduled Removal (Terminal)	.	K														
100	Normal	N	.														
	Scheduled Removal (Terminal)	.	K														
	Normal	N	.														
	Scheduled Removal (Terminal)	.	K														

N=Normal; K=Scheduled Removal

TABLE 2-1

Body Weight - Summary

Mouse

Body Weight (g)

Sex: Male		Day(s) Relative to Start Date					
		-5 [a]	1 [a]	8 [a]	15 [a]	22 [a1]	29 [a1]
Group 1: Control	Mean	21.73	24.55	25.59	25.31	25.99	27.03
	SD	1.09	0.82	0.85	0.64	0.85	0.85
	N	15	15	15	15	15	15
Group 2: 50 Units/kg	Mean	21.70	24.69	25.69	25.37	26.09	27.05
	SD	1.20	0.63	0.63	0.66	0.47	0.65
	N	10	10	10	10	10	10
	%Diff	-0.1	0.6	0.4	0.3	0.4	0.1
Group 3: 250 Units/kg	Mean	21.72	24.47	25.36	25.23	26.12	26.88
	SD	1.24	0.95	1.17	0.99	1.46	1.60
	N	10	10	10	10	10	10
	%Diff	0.0	-0.3	-0.9	-0.3	0.5	-0.5
Group 4: 500 Units/kg	Mean	22.04	24.31	25.42	25.37	26.53	27.02
	SD	1.24	0.76	0.83	0.65	0.80	0.87
	N	15	15	15	15	15	15
	%Diff	1.4	-1.0	-0.7	0.3	2.1	0.0

[a] - Anova & Dunnett

[a1] - Anova & Dunnett(Rank)

TABLE 2-1 Body Weight - Summary Mouse

Body Weight (g)			
Sex: Male		Day(s) Relative to Start Date	
		36	43
Group 1: Control	Mean	27.60	27.72
	SD	1.16	0.81
	N	5	5
Group 4: 500 Units/kg	Mean	28.12	28.52
	SD	1.01	1.18
	N	5	5
	%Diff	1.9	2.9

Anova & Dunnett

TABLE 2-1

Body Weight - Summary

Mouse

Body Weight (g)

Sex: Female		Day(s) Relative to Start Date					
		-5 [a]	1 [a]	8 [a1]	15 [a]	22 [a1]	29 [a1]
Group 1: Control	Mean	19.07	20.89	21.48	23.17	24.04	24.18
	SD	0.88	0.47	0.65	0.67	0.65	1.15
	N	15	15	15	15	15	15
Group 2: 50 Units/kg	Mean	18.75	20.62	21.09	22.46	23.39	23.90
	SD	0.83	0.79	0.99	1.11	1.25	1.65
	N	10	10	10	10	10	10
	%Diff	-1.7	-1.3	-1.8	-3.1	-2.7	-1.2
Group 3: 250 Units/kg	Mean	19.29	20.60	20.72	22.49	23.42	24.47
	SD	0.92	0.86	0.93	1.13	0.82	0.69
	N	10	10	10	10	10	10
	%Diff	1.1	-1.4	-3.5	-2.9	-2.6	1.2
Group 4: 500 Units/kg	Mean	18.77	20.85	21.23	22.79	24.13	25.05
	SD	1.22	0.44	0.69	0.65	0.42	0.51
	N	15	15	15	15	15	15
	%Diff	-1.6	-0.2	-1.1	-1.6	0.4	3.6

[a] - Anova & Dunnett

[a1] - Anova & Dunnett(Rank)

TABLE 2-1

Body Weight - Summary

Mouse

Body Weight (g)		Day(s) Relative to Start Date	
Sex: Female		36	43
Group 1: Control	Mean	23.50	24.08
	SD	0.55	0.50
	N	5	5
Group 4: 500 Units/kg	Mean	24.42	25.24**
	SD	0.95	0.44
	N	5	5
	%Diff	3.9	4.8

Anova & Dunnett: ** = $p \leq 0.01$

TABLE 2-1 Body Weight - Summary Mouse

<u>Comments and Markers</u>						
<u>Page</u>	<u>Measurement</u>	<u>Group</u>	<u>Sex</u>	<u>Day</u>	<u>Marker</u>	<u>Comment</u>
	Body Weight	4	Female	43	**	Anova & Dunnett: ** = $p \leq 0.01$

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TABLE 2-2 Body Weight - Individual Data Mouse

Sex: Male Body Weight (g)

Group 1: Control	Day(s) Relative to Start Date					
	-5	1	8	15	22	29
1	20.4	23.9	25.0	25.4	26.1	27.3
2	21.0	23.3	23.6	23.8	23.8	25.3
3	20.2	24.8	26.2	26.3	27.0	29.0
4	22.3	24.3	26.1	25.5	26.1	26.5
5	22.8	24.8	26.0	25.5	26.4	27.4
6	22.1	25.0	26.2	25.8	25.9	26.4
7	21.3	24.9	25.8	25.4	26.5	27.3
8	21.1	23.3	25.7	24.6	25.6	26.2
9	23.4	25.5	26.7	25.9	26.2	27.4
10	23.6	25.8	26.7	25.6	26.8	27.1
11	21.3	23.3	24.8	24.3	24.8	26.4
12	23.1	25.3	25.2	25.6	26.0	27.6
13	20.6	24.2	24.5	25.1	25.5	26.5
14	21.4	25.3	25.8	25.6	27.1	27.7
15	21.3	24.6	25.5	25.2	26.1	27.3
Mean	21.73	24.55	25.59	25.31	25.99	27.03
SD	1.09	0.82	0.85	0.64	0.85	0.85
N	15	15	15	15	15	15

TABLE 2-2

Body Weight - Individual Data

Mouse

Sex: Male Body Weight (g)

Group 1: Control	Day(s) Relative to Start Date	
	36	43
11	26.1	26.9
12	28.8	28.7
13	26.8	26.9
14	28.6	28.3
15	27.7	27.8
Mean	27.60	27.72
SD	1.16	0.81
N	5	5

Allogenic APOSEC™

TABLE 2-2 Body Weight - Individual Data Mouse

Sex: Male Body Weight (g)

Group 2: 50 Units/kg	Day(s) Relative to Start Date					
	-5	1	8	15	22	29
31	21.7	25.4	25.8	25.7	26.5	27.4
32	22.8	23.8	24.3	24.1	25.6	26.9
33	20.7	23.7	25.9	25.8	26.0	26.6
34	19.6	24.6	25.6	25.8	26.2	26.3
35	21.8	25.2	26.1	25.6	26.5	28.1
36	22.1	24.3	25.0	25.2	26.2	27.0
37	20.4	24.8	26.2	25.6	26.4	27.8
38	21.8	25.1	26.1	25.5	26.2	27.3
39	22.4	24.5	25.5	24.3	25.0	26.0
40	23.7	25.5	26.4	26.1	26.3	27.1
Mean	21.70	24.69	25.69	25.37	26.09	27.05
SD	1.20	0.63	0.63	0.66	0.47	0.65
N	10	10	10	10	10	10

Allogenic APOSEC™

TABLE 2-2 Body Weight - Individual Data Mouse

Sex: Male Body Weight (g)

Group 3: 250 Units/kg	Day(s) Relative to Start Date					
	-5	1	8	15	22	29
51	23.0	25.9	27.2	27.6	29.2	29.9
52	24.6	26.3	26.4	25.8	26.7	26.8
53	20.7	23.7	23.8	24.0	23.7	24.2
54	22.0	24.5	26.6	25.6	26.7	27.4
55	20.8	23.3	24.9	24.7	25.9	25.3
56	21.5	23.9	24.3	24.3	24.8	25.9
57	21.5	24.4	26.3	25.3	25.1	26.4
58	21.0	24.0	24.4	25.0	26.2	27.7
59	20.6	24.1	24.6	25.0	26.3	26.9
60	21.5	24.6	25.1	25.0	26.6	28.3
Mean	21.72	24.47	25.36	25.23	26.12	26.88
SD	1.24	0.95	1.17	0.99	1.46	1.60
N	10	10	10	10	10	10

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TABLE 2-2 Body Weight - Individual Data Mouse

Sex: Male Body Weight (g)

Group 4: 500 Units/kg	Day(s) Relative to Start Date					
	-5	1	8	15	22	29
71	24.0	25.1	27.0	26.8	28.1	29.0
72	21.6	23.8	24.4	24.9	25.0	26.7
73	20.9	23.5	24.6	25.0	26.6	26.5
74	22.4	24.4	25.7	25.8	26.8	27.7
75	21.9	25.2	26.1	25.4	27.4	28.4
76	20.1	23.1	24.1	24.4	26.1	26.2
77	20.4	24.1	25.3	25.2	26.6	27.3
78	23.0	24.4	26.3	25.7	27.2	27.3
79	21.5	23.9	25.3	25.0	26.0	26.3
80	21.1	23.7	24.8	24.7	25.4	26.0
81	24.2	25.0	26.0	25.5	26.2	27.0
82	23.4	25.6	26.3	26.0	26.9	27.0
83	21.3	23.4	24.5	24.6	25.9	26.4
84	22.3	24.3	25.3	26.2	27.2	27.5
85	22.5	25.1	25.6	25.4	26.5	26.0
Mean	22.04	24.31	25.42	25.37	26.53	27.02
SD	1.24	0.76	0.83	0.65	0.80	0.87
N	15	15	15	15	15	15

TABLE 2-2 Body Weight - Individual Data Mouse

Sex: Male Body Weight (g)

Group 4: 500 Units/kg	Day(s) Relative to Start Date	
	36	43
81	28.2	28.6
82	28.6	28.8
83	27.0	27.3
84	29.5	30.3
85	27.3	27.6
Mean	28.12	28.52
SD	1.01	1.18
N	5	5

TABLE 2-2

Body Weight - Individual Data

Mouse

Sex: Female Body Weight (g)

Group 1: Control	Day(s) Relative to Start Date					
	-5	1	8	15	22	29
16	19.8	21.6	22.0	24.2	24.8	25.3
17	17.8	21.2	22.3	23.7	25.0	25.6
18	18.1	20.6	20.7	22.4	23.8	25.0
19	19.8	20.5	22.1	23.2	24.0	24.9
20	19.8	21.2	21.9	24.0	24.0	24.9
21	18.0	21.2	21.9	23.4	24.1	24.2
22	20.5	21.3	22.1	24.0	25.4	25.8
23	18.8	21.3	22.2	23.4	24.2	23.8
24	19.7	20.3	20.8	22.8	24.1	24.1
25	18.8	20.3	20.9	23.1	23.8	24.0
26	17.9	21.4	20.6	22.3	23.4	23.1
27	18.4	20.0	21.0	22.6	23.0	22.2
28	19.7	20.7	20.8	22.9	23.6	22.4
29	19.1	20.8	21.0	22.0	23.2	22.7
30	19.9	20.9	21.9	23.6	24.2	24.7
Mean	19.07	20.89	21.48	23.17	24.04	24.18
SD	0.88	0.47	0.65	0.67	0.65	1.15
N	15	15	15	15	15	15

TABLE 2-2 Body Weight - Individual Data Mouse

Sex: Female Body Weight (g)

Group 1: Control	Day(s) Relative to Start Date	
	36	43
26	23.0	24.0
27	22.9	24.4
28	23.6	24.7
29	23.8	23.4
30	24.2	23.9
Mean	23.50	24.08
SD	0.55	0.50
N	5	5

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TABLE 2-2 Body Weight - Individual Data Mouse

Sex: Female Body Weight (g)

Group 2: 50 Units/kg	Day(s) Relative to Start Date					
	-5	1	8	15	22	29
41	19.9	21.7	21.9	22.7	24.5	25.7
42	18.4	21.4	21.4	23.7	24.4	25.2
43	18.7	20.7	21.1	22.6	23.6	25.1
44	17.6	19.8	20.8	22.8	23.6	24.3
45	17.9	21.3	22.7	23.3	24.3	25.1
46	18.7	20.1	19.9	21.2	21.5	21.7
47	19.5	21.4	22.2	23.2	23.7	24.4
48	17.8	20.1	21.1	23.0	24.1	23.5
49	19.7	20.3	19.9	20.0	20.8	20.6
50	19.3	19.4	19.9	22.1	23.4	23.4
Mean	18.75	20.62	21.09	22.46	23.39	23.90
SD	0.83	0.79	0.99	1.11	1.25	1.65
N	10	10	10	10	10	10

Allogenic APOSEC™

TABLE 2-2 Body Weight - Individual Data Mouse

Sex: Female Body Weight (g)

Group 3: 250 Units/kg	Day(s) Relative to Start Date					
	-5	1	8	15	22	29
61	19.3	20.5	19.5	20.9	21.9	23.3
62	17.6	20.8	21.6	23.3	24.0	25.0
63	17.8	18.8	19.5	21.4	22.8	23.5
64	19.8	21.2	21.9	23.6	24.3	24.8
65	19.1	20.9	21.5	23.9	23.7	23.7
66	20.4	22.2	21.4	22.8	24.0	24.6
67	19.7	20.7	21.1	23.2	24.2	24.8
68	19.3	20.1	19.6	21.4	23.2	25.1
69	20.1	20.3	20.8	23.2	23.7	24.9
70	19.8	20.5	20.3	21.2	22.4	25.0
Mean	19.29	20.60	20.72	22.49	23.42	24.47
SD	0.92	0.86	0.93	1.13	0.82	0.69
N	10	10	10	10	10	10

Allogenic APOSEC™

TABLE 2-2 Body Weight - Individual Data Mouse

Sex: Female Body Weight (g)

Group 4: 500 Units/kg	Day(s) Relative to Start Date					
	-5	1	8	15	22	29
86	17.8	21.4	21.8	22.6	24.0	25.5
87	20.5	21.4	21.3	23.3	24.5	25.3
88	19.0	20.4	20.5	22.1	23.7	25.1
89	19.0	21.1	21.8	22.9	24.0	25.6
90	17.0	20.9	20.1	22.7	23.3	24.4
91	20.2	20.8	22.2	23.1	24.1	24.4
92	20.4	21.4	22.1	24.2	24.9	25.0
93	18.7	20.8	20.7	22.4	24.3	24.7
94	17.6	20.7	20.6	22.6	23.7	24.6
95	19.2	20.4	22.1	22.7	24.0	25.3
96	19.4	21.4	21.7	23.3	24.8	25.3
97	16.8	20.3	20.7	22.2	24.4	24.7
98	17.3	21.2	21.4	23.8	24.3	25.9
99	19.8	20.4	20.6	22.0	24.0	24.3
100	18.9	20.2	20.9	22.0	23.9	25.6
Mean	18.77	20.85	21.23	22.79	24.13	25.05
SD	1.22	0.44	0.69	0.65	0.42	0.51
N	15	15	15	15	15	15

TABLE 2-2 Body Weight - Individual Data Mouse

Sex: Female Body Weight (g)

Group 4: 500 Units/kg	Day(s) Relative to Start Date	
	36	43
96	24.5	25.0
97	24.5	25.1
98	25.9	26.0
99	23.8	25.2
100	23.4	24.9
Mean	24.42	25.24
SD	0.95	0.44
N	5	5

TABLE 2-3

Body Weight Gain - Summary

Mouse

Body Weight Gain (%)

Sex: Male		Day(s) Relative to Start Date			
		1 → 8	1 → 15	1 → 22	1 → 29
Group 1: Control	Mean	4.24	3.11	5.89	10.12
	SD	2.68	2.03	2.45	3.15
	N	15	15	15	15
Group 2: 50 Units/kg	Mean	4.07	2.78	5.71	9.59
	SD	2.15	2.65	2.33	2.69
	N	10	10	10	10
Group 3: 250 Units/kg	Mean	3.65	3.13	6.75	9.85
	SD	3.12	2.51	4.35	5.01
	N	10	10	10	10
Group 4: 500 Units/kg	Mean	4.59	4.42	9.17	11.21
	SD	1.64	2.12	3.00	3.28
	N	15	15	15	15

TABLE 2-3 Body Weight Gain - Summary Mouse

Body Weight Gain (%)

Sex: Male		Day(s) Relative to Start Date	
		29 → 36	29 → 43
Group 1: Control	Mean	1.81	2.28
	SD	2.11	0.98
	N	5	5
Group 4: 500 Units/kg	Mean	4.98	6.47
	SD	1.86	2.43
	N	5	5

TABLE 2-3

Body Weight Gain - Summary

Mouse

Body Weight Gain (%)

Sex: Female		Day(s) Relative to Start Date			
		1 → 8	1 → 15	1 → 22	1 → 29
Group 1: Control	Mean	2.86	10.97	15.12	15.77
	SD	2.68	2.83	2.70	4.97
	N	15	15	15	15
Group 2: 50 Units/kg	Mean	2.28	8.98	13.49	15.90
	SD	2.82	5.13	5.75	6.56
	N	10	10	10	10
Group 3: 250 Units/kg	Mean	0.62	9.24	13.80	18.93
	SD	3.29	5.06	4.49	5.01
	N	10	10	10	10
Group 4: 500 Units/kg	Mean	1.83	9.30	15.73	20.14
	SD	2.99	1.91	2.31	2.91
	N	15	15	15	15

TABLE 2-3 Body Weight Gain - Summary Mouse

Body Weight Gain (%)

Sex: Female		Day(s) Relative to Start Date	
		29 → 36	29 → 43
Group 1: Control	Mean	2.18	4.78
	SD	3.27	5.58
	N	5	5
Group 4: 500 Units/kg	Mean	-2.92	0.36
	SD	3.39	2.49
	N	5	5

TABLE 2-4

Body Weight Gain - Individual Data

Mouse

Sex: Male Body Weight Gain (%)

Group 1: Control	Day(s) Relative to Start Date			
	1 → 8	1 → 15	1 → 22	1 → 29
1	4.6	6.3	9.2	14.2
2	1.3	2.1	2.1	8.6
3	5.6	6.0	8.9	16.9
4	7.4	4.9	7.4	9.1
5	4.8	2.8	6.5	10.5
6	4.8	3.2	3.6	5.6
7	3.6	2.0	6.4	9.6
8	10.3	5.6	9.9	12.4
9	4.7	1.6	2.7	7.5
10	3.5	-0.8	3.9	5.0
11	6.4	4.3	6.4	13.3
12	-0.4	1.2	2.8	9.1
13	1.2	3.7	5.4	9.5
14	2.0	1.2	7.1	9.5
15	3.7	2.4	6.1	11.0
Mean	4.24	3.11	5.89	10.12
SD	2.68	2.03	2.45	3.15
N	15	15	15	15

TABLE 2-4 Body Weight Gain - Individual Data Mouse

Sex: Male Body Weight Gain (%)

Group 1: Control	Day(s) Relative to Start Date	
	29 → 36	29 → 43
11	-1.1	1.9
12	4.3	4.0
13	1.1	1.5
14	3.2	2.2
15	1.5	1.8
Mean	1.81	2.28
SD	2.11	0.98
N	5	5

TABLE 2-4

Body Weight Gain - Individual Data

Mouse

Sex: Male Body Weight Gain (%)

Group 2: 50 Units/kg	Day(s) Relative to Start Date			
	1 → 8	1 → 15	1 → 22	1 → 29
31	1.6	1.2	4.3	7.9
32	2.1	1.3	7.6	13.0
33	9.3	8.9	9.7	12.2
34	4.1	4.9	6.5	6.9
35	3.6	1.6	5.2	11.5
36	2.9	3.7	7.8	11.1
37	5.6	3.2	6.5	12.1
38	4.0	1.6	4.4	8.8
39	4.1	-0.8	2.0	6.1
40	3.5	2.4	3.1	6.3
Mean	4.07	2.78	5.71	9.59
SD	2.15	2.65	2.33	2.69
N	10	10	10	10

TABLE 2-4

Body Weight Gain - Individual Data

Mouse

Sex: Male Body Weight Gain (%)

Group 3: 250 Units/kg	Day(s) Relative to Start Date			
	1 → 8	1 → 15	1 → 22	1 → 29
51	5.0	6.6	12.7	15.4
52	0.4	-1.9	1.5	1.9
53	0.4	1.3	0.0	2.1
54	8.6	4.5	9.0	11.8
55	6.9	6.0	11.2	8.6
56	1.7	1.7	3.8	8.4
57	7.8	3.7	2.9	8.2
58	1.7	4.2	9.2	15.4
59	2.1	3.7	9.1	11.6
60	2.0	1.6	8.1	15.0
Mean	3.65	3.13	6.75	9.85
SD	3.12	2.51	4.35	5.01
N	10	10	10	10

TABLE 2-4

Body Weight Gain - Individual Data

Mouse

Sex: Male Body Weight Gain (%)

Group 4: 500 Units/kg	Day(s) Relative to Start Date			
	1 → 8	1 → 15	1 → 22	1 → 29
71	7.6	6.8	12.0	15.5
72	2.5	4.6	5.0	12.2
73	4.7	6.4	13.2	12.8
74	5.3	5.7	9.8	13.5
75	3.6	0.8	8.7	12.7
76	4.3	5.6	13.0	13.4
77	5.0	4.6	10.4	13.3
78	7.8	5.3	11.5	11.9
79	5.9	4.6	8.8	10.0
80	4.6	4.2	7.2	9.7
81	4.0	2.0	4.8	8.0
82	2.7	1.6	5.1	5.5
83	4.7	5.1	10.7	12.8
84	4.1	7.8	11.9	13.2
85	2.0	1.2	5.6	3.6
Mean	4.59	4.42	9.17	11.21
SD	1.64	2.12	3.00	3.28
N	15	15	15	15

TABLE 2-4 Body Weight Gain - Individual Data Mouse

Sex: Male Body Weight Gain (%)

Group 4: 500 Units/kg	Day(s) Relative to Start Date	
	29 → 36	29 → 43
81	4.4	5.9
82	5.9	6.7
83	2.3	3.4
84	7.3	10.2
85	5.0	6.2
Mean	4.98	6.47
SD	1.86	2.43
N	5	5

TABLE 2-4

Body Weight Gain - Individual Data

Mouse

Sex: Female Body Weight Gain (%)

Group 1: Control	Day(s) Relative to Start Date			
	1 → 8	1 → 15	1 → 22	1 → 29
16	1.9	12.0	14.8	17.1
17	5.2	11.8	17.9	20.8
18	0.5	8.7	15.5	21.4
19	7.8	13.2	17.1	21.5
20	3.3	13.2	13.2	17.5
21	3.3	10.4	13.7	14.2
22	3.8	12.7	19.2	21.1
23	4.2	9.9	13.6	11.7
24	2.5	12.3	18.7	18.7
25	3.0	13.8	17.2	18.2
26	-3.7	4.2	9.3	7.9
27	5.0	13.0	15.0	11.0
28	0.5	10.6	14.0	8.2
29	1.0	5.8	11.5	9.1
30	4.8	12.9	15.8	18.2
Mean	2.86	10.97	15.12	15.77
SD	2.68	2.83	2.70	4.97
N	15	15	15	15

TABLE 2-4 Body Weight Gain - Individual Data Mouse

Sex: Female Body Weight Gain (%)

Group 1: Control	Day(s) Relative to Start Date	
	29 → 36	29 → 43
26	-0.4	3.9
27	3.2	9.9
28	5.4	10.3
29	4.8	3.1
30	-2.0	-3.2
Mean	2.18	4.78
SD	3.27	5.58
N	5	5

TABLE 2-4

Body Weight Gain - Individual Data

Mouse

Sex: Female Body Weight Gain (%)

Group 2: 50 Units/kg	Day(s) Relative to Start Date			
	1 → 8	1 → 15	1 → 22	1 → 29
41	0.9	4.6	12.9	18.4
42	0.0	10.7	14.0	17.8
43	1.9	9.2	14.0	21.3
44	5.1	15.2	19.2	22.7
45	6.6	9.4	14.1	17.8
46	-1.0	5.5	7.0	8.0
47	3.7	8.4	10.7	14.0
48	5.0	14.4	19.9	16.9
49	-2.0	-1.5	2.5	1.5
50	2.6	13.9	20.6	20.6
Mean	2.28	8.98	13.49	15.90
SD	2.82	5.13	5.75	6.56
N	10	10	10	10

TABLE 2-4

Body Weight Gain - Individual Data

Mouse

Sex: Female Body Weight Gain (%)

Group 3: 250 Units/kg	Day(s) Relative to Start Date			
	1 → 8	1 → 15	1 → 22	1 → 29
61	-4.9	2.0	6.8	13.7
62	3.8	12.0	15.4	20.2
63	3.7	13.8	21.3	25.0
64	3.3	11.3	14.6	17.0
65	2.9	14.4	13.4	13.4
66	-3.6	2.7	8.1	10.8
67	1.9	12.1	16.9	19.8
68	-2.5	6.5	15.4	24.9
69	2.5	14.3	16.7	22.7
70	-1.0	3.4	9.3	22.0
Mean	0.62	9.24	13.80	18.93
SD	3.29	5.06	4.49	5.01
N	10	10	10	10

TABLE 2-4

Body Weight Gain - Individual Data

Mouse

Sex: Female Body Weight Gain (%)

Group 4: 500 Units/kg	Day(s) Relative to Start Date			
	1 → 8	1 → 15	1 → 22	1 → 29
86	1.9	5.6	12.1	19.2
87	-0.5	8.9	14.5	18.2
88	0.5	8.3	16.2	23.0
89	3.3	8.5	13.7	21.3
90	-3.8	8.6	11.5	16.7
91	6.7	11.1	15.9	17.3
92	3.3	13.1	16.4	16.8
93	-0.5	7.7	16.8	18.8
94	-0.5	9.2	14.5	18.8
95	8.3	11.3	17.6	24.0
96	1.4	8.9	15.9	18.2
97	2.0	9.4	20.2	21.7
98	0.9	12.3	14.6	22.2
99	1.0	7.8	17.6	19.1
100	3.5	8.9	18.3	26.7
Mean	1.83	9.30	15.73	20.14
SD	2.99	1.91	2.31	2.91
N	15	15	15	15

TABLE 2-4

Body Weight Gain - Individual Data

Mouse

Sex: Female Body Weight Gain (%)

Group 4: 500 Units/kg	Day(s) Relative to Start Date	
	29 → 36	29 → 43
96	-3.2	-1.2
97	-0.8	1.6
98	0.0	0.4
99	-2.1	3.7
100	-8.6	-2.7
Mean	-2.92	0.36
SD	3.39	2.49
N	5	5

TABLE 2-5

Body Weight at Autopsy - Individual Data

Mouse

Sex: Male Body Weight at Autopsy (g)

Group 1: Control	Day(s) Relative to Start Date	
	30	44
1	20.8	-
2	19.2	-
3	22.2	-
4	19.8	-
5	21.0	-
6	24.5	-
7	21.5	-
8	20.3	-
9	21.4	-
10	21.0	-
11	-	20.6
12	-	22.6
13	-	21.1
14	-	22.0
15	-	21.7
Mean	21.17	21.60
SD	1.45	0.78
N	10	5

TABLE 2-5 Body Weight at Autopsy - Individual Data Mouse

Sex: Male Body Weight at Autopsy (g)

Group 2: 50 Units/kg	Day(s) Relative to Start Date	
	30	44
31	20.2	-
32	20.5	-
33	20.7	-
34	19.8	-
35	21.1	-
36	20.6	-
37	20.8	-
38	21.3	-
39	20.0	-
40	21.0	-
Mean	20.60	-
SD	0.49	-
N	10	-

TABLE 2-5

Body Weight at Autopsy - Individual Data

Mouse

Sex: Male Body Weight at Autopsy (g)

Group 3: 250 Units/kg	Day(s) Relative to Start Date	
	30	44
51	23.2	-
52	21.4	-
53	18.4	-
54	21.6	-
55	20.3	-
56	20.0	-
57	20.4	-
58	21.9	-
59	20.4	-
60	20.5	-
Mean	20.81	-
SD	1.29	-
N	10	-

TABLE 2-5

Body Weight at Autopsy - Individual Data

Mouse

Sex: Male Body Weight at Autopsy (g)

Group 4: 500 Units/kg	Day(s) Relative to Start Date	
	30	44
71	22.5	-
72	21.3	-
73	20.6	-
74	21.3	-
75	22.1	-
76	19.6	-
77	21.2	-
78	22.4	-
79	20.2	-
80	19.8	-
81	-	22.2
82	-	22.4
83	-	21.5
84	-	22.7
85	-	21.3
Mean	21.10	22.02
SD	1.04	0.60
N	10	5

TABLE 2-5

Body Weight at Autopsy - Individual Data

Mouse

Sex: Female Body Weight at Autopsy (g)

Group 1: Control	Day(s) Relative to Start Date	
	30	44
16	18.3	-
17	19.3	-
18	17.9	-
19	18.4	-
20	19.2	-
21	17.9	-
22	19.4	-
23	17.9	-
24	18.2	-
25	17.7	-
26	-	17.6
27	-	16.8
28	-	17.6
29	-	17.3
30	-	17.7
Mean	18.42	17.40
SD	0.64	0.37
N	10	5

TABLE 2-5

Body Weight at Autopsy - Individual Data

Mouse

Sex: Female Body Weight at Autopsy (g)

Group 2: 50 Units/kg	Day(s) Relative to Start Date	
	30	44
41	18.5	-
42	17.7	-
43	19.0	-
44	18.0	-
45	18.8	-
46	16.6	-
47	18.4	-
48	17.1	-
49	14.8	-
50	16.8	-
Mean	17.57	-
SD	1.28	-
N	10	-

TABLE 2-5

Body Weight at Autopsy - Individual Data

Mouse

Sex: Female Body Weight at Autopsy (g)

Group 3: 250 Units/kg	Day(s) Relative to Start Date	
	30	44
61	16.1	-
62	19.9	-
63	17.3	-
64	17.7	-
65	16.7	-
66	18.3	-
67	18.2	-
68	16.7	-
69	18.5	-
70	17.0	-
Mean	17.64	-
SD	1.12	-
N	10	-

TABLE 2-5

Body Weight at Autopsy - Individual Data

Mouse

Sex: Female Body Weight at Autopsy (g)

Group 4: 500 Units/kg	Day(s) Relative to Start Date	
	30	44
86	19.0	-
87	19.0	-
88	18.2	-
89	19.3	-
90	17.0	-
91	17.9	-
92	17.8	-
93	18.6	-
94	17.9	-
95	18.3	-
96	-	18.1
97	-	17.6
98	-	19.0
99	-	19.4
100	-	18.2
Mean	18.30	18.46
SD	0.69	0.73
N	10	5

TABLE 3-1

Food Consumption - Summary

Mouse

Relative Food Consumption (g/kg b.w./day)

Sex: Male		Day(s) Relative to Start Date			
		TW 1 [a]	TW 2 [a]	TW 3 [a]	TW 4 [a1]
Group 1: Control	Mean	202.12	213.55	197.66	189.61
	SD	16.04	23.61	8.80	10.20
	N	15	15	15	15
Group 2: 50 Units/kg	Mean	203.42	218.79	207.45	191.65
	SD	21.64	28.22	22.63	18.37
	N	10	10	10	10
	%Diff	0.6	2.5	4.9	1.1
Group 3: 250 Units/kg	Mean	221.91	215.62	206.41	191.93
	SD	29.47	25.32	21.28	18.27
	N	10	10	10	10
	%Diff	9.8	1.0	4.4	1.2
Group 4: 500 Units/kg	Mean	232.00**	232.85	214.99	193.55
	SD	37.48	50.22	44.08	20.83
	N	15	15	15	15
	%Diff	14.8	9.0	8.8	2.1

[a] - Anova & Dunnett(Rank): ** = $p \leq 0.01$

[a1] - Anova & Dunnett

TABLE 3-1

Food Consumption - Summary

Mouse

Relative Food Consumption (g/kg b.w./day)

Sex: Male		Day(s) Relative to Start Date	
		TW 5	TW 6
Group 1: Control	Mean	174.07	192.58
	SD	14.75	10.82
	N	5	5
Group 4: 500 Units/kg	Mean	202.03	220.53
	SD	22.88	32.65
	N	5	5
	%Diff	16.1	14.5

Anova & Dunnett

TABLE 3-1

Food Consumption - Summary

Mouse

Relative Food Consumption (g/kg b.w./day)

Sex: Female		Day(s) Relative to Start Date			
		TW 1	TW 2	TW 3	TW 4
Group 1: Control	Mean	284.53	246.44	242.80	230.31
	SD	33.56	26.95	26.49	24.38
	N	15	15	15	15
Group 2: 50 Units/kg	Mean	282.73	256.59	237.93	222.08
	SD	21.54	20.64	22.84	14.97
	N	10	10	10	10
	%Diff	-0.6	4.1	-2.0	-3.6
Group 3: 250 Units/kg	Mean	286.75	254.60	234.20	220.52
	SD	23.64	18.08	16.19	16.00
	N	10	10	10	10
	%Diff	0.8	3.3	-3.5	-4.2
Group 4: 500 Units/kg	Mean	278.34	251.93	225.46	219.51
	SD	17.14	29.54	21.03	22.00
	N	15	15	15	15
	%Diff	-2.2	2.2	-7.1	-4.7

Anova & Dunnett

TABLE 3-1

Food Consumption - Summary

Mouse

Relative Food Consumption (g/kg b.w./day)

Sex: Female		Day(s) Relative to Start Date	
		TW 5	TW 6
Group 1: Control	Mean	245.59	221.78
	SD	20.47	25.25
	N	5	5
Group 4: 500 Units/kg	Mean	236.75	228.14
	SD	15.29	25.05
	N	5	5
	%Diff	-3.6	2.9

Anova & Dunnett

TABLE 3-1 Food Consumption - Summary Mouse

<u>Comments and Markers</u>						
<u>Page</u>	<u>Measurement</u>	<u>Group</u>	<u>Sex</u>	<u>Day</u>	<u>Marker</u>	<u>Comment</u>
	Relative Food Consumption	4	Male	TW 1	**	Anova & Dunnett(Rank): ** = $p \leq 0.01$

TABLE 3-2 Food Consumption - Individual Data Mouse

Sex: Male Relative Food Consumption (g/kg b.w./day)

Group 1: Control	Day(s) Relative to Start Date			
	TW 1	TW 2	TW 3	TW 4
1	206.9	286.3	209.1	185.2
2	166.5	201.7	198.1	185.8
3	204.5	204.8	197.4	196.1
4	198.7	204.5	205.8	215.6
5	208.8	223.5	209.4	192.4
6	208.8	218.7	191.9	186.7
7	189.4	210.3	192.5	180.5
8	192.3	214.9	207.6	191.9
9	183.5	178.2	185.4	175.2
10	231.7	216.0	204.7	193.5
11	199.9	212.2	188.9	180.2
12	205.8	205.9	203.8	186.3
13	228.6	229.4	197.8	187.6
14	204.3	203.7	189.2	182.6
15	202.2	193.3	183.4	204.6
Mean	202.12	213.55	197.66	189.61
SD	16.04	23.61	8.80	10.20
N	15	15	15	15

TABLE 3-2 Food Consumption - Individual Data Mouse

Sex: Male Relative Food Consumption (g/kg b.w./day)

Group 1: Control	Day(s) Relative to Start Date	
	TW 5	TW 6
11	180.1	196.5
12	188.0	188.2
13	175.9	185.9
14	177.3	182.7
15	149.0	209.7
Mean	174.07	192.58
SD	14.75	10.82
N	5	5

TABLE 3-2 Food Consumption - Individual Data Mouse

Sex: Male Relative Food Consumption (g/kg b.w./day)

Group 2: 50 Units/kg	Day(s) Relative to Start Date			
	TW 1	TW 2	TW 3	TW 4
31	158.9	255.1	193.0	226.3
32	219.3	223.5	234.4	184.8
33	204.6	198.2	191.8	175.6
34	223.2	213.2	210.5	207.5
35	198.1	190.8	186.5	199.8
36	174.9	184.2	178.8	167.7
37	226.3	258.4	239.7	178.8
38	216.2	256.0	233.9	204.6
39	201.7	206.9	189.1	174.7
40	211.0	201.4	216.7	196.6
Mean	203.42	218.79	207.45	191.65
SD	21.64	28.22	22.63	18.37
N	10	10	10	10

TABLE 3-2 Food Consumption - Individual Data Mouse

Sex: Male Relative Food Consumption (g/kg b.w./day)

Group 3: 250 Units/kg	Day(s) Relative to Start Date			
	TW 1	TW 2	TW 3	TW 4
51	199.6	207.6	206.0	207.4
52	215.9	209.3	204.9	179.1
53	226.3	230.4	221.8	217.8
54	187.4	183.6	177.6	176.7
55	219.2	207.1	197.5	190.3
56	264.6	268.7	251.2	219.5
57	204.8	195.9	190.7	171.0
58	211.9	198.9	193.6	179.0
59	282.2	244.6	226.0	201.8
60	207.2	210.3	195.0	176.7
Mean	221.91	215.62	206.41	191.93
SD	29.47	25.32	21.28	18.27
N	10	10	10	10

TABLE 3-2 Food Consumption - Individual Data Mouse

Sex: Male Relative Food Consumption (g/kg b.w./day)

Group 4: 500 Units/kg	Day(s) Relative to Start Date			
	TW 1	TW 2	TW 3	TW 4
71	186.8	195.1	185.6	166.5
72	229.5	205.4	190.9	177.6
73	212.5	206.3	189.0	173.0
74	214.0	215.9	187.1	191.9
75	220.0	195.2	173.6	171.0
76	207.5	246.5	209.1	221.9
77	214.6	206.9	206.8	174.8
78	207.5	205.7	183.3	187.3
79	275.0	318.9	248.4	230.3
80	342.7	331.4	352.1	172.0
81	255.5	328.3	251.9	218.5
82	235.7	189.0	214.6	201.1
83	238.5	224.2	216.2	208.9
84	231.5	215.9	215.9	205.7
85	208.7	208.1	200.5	202.7
Mean	232.00	232.85	214.99	193.55
SD	37.48	50.22	44.08	20.83
N	15	15	15	15

TABLE 3-2 Food Consumption - Individual Data Mouse

Sex: Male Relative Food Consumption (g/kg b.w./day)

Group 4: 500 Units/kg	Day(s) Relative to Start Date	
	TW 5	TW 6
81	238.1	254.2
82	189.8	189.5
83	200.5	210.9
84	204.8	256.0
85	176.9	192.0
Mean	202.03	220.53
SD	22.88	32.65
N	5	5

TABLE 3-2 Food Consumption - Individual Data Mouse

Sex: Female Relative Food Consumption (g/kg b.w./day)

Group 1: Control	Day(s) Relative to Start Date			
	TW 1	TW 2	TW 3	TW 4
16	281.2	220.8	210.8	188.6
17	238.9	202.5	206.3	196.4
18	318.2	273.6	265.9	254.9
19	282.5	235.8	253.6	214.0
20	210.0	222.6	222.6	207.7
21	277.9	239.3	231.8	224.3
22	305.1	241.7	237.9	227.0
23	283.1	243.0	273.9	255.1
24	343.4	310.8	278.6	250.1
25	277.5	247.4	273.1	247.6
26	282.2	251.8	232.6	233.8
27	310.2	263.0	270.2	270.9
28	252.7	220.2	205.2	220.0
29	321.1	277.3	259.9	253.6
30	283.8	247.0	219.6	210.5
Mean	284.53	246.44	242.80	230.31
SD	33.56	26.95	26.49	24.38
N	15	15	15	15

TABLE 3-2 Food Consumption - Individual Data Mouse

Sex: Female Relative Food Consumption (g/kg b.w./day)

Group 1: Control	Day(s) Relative to Start Date	
	TW 5	TW 6
26	236.6	231.5
27	266.4	248.2
28	215.5	193.8
29	247.9	239.3
30	261.5	196.1
Mean	245.59	221.78
SD	20.47	25.25
N	5	5

TABLE 3-2 Food Consumption - Individual Data Mouse

Sex: Female Relative Food Consumption (g/kg b.w./day)

Group 2: 50 Units/kg	Day(s) Relative to Start Date			
	TW 1	TW 2	TW 3	TW 4
41	272.7	259.9	235.0	213.5
42	283.7	270.6	231.3	223.4
43	263.4	259.2	207.6	208.9
44	262.4	235.0	227.6	212.8
45	264.3	233.0	233.4	209.4
46	279.3	242.6	221.3	216.6
47	267.1	234.0	219.4	211.4
48	299.9	257.8	257.9	249.8
49	318.0	291.4	280.9	245.5
50	316.6	282.5	265.0	229.5
Mean	282.73	256.59	237.93	222.08
SD	21.54	20.64	22.84	14.97
N	10	10	10	10

TABLE 3-2 Food Consumption - Individual Data Mouse

Sex: Female Relative Food Consumption (g/kg b.w./day)

Group 3: 250 Units/kg	Day(s) Relative to Start Date			
	TW 1	TW 2	TW 3	TW 4
61	298.9	248.8	252.4	225.6
62	249.3	234.2	216.7	197.1
63	265.2	251.0	213.0	213.4
64	307.2	277.8	229.9	233.3
65	294.4	260.6	258.6	244.7
66	268.4	233.1	235.7	224.2
67	274.9	234.0	213.7	211.4
68	317.8	279.0	245.7	220.8
69	274.0	252.5	244.1	237.5
70	317.4	274.9	232.1	197.1
Mean	286.75	254.60	234.20	220.52
SD	23.64	18.08	16.19	16.00
N	10	10	10	10

TABLE 3-2 Food Consumption - Individual Data Mouse

Sex: Female Relative Food Consumption (g/kg b.w./day)

Group 4: 500 Units/kg	Day(s) Relative to Start Date			
	TW 1	TW 2	TW 3	TW 4
86	305.4	207.3	208.3	234.7
87	285.7	248.3	222.7	224.2
88	282.9	276.0	262.2	273.2
89	244.4	219.6	209.5	193.1
90	260.1	230.3	206.6	193.8
91	294.7	276.4	203.3	225.4
92	267.6	253.2	230.1	233.7
93	283.6	246.2	213.4	186.8
94	279.5	283.2	254.4	232.9
95	254.0	232.9	219.6	204.4
96	295.6	270.4	244.2	214.0
97	277.4	269.0	260.5	237.7
98	263.7	240.1	221.0	208.5
99	286.4	212.3	228.6	219.9
100	293.9	313.6	197.3	210.4
Mean	278.34	251.93	225.46	219.51
SD	17.14	29.54	21.03	22.00
N	15	15	15	15

TABLE 3-2 Food Consumption - Individual Data Mouse

Sex: Female Relative Food Consumption (g/kg b.w./day)

Group 4: 500 Units/kg	Day(s) Relative to Start Date	
	TW 5	TW 6
96	222.2	211.4
97	241.4	267.5
98	219.0	202.7
99	250.3	233.6
100	250.9	225.5
Mean	236.75	228.14
SD	15.29	25.05
N	5	5

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 25 Relative to Start Date

Sex: Male		Haematological Parameters					
		HGB	RBC	WBC	Reti	PLT	HCT
		(mmol/L)	(x10E6/ μ L)	(x10E3/ μ L)	(%)	(x10E3/ μ L)	(%)
		[a]	[a]	[a]	[a]	[a1]	[a]
Group 1: Control	Mean	9.67	10.293	7.803	3.09	1206.6	50.64
	SD	0.16	0.246	1.024	0.22	82.5	0.97
	N	10	10	10	10	10	10
Group 2: 50 Units/kg	Mean	9.52	10.093	8.016	3.28	1149.2	49.86
	SD	0.32	0.273	1.747	0.34	134.1	1.40
	N	10	10	10	10	10	10
	%Diff	-1.6	-1.9	2.7	6.1	-4.8	-1.5
Group 3: 250 Units/kg	Mean	9.58	10.115	7.134	3.06	1155.7	49.92
	SD	0.25	0.259	0.968	0.29	71.0	1.24
	N	10	10	10	10	10	10
	%Diff	-0.9	-1.7	-8.6	-1.0	-4.2	-1.4
Group 4: 500 Units/kg	Mean	9.50	10.037	7.626	3.26	1085.0**	49.52
	SD	0.28	0.325	1.329	0.18	55.5	1.51
	N	10	10	10	10	10	10
	%Diff	-1.8	-2.5	-2.3	5.5	-10.1	-2.2

[a] - Anova & Dunnett

[a1] - Anova & Dunnett(Rank): ** = $p \leq 0.01$

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 39 Relative to Start Date

Sex: Male		Haematological Parameters					
		HGB	RBC	WBC	Reti	PLT	HCT
		(mmol/L)	(x10E6/ μ L)	(x10E3/ μ L)	(%)	(x10E3/ μ L)	(%)
		[a]	[a]	[a1]	[a]	[a]	[a]
Group 1: Control	Mean	9.52	10.286	7.534	3.08	1161.4	49.30
	SD	0.25	0.222	0.492	0.18	31.0	1.29
	N	5	5	5	5	5	5
Group 4: 500 Units/kg	Mean	9.48	10.072	8.930	2.96	1158.2	48.74
	SD	0.33	0.293	1.985	0.17	46.6	1.54
	N	5	5	5	5	5	5
	%Diff	-0.4	-2.1	18.5	-3.9	-0.3	-1.1

[a] - Anova & Dunnett

[a1] - Anova & Dunnett(Rank)

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 25 Relative to Start Date

Sex: Male		Haematological Parameters					
		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
Group 1: Control	Mean	7.05	88.69	1.34	1.93	0.71	0.29
	SD	0.70	0.93	0.32	0.28	0.12	0.07
	N	10	10	10	10	10	10
Group 2: 50 Units/kg	Mean	12.55	82.75	1.43	1.96	0.98	0.34
	SD	11.97	12.47	0.46	0.29	0.43	0.07
	N	10	10	10	10	10	10
	%Diff	78.0	-6.7	6.7	1.6	38.0	17.2
Group 3: 250 Units/kg	Mean	6.76	89.17	1.33	1.74	0.68	0.31
	SD	1.39	1.78	0.25	0.31	0.22	0.11
	N	10	10	10	10	10	10
	%Diff	-4.1	0.5	-0.7	-9.8	-4.2	6.9
Group 4: 500 Units/kg	Mean	7.62	87.64	1.36	2.26	0.82	0.31
	SD	1.31	1.50	0.29	0.53	0.19	0.10
	N	10	10	10	10	10	10
	%Diff	8.1	-1.2	1.5	17.1	15.5	6.9

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 39 Relative to Start Date

Sex: Male		Haematological Parameters					
		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
Group 1: Control	Mean	10.52	84.86	1.22	2.46	0.70	0.30
	SD	4.19	4.54	0.31	0.56	0.20	0.10
	N	5	5	5	5	5	5
Group 4: 500 Units/kg	Mean	8.12	87.26	1.34	2.16	0.88	0.26
	SD	2.96	3.84	0.29	0.71	0.38	0.09
	N	5	5	5	5	5	5
	%Diff	-22.8	2.8	9.8	-12.2	25.7	-13.3

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 25 Relative to Start Date

Sex: Male		Haematological Parameters					
		Neut	Lym	Mono	Eos	LUC	Baso
		(x10E3/ μ L)	(x10E3/ μ L)	(x10E3/ μ L)	(x10E3/ μ L)	(x10E3/ μ L)	(x10E3/ μ L)
		[a]	[a1]	[a1]	[a2]	[a2]	[a]
Group 1: Control	Mean	0.547	6.926	0.104	0.148	0.056	0.023
	SD	0.061	0.949	0.025	0.020	0.017	0.007
	N	10	10	10	10	10	10
Group 2: 50 Units/kg	Mean	1.033	6.609	0.110	0.153	0.083	0.027
	SD	1.153	1.637	0.032	0.033	0.051	0.009
	N	10	10	10	10	10	10
	%Diff	88.8	-4.6	5.8	3.4	48.2	17.4
Group 3: 250 Units/kg	Mean	0.492	6.349	0.097	0.125	0.051	0.024
	SD	0.165	0.746	0.028	0.030	0.019	0.008
	N	10	10	10	10	10	10
	%Diff	-10.1	-8.3	-6.7	-15.5	-8.9	4.3
Group 4: 500 Units/kg	Mean	0.574	6.690	0.101	0.175	0.062	0.024
	SD	0.112	1.206	0.023	0.057	0.021	0.007
	N	10	10	10	10	10	10
	%Diff	4.9	-3.4	-2.9	18.2	10.7	4.3

[a] - Anova & Dunnett(Rank)

[a1] - Anova & Dunnett

[a2] - Anova & Dunnett(Log)

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 39 Relative to Start Date

Sex: Male		Haematological Parameters					
		Neut	Lym	Mono	Eos	LUC	Baso
		(x10E3/ μ L)	(x10E3/ μ L)	(x10E3/ μ L)	(x10E3/ μ L)	(x10E3/ μ L)	(x10E3/ μ L)
		[a]	[a1]	[a2]	[a2]	[a1]	[a1]
Group 1: Control	Mean	0.790	6.394	0.092	0.186	0.054	0.022
	SD	0.310	0.556	0.026	0.049	0.018	0.008
	N	5	5	5	5	5	5
Group 4: 500 Units/kg	Mean	0.742	7.766	0.118	0.192	0.082	0.026
	SD	0.411	1.613	0.047	0.094	0.040	0.013
	N	5	5	5	5	5	5
	%Diff	-6.1	21.5	28.3	3.2	51.9	18.2

[a] - Anova & Dunnett(Rank)

[a1] - Anova & Dunnett

[a2] - Anova & Dunnett(Log)

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 25 Relative to Start Date

Sex: Male		Haematological Parameters		
		MCV	MCH	MCHC
		(fL)	(fmol)	(mmol/L)
		[a]	[a]	[a]
Group 1: Control	Mean	49.22	0.941	19.123
	SD	0.37	0.017	0.225
	N	10	10	10
Group 2: 50 Units/kg	Mean	49.40	0.944	19.089
	SD	0.48	0.013	0.206
	N	10	10	10
	%Diff	0.4	0.3	-0.2
Group 3: 250 Units/kg	Mean	49.37	0.949	19.212
	SD	0.34	0.010	0.175
	N	10	10	10
	%Diff	0.3	0.9	0.5
Group 4: 500 Units/kg	Mean	49.34	0.946	19.173
	SD	0.25	0.008	0.146
	N	10	10	10
	%Diff	0.2	0.5	0.3

[a] - Anova & Dunnett

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 39 Relative to Start Date

Sex: Male		Haematological Parameters		
		MCV	MCH	MCHC
		(fL)	(fmol)	(mmol/L)
		[a]	[a]	[a]
Group 1: Control	Mean	47.90	0.926	19.320
	SD	0.36	0.011	0.137
	N	5	5	5
Group 4: 500 Units/kg	Mean	48.38	0.940	19.442
	SD	0.88	0.019	0.189
	N	5	5	5
	%Diff	1.0	1.5	0.6

[a] - Anova & Dunnett

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 30 Relative to Start Date

Sex: Male		Haematological Parameters		
		TPT	aPTT	TT
		(Seconds)	(Seconds)	(Seconds)
		[a]	[a]	[a1]
Group 1: Control	Mean	8.93	26.34	12.61
	SD	0.63	3.62	0.70
	N	10	10	10
Group 2: 50 Units/kg	Mean	9.01	24.59	13.12
	SD	0.50	1.72	0.88
	N	10	10	10
	%Diff	0.9	-6.6	4.0
Group 3: 250 Units/kg	Mean	8.95	25.43	12.50
	SD	0.51	1.47	1.08
	N	10	10	10
	%Diff	0.2	-3.5	-0.9
Group 4: 500 Units/kg	Mean	9.08	24.34	13.29
	SD	0.53	6.62	0.71
	N	9	10	10
	%Diff	1.7	-7.6	5.4

[a] - Anova & Dunnett(Rank)

[a1] - Anova & Dunnett

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 44 Relative to Start Date

Sex: Male		Haematological Parameters		
		TPT	aPTT	TT
		(Seconds)	(Seconds)	(Seconds)
		[a]	[a]	[a]
Group 1: Control	Mean	8.68	25.26	12.84
	SD	0.08	1.00	0.30
	N	5	5	5
Group 4: 500 Units/kg	Mean	8.72	23.90	13.40*
	SD	0.13	1.48	0.37
	N	5	5	5
	%Diff	0.5	-5.4	4.4

[a] - Anova & Dunnett: * = $p \leq 0.05$

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 25 Relative to Start Date

Sex: Female		Haematological Parameters					
		HGB	RBC	WBC	Reti	PLT	HCT
		(mmol/L)	(x10E6/ μ L)	(x10E3/ μ L)	(%)	(x10E3/ μ L)	(%)
		[a]	[a]	[a1]	[a]	[a1]	[a]
Group 1: Control	Mean	9.26	9.629	5.956	3.26	1053.1	47.43
	SD	0.28	0.242	1.043	0.53	61.3	1.39
	N	10	10	10	10	10	10
Group 2: 50 Units/kg	Mean	9.36	9.677	5.722	3.31	988.1	47.95
	SD	0.28	0.337	0.932	0.56	107.9	1.52
	N	10	10	10	10	10	10
	%Diff	1.1	0.5	-3.9	1.5	-6.2	1.1
Group 3: 250 Units/kg	Mean	9.25	9.616	5.344	3.33	1008.9	47.53
	SD	0.30	0.371	0.820	0.48	138.2	1.47
	N	10	10	10	10	10	10
	%Diff	-0.1	-0.1	-10.3	2.1	-4.2	0.2
Group 4: 500 Units/kg	Mean	9.20	9.530	5.789	4.15**	992.3	47.33
	SD	0.26	0.284	1.098	0.68	115.5	1.23
	N	10	10	10	10	10	10
	%Diff	-0.6	-1.0	-2.8	27.3	-5.8	-0.2

[a] - Anova & Dunnett: ** = $p \leq 0.01$

[a1] - Anova & Dunnett(Rank)

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 39 Relative to Start Date

Sex: Female		Haematological Parameters					
		HGB	RBC	WBC	Reti	PLT	HCT
		(mmol/L)	(x10E6/ μ L)	(x10E3/ μ L)	(%)	(x10E3/ μ L)	(%)
		[a]	[a]	[a1]	[a]	[a]	[a]
Group 1: Control	Mean	9.68	10.108	8.272	2.36	976.2	49.12
	SD	0.18	0.191	0.377	0.17	32.6	1.08
	N	5	5	5	5	5	5
Group 4: 500 Units/kg	Mean	9.56	9.914	9.036	2.48	977.0	48.08
	SD	0.18	0.102	1.247	0.26	42.7	0.73
	N	5	5	5	5	5	5
	%Diff	-1.2	-1.9	9.2	5.1	0.1	-2.1

[a] - Anova & Dunnett

[a1] - Anova & Dunnett(Log)

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 25 Relative to Start Date

Sex: Female		Haematological Parameters					
		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
Group 1: Control	Mean	7.91	88.09	1.22	1.90	0.61	0.28
	SD	1.77	1.74	0.31	0.69	0.16	0.10
	N	10	10	10	10	10	10
Group 2: 50 Units/kg	Mean	7.27	88.45	1.11	2.12	0.66	0.34
	SD	1.94	2.43	0.27	1.04	0.18	0.07
	N	10	10	10	10	10	10
	%Diff	-8.1	0.4	-9.0	11.6	8.2	21.4
Group 3: 250 Units/kg	Mean	7.87	87.92	1.12	2.19	0.59	0.30
	SD	0.98	1.01	0.24	0.53	0.21	0.11
	N	10	10	10	10	10	10
	%Diff	-0.5	-0.2	-8.2	15.3	-3.3	7.1
Group 4: 500 Units/kg	Mean	7.93	87.72	1.10	2.19	0.73	0.31
	SD	1.40	1.31	0.34	0.67	0.24	0.09
	N	10	10	10	10	10	10
	%Diff	0.3	-0.4	-9.8	15.3	19.7	10.7

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 39 Relative to Start Date

Sex: Female		Haematological Parameters					
		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
Group 1: Control	Mean	8.12	87.44	1.22	2.16	0.70	0.36
	SD	1.10	1.28	0.26	0.43	0.19	0.09
	N	5	5	5	5	5	5
Group 4: 500 Units/kg	Mean	7.40	87.36	1.20	2.94	0.74	0.34
	SD	0.67	1.05	0.14	0.88	0.15	0.11
	N	5	5	5	5	5	5
	%Diff	-8.9	-0.1	-1.6	36.1	5.7	-5.6

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 25 Relative to Start Date

Sex: Female		Haematological Parameters					
		Neut	Lym	Mono	Eos	LUC	Baso
		(x10E3/ μ L)	(x10E3/ μ L)	(x10E3/ μ L)	(x10E3/ μ L)	(x10E3/ μ L)	(x10E3/ μ L)
		[a]	[a1]	[a]	[a]	[a1]	[a2]
Group 1: Control	Mean	0.473	5.243	0.073	0.111	0.037	0.016
	SD	0.149	0.904	0.023	0.035	0.013	0.011
	N	10	10	10	10	10	10
Group 2: 50 Units/kg	Mean	0.422	5.058	0.063	0.119	0.037	0.021
	SD	0.143	0.809	0.019	0.052	0.016	0.006
	N	10	10	10	10	10	10
	%Diff	-10.8	-3.5	-13.7	7.2	0.0	31.3
Group 3: 250 Units/kg	Mean	0.418	4.702	0.061	0.115	0.035	0.015
	SD	0.065	0.743	0.015	0.032	0.014	0.008
	N	10	10	10	10	10	10
	%Diff	-11.6	-10.3	-16.4	3.6	-5.4	-6.3
Group 4: 500 Units/kg	Mean	0.466	5.073	0.062	0.124	0.046	0.019
	SD	0.137	0.954	0.019	0.028	0.022	0.006
	N	10	10	10	10	10	10
	%Diff	-1.5	-3.2	-15.1	11.7	24.3	18.8

[a] - Anova & Dunnett

[a1] - Anova & Dunnett(Log)

[a2] - Anova & Dunnett(Rank)

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 39 Relative to Start Date

Sex: Female		Haematological Parameters					
		Neut	Lym	Mono	Eos	LUC	Baso
		(x10E3/μL)	(x10E3/μL)	(x10E3/μL)	(x10E3/μL)	(x10E3/μL)	(x10E3/μL)
		[a]	[a]	[a]	[a]	[a]	[a]
Group 1: Control	Mean	0.670	7.236	0.098	0.180	0.058	0.030
	SD	0.079	0.391	0.019	0.041	0.015	0.007
	N	5	5	5	5	5	5
Group 4: 500 Units/kg	Mean	0.662	7.900	0.112	0.266*	0.072	0.032
	SD	0.033	1.153	0.026	0.064	0.019	0.013
	N	5	5	5	5	5	5
	%Diff	-1.2	9.2	14.3	47.8	24.1	6.7

[a] - Anova & Dunnett: * = $p \leq 0.05$

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 25 Relative to Start Date

Sex: Female		Haematological Parameters		
		MCV	MCH	MCHC
		(fL)	(fmol)	(mmol/L)
		[a]	[a1]	[a1]
Group 1: Control	Mean	49.27	0.963	19.516
	SD	0.45	0.008	0.161
	N	10	10	10
Group 2: 50 Units/kg	Mean	49.56	0.967	19.526
	SD	0.52	0.012	0.223
	N	10	10	10
	%Diff	0.6	0.4	0.1
Group 3: 250 Units/kg	Mean	49.44	0.961	19.461
	SD	0.81	0.017	0.188
	N	10	10	10
	%Diff	0.3	-0.2	-0.3
Group 4: 500 Units/kg	Mean	49.70	0.963	19.436
	SD	0.81	0.013	0.217
	N	10	10	10
	%Diff	0.9	0.0	-0.4

[a] - Anova & Dunnett(Rank)

[a1] - Anova & Dunnett

TABLE 4-1 Haematological Parameters - Summary Mouse

Day: 39 Relative to Start Date

Sex: Female		Haematological Parameters		
		MCV	MCH	MCHC
		(fL)	(fmol)	(mmol/L)
		[a]	[a]	[a]
Group 1: Control	Mean	48.58	0.958	19.690
	SD	0.33	0.011	0.182
	N	5	5	5
Group 4: 500 Units/kg	Mean	48.50	0.964	19.858
	SD	0.41	0.011	0.132
	N	5	5	5
	%Diff	-0.2	0.6	0.9

[a] - Anova & Dunnett

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 30 Relative to Start Date

Sex: Female		Haematological Parameters		
		TPT	aPTT	TT
		(Seconds)	(Seconds)	(Seconds)
		[a]	[a]	[a1]
Group 1: Control	Mean	8.43	22.36	12.94
	SD	0.21	1.08	0.34
	N	10	10	10
Group 2: 50 Units/kg	Mean	8.78	22.48	12.53
	SD	0.69	1.10	0.49
	N	10	10	10
	%Diff	4.2	0.5	-3.2
Group 3: 250 Units/kg	Mean	8.82	22.13	12.68
	SD	0.50	2.81	0.35
	N	10	10	10
	%Diff	4.6	-1.0	-2.0
Group 4: 500 Units/kg	Mean	8.67	22.18	12.75
	SD	0.64	1.91	0.30
	N	10	10	10
	%Diff	2.8	-0.8	-1.5

[a] - Anova & Dunnett(Rank)

[a1] - Anova & Dunnett

TABLE 4-1

Haematological Parameters - Summary

Mouse

Day: 44 Relative to Start Date

Sex: Female		Haematological Parameters		
		TPT	aPTT	TT
		(Seconds)	(Seconds)	(Seconds)
		[a]	[a]	[a]
Group 1: Control	Mean	8.90	22.98	12.76
	SD	0.28	1.46	0.36
	N	5	5	5
Group 4: 500 Units/kg	Mean	8.92	23.40	13.02
	SD	0.31	1.54	0.48
	N	5	5	5
	%Diff	0.2	1.8	2.0

[a] - Anova & Dunnett

TABLE 4-1 Haematological Parameters - Summary Mouse

<u>Comments and Markers</u>					
<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker</u> <u>Comment</u>
	25	4	Male	PLT	** Anova & Dunnett(Rank): ** = p ≤ 0.01

TABLE 4-1 Haematological Parameters - Summary Mouse

<u>Comments and Markers</u>					
<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker</u> <u>Comment</u>
44		4	Male	TT	* Anova & Dunnett: * = p ≤ 0.05

TABLE 4-1

Haematological Parameters - Summary

Mouse

						<u>Comments and Markers</u>	
<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>		<u>Marker</u>	<u>Comment</u>
	25	4	Female	Reticulocyte (Relative)		**	Anova & Dunnett: ** = p ≤ 0.01

TABLE 4-1 Haematological Parameters - Summary Mouse

<u>Comments and Markers</u>					
<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker</u> <u>Comment</u>
39		4	Female	Eosinophils (Absolute)	* Anova & Dunnett: * = p ≤ 0.05

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 25 Relative to Start Date

Group 1: Control	Haematological Parameters					
	HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
1	9.9	10.43	8.40	3.0	1072	51.5
2	9.9	10.63	7.24	3.1	1158	52.0
3	9.5	9.89	9.15	3.3	1105	49.2
4	9.6	10.03	5.79	3.1	1218	50.0
5	9.5	10.06	8.09	3.1	1345	49.6
6	9.8	10.55	7.11	2.7	1200	51.7
7	9.5	10.27	7.87	3.3	1273	50.3
8	9.7	10.18	7.40	3.4	1224	49.9
9	9.7	10.44	9.27	3.1	1284	51.2
10	9.6	10.45	7.71	2.8	1187	51.0
Mean	9.67	10.293	7.803	3.09	1206.6	50.64
SD	0.16	0.246	1.024	0.22	82.5	0.97
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 25 Relative to Start Date

Group 2: 50 Units/kg	Haematological Parameters					
	HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
31	9.3	10.03	5.75	3.6	1216	48.8
32	9.7	10.15	7.82	3.4	1159	50.1
33	9.7	10.25	7.47	2.9	1065	50.3
34	9.1	9.65	8.06	3.9	831	48.1
35	8.9	9.68	10.51	3.5	1130	47.4
36	9.8	10.57	5.93	3.2	1317	51.8
37	9.6	10.15	9.41	3.2	1112	50.7
38	9.6	10.14	7.34	2.8	1246	49.9
39	9.9	10.28	10.85	3.0	1171	51.5
40	9.6	10.03	7.02	3.3	1245	50.0
Mean	9.52	10.093	8.016	3.28	1149.2	49.86
SD	0.32	0.273	1.747	0.34	134.1	1.40
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 25 Relative to Start Date

Group 3: 250 Units/kg	Haematological Parameters					
	HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
51	10.0	10.41	7.81	3.5	1220	51.6
52	9.7	10.36	7.85	2.9	1240	50.9
53	9.7	10.20	6.61	2.5	1014	50.1
54	9.6	10.27	6.83	2.8	1187	50.1
55	9.3	9.74	6.06	3.1	1157	48.0
56	9.9	10.35	8.60	3.3	1123	51.1
57	9.4	10.10	6.67	3.2	1162	49.7
58	9.5	10.05	7.05	2.9	1113	50.0
59	9.5	10.02	8.25	3.2	1240	50.0
60	9.2	9.65	5.61	3.2	1101	47.7
Mean	9.58	10.115	7.134	3.06	1155.7	49.92
SD	0.25	0.259	0.968	0.29	71.0	1.24
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 25 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters					
	HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
71	10.1	10.78	9.37	3.4	1055	52.9
72	9.7	10.13	6.90	3.4	1116	50.3
73	9.7	10.19	7.75	3.2	1081	49.7
74	9.4	9.95	7.53	3.1	1150	49.1
75	9.6	10.12	7.25	3.2	1060	50.1
76	9.2	9.76	6.63	3.0	1119	48.2
77	9.2	9.63	9.55	3.6	968	47.6
78	9.5	10.16	8.85	3.2	1105	50.2
79	9.3	9.88	7.21	3.4	1046	48.7
80	9.3	9.77	5.22	3.1	1150	48.4
Mean	9.50	10.037	7.626	3.26	1085.0	49.52
SD	0.28	0.325	1.329	0.18	55.5	1.51
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 39 Relative to Start Date

Group 1: Control	Haematological Parameters					
	HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
11	9.5	10.40	7.98	2.9	1191	49.5
12	9.7	10.50	6.95	3.3	1163	50.5
13	9.7	10.35	7.45	2.9	1157	49.7
14	9.6	10.26	7.20	3.2	1112	49.7
15	9.1	9.92	8.09	3.1	1184	47.1
Mean	9.52	10.286	7.534	3.08	1161.4	49.30
SD	0.25	0.222	0.492	0.18	31.0	1.29
N	5	5	5	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 39 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters					
	HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
81	9.3	10.06	6.16	2.9	1107	47.7
82	9.8	10.44	11.20	3.1	1168	50.9
83	9.6	9.84	10.31	3.1	1200	48.9
84	9.0	9.74	9.06	2.7	1112	46.9
85	9.7	10.28	7.92	3.0	1204	49.3
Mean	9.48	10.072	8.930	2.96	1158.2	48.74
SD	0.33	0.293	1.985	0.17	46.6	1.54
N	5	5	5	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 25 Relative to Start Date

Group 1: Control	Haematological Parameters					
	Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
1	6.8	88.9	1.4	1.9	0.7	0.3
2	7.0	89.3	0.9	2.0	0.6	0.2
3	6.0	90.3	1.2	1.5	0.8	0.2
4	7.6	88.2	1.1	2.1	0.7	0.3
5	7.6	88.0	1.3	2.2	0.6	0.4
6	8.4	87.0	1.8	1.7	0.7	0.4
7	6.2	89.4	1.2	2.3	0.7	0.2
8	7.2	88.0	1.5	2.2	0.7	0.3
9	6.9	89.1	1.1	1.6	1.0	0.3
10	6.8	88.7	1.9	1.8	0.6	0.3
Mean	7.05	88.69	1.34	1.93	0.71	0.29
SD	0.70	0.93	0.32	0.28	0.12	0.07
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 25 Relative to Start Date

Group 2: 50 Units/kg	Haematological Parameters					
	Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
31	30.5	63.8	2.3	2.1	0.8	0.4
32	7.1	88.9	1.1	1.7	0.9	0.4
33	4.5	90.8	1.1	2.2	1.0	0.4
34	8.2	86.0	1.8	2.5	1.1	0.4
35	39.1	55.4	1.5	1.7	2.1	0.2
36	8.2	87.7	1.2	2.1	0.6	0.3
37	7.9	87.8	1.2	1.7	1.1	0.3
38	8.2	86.5	2.0	2.1	0.9	0.3
39	6.5	89.7	0.9	1.9	0.6	0.4
40	5.3	90.9	1.2	1.6	0.7	0.3
Mean	12.55	82.75	1.43	1.96	0.98	0.34
SD	11.97	12.47	0.46	0.29	0.43	0.07
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 25 Relative to Start Date

Group 3: 250 Units/kg	Haematological Parameters					
	Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
51	8.6	87.0	1.5	1.9	0.5	0.5
52	7.5	88.1	1.4	1.8	0.9	0.3
53	6.0	89.9	1.0	1.8	1.0	0.2
54	5.9	89.9	1.5	1.8	0.5	0.4
55	5.2	90.5	1.3	2.2	0.5	0.3
56	8.2	87.0	1.8	1.9	0.8	0.3
57	5.7	91.0	1.1	1.4	0.7	0.1
58	5.8	90.4	1.4	1.2	0.8	0.4
59	8.9	86.7	1.3	2.0	0.8	0.3
60	5.8	91.2	1.0	1.4	0.3	0.3
Mean	6.76	89.17	1.33	1.74	0.68	0.31
SD	1.39	1.78	0.25	0.31	0.22	0.11
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 25 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters					
	Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
71	8.5	87.3	1.2	1.8	0.8	0.4
72	8.1	87.2	1.2	2.7	0.6	0.2
73	8.3	86.4	1.9	2.1	0.9	0.4
74	6.4	89.0	1.5	1.7	1.1	0.3
75	6.2	89.3	1.1	2.7	0.5	0.3
76	7.6	88.2	1.4	1.5	0.9	0.4
77	5.3	90.1	0.9	2.5	0.9	0.3
78	8.2	86.1	1.4	3.2	0.9	0.3
79	7.8	87.4	1.3	2.4	0.6	0.4
80	9.8	85.4	1.7	2.0	1.0	0.1
Mean	7.62	87.64	1.36	2.26	0.82	0.31
SD	1.31	1.50	0.29	0.53	0.19	0.10
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 39 Relative to Start Date

Group 1: Control	Haematological Parameters					
	Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
11	13.3	81.0	1.5	3.1	0.8	0.3
12	8.2	88.1	1.1	1.7	0.6	0.4
13	7.9	87.2	1.0	2.9	0.8	0.2
14	16.5	79.0	1.6	2.2	0.4	0.4
15	6.7	89.0	0.9	2.4	0.9	0.2
Mean	10.52	84.86	1.22	2.46	0.70	0.30
SD	4.19	4.54	0.31	0.56	0.20	0.10
N	5	5	5	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 39 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters					
	Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
81	8.3	87.1	1.4	2.6	0.5	0.1
82	13.1	80.8	1.8	3.2	0.7	0.3
83	5.6	90.6	1.1	1.6	0.9	0.3
84	7.2	88.3	1.1	1.6	1.5	0.3
85	6.4	89.5	1.3	1.8	0.8	0.3
Mean	8.12	87.26	1.34	2.16	0.88	0.26
SD	2.96	3.84	0.29	0.71	0.38	0.09
N	5	5	5	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 25 Relative to Start Date

Group 1: Control	Haematological Parameters					
	Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)	Baso (x10E3/ μ L)
1	0.57	7.46	0.12	0.16	0.06	0.03
2	0.51	6.47	0.06	0.14	0.04	0.01
3	0.55	8.26	0.11	0.14	0.08	0.02
4	0.44	5.11	0.07	0.12	0.04	0.02
5	0.62	7.11	0.10	0.17	0.05	0.03
6	0.59	6.19	0.13	0.12	0.05	0.03
7	0.49	7.04	0.10	0.18	0.06	0.02
8	0.53	6.52	0.11	0.16	0.05	0.02
9	0.64	8.26	0.10	0.15	0.09	0.03
10	0.53	6.84	0.14	0.14	0.04	0.02
Mean	0.547	6.926	0.104	0.148	0.056	0.023
SD	0.061	0.949	0.025	0.020	0.017	0.007
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 25 Relative to Start Date

Group 2: 50 Units/kg	Haematological Parameters					
	Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)	Baso (x10E3/ μ L)
31	1.76	3.67	0.13	0.12	0.05	0.02
32	0.56	6.95	0.08	0.13	0.07	0.03
33	0.34	6.79	0.08	0.16	0.07	0.03
34	0.66	6.93	0.14	0.20	0.09	0.03
35	4.11	5.82	0.15	0.18	0.22	0.02
36	0.48	5.20	0.07	0.12	0.04	0.02
37	0.74	8.27	0.12	0.16	0.10	0.03
38	0.60	6.35	0.15	0.15	0.07	0.02
39	0.71	9.73	0.10	0.20	0.07	0.05
40	0.37	6.38	0.08	0.11	0.05	0.02
Mean	1.033	6.609	0.110	0.153	0.083	0.027
SD	1.153	1.637	0.032	0.033	0.051	0.009
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 25 Relative to Start Date

Group 3: 250 Units/kg	Haematological Parameters					
	Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)	Baso (x10E3/ μ L)
51	0.67	6.79	0.12	0.15	0.04	0.04
52	0.59	6.92	0.11	0.14	0.07	0.03
53	0.40	5.94	0.07	0.12	0.07	0.02
54	0.40	6.14	0.10	0.12	0.04	0.02
55	0.31	5.49	0.08	0.14	0.03	0.02
56	0.70	7.49	0.15	0.16	0.07	0.02
57	0.38	6.07	0.07	0.09	0.04	0.01
58	0.41	6.38	0.10	0.09	0.06	0.03
59	0.74	7.15	0.11	0.16	0.07	0.03
60	0.32	5.12	0.06	0.08	0.02	0.02
Mean	0.492	6.349	0.097	0.125	0.051	0.024
SD	0.165	0.746	0.028	0.030	0.019	0.008
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 25 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters					
	Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)	Baso (x10E3/ μ L)
71	0.80	8.18	0.12	0.17	0.07	0.03
72	0.56	6.02	0.08	0.19	0.04	0.02
73	0.64	6.69	0.15	0.17	0.07	0.03
74	0.48	6.70	0.11	0.13	0.09	0.02
75	0.45	6.47	0.08	0.20	0.03	0.02
76	0.51	5.85	0.09	0.10	0.06	0.03
77	0.51	8.61	0.08	0.24	0.09	0.03
78	0.72	7.62	0.12	0.28	0.08	0.02
79	0.56	6.30	0.09	0.17	0.04	0.03
80	0.51	4.46	0.09	0.10	0.05	0.01
Mean	0.574	6.690	0.101	0.175	0.062	0.024
SD	0.112	1.206	0.023	0.057	0.021	0.007
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 39 Relative to Start Date

Group 1: Control	Haematological Parameters					
	Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)	Baso (x10E3/ μ L)
11	1.06	6.46	0.12	0.25	0.07	0.02
12	0.57	6.12	0.08	0.12	0.04	0.03
13	0.59	6.50	0.07	0.21	0.06	0.02
14	1.19	5.69	0.12	0.16	0.03	0.03
15	0.54	7.20	0.07	0.19	0.07	0.01
Mean	0.790	6.394	0.092	0.186	0.054	0.022
SD	0.310	0.556	0.026	0.049	0.018	0.008
N	5	5	5	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 39 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters					
	Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)	Baso (x10E3/ μ L)
81	0.51	5.36	0.08	0.16	0.03	0.01
82	1.47	9.04	0.20	0.36	0.08	0.04
83	0.58	9.34	0.11	0.16	0.09	0.04
84	0.65	8.00	0.10	0.14	0.14	0.02
85	0.50	7.09	0.10	0.14	0.07	0.02
Mean	0.742	7.766	0.118	0.192	0.082	0.026
SD	0.411	1.613	0.047	0.094	0.040	0.013
N	5	5	5	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 25 Relative to Start Date

Group 1: Control	Haematological Parameters		
	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
1	49.4	0.95	19.24
2	48.9	0.93	19.05
3	49.8	0.96	19.34
4	49.9	0.96	19.21
5	49.3	0.95	19.21
6	49.0	0.92	18.88
7	49.0	0.93	18.97
8	49.0	0.96	19.55
9	49.0	0.93	18.88
10	48.9	0.92	18.90
Mean	49.22	0.941	19.123
SD	0.37	0.017	0.225
N	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 25 Relative to Start Date

Group 2: 50 Units/kg	Haematological Parameters		
	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
31	48.7	0.93	19.02
32	49.3	0.96	19.44
33	49.1	0.95	19.38
34	49.8	0.95	19.01
35	49.0	0.92	18.74
36	49.0	0.93	18.95
37	49.9	0.95	18.97
38	49.2	0.94	19.16
39	50.1	0.96	19.12
40	49.9	0.95	19.10
Mean	49.40	0.944	19.089
SD	0.48	0.013	0.206
N	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 25 Relative to Start Date

Group 3: 250 Units/kg	Haematological Parameters		
	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
51	49.6	0.96	19.32
52	49.1	0.94	19.08
53	49.1	0.95	19.38
54	48.8	0.94	19.16
55	49.3	0.96	19.37
56	49.4	0.96	19.47
57	49.2	0.93	18.93
58	49.8	0.95	19.09
59	49.9	0.95	19.05
60	49.5	0.95	19.27
Mean	49.37	0.949	19.212
SD	0.34	0.010	0.175
N	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 25 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters		
	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
71	49.1	0.94	19.14
72	49.7	0.96	19.27
73	48.8	0.95	19.45
74	49.3	0.94	19.15
75	49.5	0.95	19.14
76	49.4	0.95	19.16
77	49.4	0.95	19.30
78	49.4	0.93	18.90
79	49.3	0.94	19.07
80	49.5	0.95	19.15
Mean	49.34	0.946	19.173
SD	0.25	0.008	0.146
N	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 39 Relative to Start Date

Group 1: Control	Haematological Parameters		
	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
11	47.6	0.92	19.23
12	48.0	0.93	19.28
13	48.0	0.94	19.56
14	48.4	0.93	19.29
15	47.5	0.91	19.24
Mean	47.90	0.926	19.320
SD	0.36	0.011	0.137
N	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 39 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters		
	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
81	47.4	0.92	19.52
82	48.7	0.94	19.27
83	49.7	0.97	19.61
84	48.2	0.93	19.21
85	47.9	0.94	19.60
Mean	48.38	0.940	19.442
SD	0.88	0.019	0.189
N	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 1: Control	Haematological Parameters		
	TPT (Seconds)	aPTT (Seconds)	TT (Seconds)
1	8.5	26.6	12.1
2	7.9	35.0	12.8
3	8.5	27.0	12.1
4	9.5	22.4	14.0
5	9.4	24.3	12.2
6	9.7	28.6	12.8
7	8.5	27.4	11.6
8	9.4	23.5	12.7
9	8.4	24.7	12.4
10	9.5	23.9	13.4
Mean	8.93	26.34	12.61
SD	0.63	3.62	0.70
N	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 2: 50 Units/kg	Haematological Parameters		
	TPT (Seconds)	aPTT (Seconds)	TT (Seconds)
31	8.5	25.2	12.5
32	8.6	24.1	12.7
33	8.6	27.5	15.2
34	8.8	21.0	13.7
35	9.7	25.3	13.4
36	8.3	24.8	12.3
37	9.4	25.0	13.3
38	9.3	23.7	12.3
39	9.3	25.9	13.2
40	9.6	23.4	12.6
Mean	9.01	24.59	13.12
SD	0.50	1.72	0.88
N	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 3: 250 Units/kg	Haematological Parameters		
	TPT (Seconds)	aPTT (Seconds)	TT (Seconds)
51	9.6	23.0	12.5
52	8.7	27.2	12.4
53	7.9	25.8	13.1
54	9.1	24.5	12.5
55	9.4	26.0	13.5
56	8.6	26.9	13.1
57	8.7	24.6	11.6
58	9.4	27.3	10.0
59	9.3	25.2	13.8
60	8.8	23.8	12.5
Mean	8.95	25.43	12.50
SD	0.51	1.47	1.08
N	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters		
	TPT (Seconds)	aPTT (Seconds)	TT (Seconds)
71	9.5	23.9	14.4
72	8.5	28.8	13.2
73	8.4	24.9	12.4
74	9.5	23.7	13.4
75	9.6	24.7	13.5
76	NM !	8.5	14.3
77	8.5	24.6	12.2
78	8.7	35.4	13.0
79	9.6	24.3	13.5
80	9.4	24.6	13.0
Mean	9.08	24.34	13.29
SD	0.53	6.62	0.71
N	9	10	10

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TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 44 Relative to Start Date

Group 1: Control	Haematological Parameters		
	TPT (Seconds)	aPTT (Seconds)	TT (Seconds)
11	8.7	25.2	13.2
12	8.6	25.2	12.8
13	8.7	24.8	12.8
14	8.6	26.9	12.4
15	8.8	24.2	13.0
Mean	8.68	25.26	12.84
SD	0.08	1.00	0.30
N	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Male Day: 44 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters		
	TPT (Seconds)	aPTT (Seconds)	TT (Seconds)
81	8.8	22.7	13.0
82	8.8	22.4	13.4
83	8.5	23.9	13.6
84	8.8	24.4	13.1
85	8.7	26.1	13.9
Mean	8.72	23.90	13.40
SD	0.13	1.48	0.37
N	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 25 Relative to Start Date

Group 1: Control	Haematological Parameters					
	HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
16	9.2	9.54	5.40	2.7	1001	47.0
17	9.6	9.81	6.71	2.5	1062	48.6
18	9.5	9.87	4.97	3.8	1132	48.7
19	8.7	9.18	5.91	3.4	1036	44.9
20	9.5	9.84	5.89	2.6	1150	49.0
21	9.5	9.90	7.84	3.6	983	49.2
22	9.0	9.37	5.61	3.9	1062	46.4
23	9.1	9.44	5.22	3.1	1109	46.6
24	9.3	9.71	7.37	3.8	1019	47.2
25	9.2	9.63	4.64	3.2	977	46.7
Mean	9.26	9.629	5.956	3.26	1053.1	47.43
SD	0.28	0.242	1.043	0.53	61.3	1.39
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 25 Relative to Start Date

Group 2: 50 Units/kg	Haematological Parameters					
	HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
41	9.1	9.34	5.03	3.4	965	46.2
42	9.5	9.68	5.37	3.3	1055	47.8
43	9.1	9.33	7.08	4.2	723	47.5
44	9.5	9.77	5.43	3.6	1001	48.5
45	9.4	9.64	7.19	3.2	995	47.9
46	9.5	9.95	4.99	2.8	1027	48.6
47	9.2	9.60	5.64	3.9	1040	47.4
48	9.1	9.36	6.77	3.5	907	46.2
49	10.0	10.45	4.93	2.2	1088	51.6
50	9.2	9.65	4.79	3.0	1080	47.8
Mean	9.36	9.677	5.722	3.31	988.1	47.95
SD	0.28	0.337	0.932	0.56	107.9	1.52
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 25 Relative to Start Date

Group 3: 250 Units/kg	Haematological Parameters					
	HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
61	9.5	9.93	5.64	3.2	1055	49.0
62	9.3	9.66	6.02	3.2	1089	48.3
63	9.3	9.62	5.76	4.0	975	47.5
64	8.9	9.05	5.75	4.0	626	46.5
65	9.8	10.43	4.25	2.4	1064	50.5
66	8.7	9.28	5.74	3.2	1064	45.4
67	9.2	9.47	6.68	3.5	1069	46.5
68	9.4	9.68	4.58	2.9	1050	47.9
69	9.2	9.54	4.68	3.3	1026	47.1
70	9.2	9.50	4.34	3.6	1071	46.6
Mean	9.25	9.616	5.344	3.33	1008.9	47.53
SD	0.30	0.371	0.820	0.48	138.2	1.47
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 25 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters					
	HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
86	9.3	9.54	5.74	4.1	1075	46.8
87	9.3	9.67	4.79	3.8	1001	48.0
88	9.1	9.43	6.14	5.9	1067	47.4
89	9.7	10.03	6.75	3.7	1025	49.9
90	9.3	9.61	7.72	4.0	1089	47.7
91	9.3	9.66	6.14	3.4	999	47.7
92	8.8	9.18	4.56	3.8	873	45.1
93	8.9	9.42	4.72	4.4	1031	46.6
94	9.0	9.03	6.73	4.2	713	46.7
95	9.3	9.73	4.60	4.2	1050	47.4
Mean	9.20	9.530	5.789	4.15	992.3	47.33
SD	0.26	0.284	1.098	0.68	115.5	1.23
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 39 Relative to Start Date

Group 1: Control	Haematological Parameters					
	HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
26	9.4	9.90	8.62	2.4	942	47.6
27	9.8	10.29	7.77	2.3	979	50.1
28	9.6	9.94	8.66	2.5	971	48.7
29	9.8	10.10	8.25	2.5	960	49.0
30	9.8	10.31	8.06	2.1	1029	50.2
Mean	9.68	10.108	8.272	2.36	976.2	49.12
SD	0.18	0.191	0.377	0.17	32.6	1.08
N	5	5	5	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 39 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters					
	HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
96	9.5	9.93	8.29	2.1	970	47.8
97	9.7	9.95	8.24	2.8	908	48.8
98	9.8	10.03	9.94	2.5	985	48.9
99	9.4	9.75	10.77	2.4	1018	47.3
100	9.4	9.91	7.94	2.6	1004	47.6
Mean	9.56	9.914	9.036	2.48	977.0	48.08
SD	0.18	0.102	1.247	0.26	42.7	0.73
N	5	5	5	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 25 Relative to Start Date

Group 1: Control	Haematological Parameters					
	Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
16	9.9	86.4	1.0	2.1	0.3	0.2
17	7.1	88.4	1.2	2.3	0.7	0.3
18	6.4	87.3	1.8	3.6	0.5	0.3
19	5.8	90.5	1.7	1.2	0.6	0.2
20	6.9	89.2	1.1	1.9	0.7	0.2
21	10.2	85.9	1.3	1.4	0.8	0.4
22	9.4	87.1	1.0	1.8	0.5	0.3
23	5.7	91.0	0.8	1.8	0.5	0.2
24	7.9	88.5	1.1	1.4	0.7	0.5
25	9.8	86.6	1.2	1.5	0.8	0.2
Mean	7.91	88.09	1.22	1.90	0.61	0.28
SD	1.77	1.74	0.31	0.69	0.16	0.10
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 25 Relative to Start Date

Group 2: 50 Units/kg	Haematological Parameters					
	Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
41	10.1	86.1	1.2	1.4	0.8	0.3
42	4.6	91.9	0.8	1.7	0.6	0.3
43	8.1	87.6	1.1	2.0	0.8	0.4
44	5.3	90.4	1.6	1.9	0.6	0.2
45	9.2	87.1	1.1	1.5	0.8	0.3
46	9.3	83.7	1.5	4.5	0.6	0.3
47	6.5	90.1	0.8	1.7	0.5	0.4
48	7.2	88.0	1.1	2.4	0.9	0.4
49	4.9	90.1	1.0	3.2	0.3	0.4
50	7.5	89.5	0.9	0.9	0.7	0.4
Mean	7.27	88.45	1.11	2.12	0.66	0.34
SD	1.94	2.43	0.27	1.04	0.18	0.07
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 25 Relative to Start Date

Group 3: 250 Units/kg	Haematological Parameters					
	Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
61	6.9	88.6	1.2	2.2	0.8	0.2
62	9.1	87.3	1.2	1.4	0.8	0.2
63	7.0	89.0	1.0	2.1	0.3	0.5
64	8.0	87.6	1.5	1.8	0.8	0.4
65	7.5	88.0	0.8	3.0	0.4	0.2
66	8.3	86.8	1.3	2.8	0.5	0.3
67	6.2	89.2	0.8	2.6	0.8	0.4
68	7.8	88.6	0.9	1.9	0.6	0.3
69	8.8	88.1	1.1	1.6	0.3	0.2
70	9.1	86.0	1.4	2.5	0.6	0.3
Mean	7.87	87.92	1.12	2.19	0.59	0.30
SD	0.98	1.01	0.24	0.53	0.21	0.11
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 25 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters					
	Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
86	8.9	87.0	1.0	1.8	0.8	0.5
87	9.1	86.6	1.1	2.5	0.4	0.3
88	8.7	87.3	0.9	2.3	0.5	0.4
89	9.9	85.6	0.9	2.5	0.8	0.3
90	8.0	88.3	1.1	1.2	1.2	0.2
91	7.2	89.1	0.8	1.7	0.9	0.3
92	5.4	88.9	1.0	3.7	0.6	0.3
93	7.8	87.0	2.0	2.1	0.6	0.3
94	8.3	87.5	1.2	1.8	0.9	0.3
95	6.0	89.9	1.0	2.3	0.6	0.2
Mean	7.93	87.72	1.10	2.19	0.73	0.31
SD	1.40	1.31	0.34	0.67	0.24	0.09
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 39 Relative to Start Date

Group 1: Control	Haematological Parameters					
	Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
26	6.5	88.5	1.1	2.8	0.7	0.3
27	9.2	85.9	1.6	2.1	1.0	0.3
28	8.8	86.7	1.3	2.1	0.6	0.5
29	7.5	89.0	0.9	1.6	0.7	0.4
30	8.6	87.1	1.2	2.2	0.5	0.3
Mean	8.12	87.44	1.22	2.16	0.70	0.36
SD	1.10	1.28	0.26	0.43	0.19	0.09
N	5	5	5	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 39 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters					
	Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
96	8.1	87.7	1.1	2.2	0.5	0.3
97	7.6	87.3	1.1	3.0	0.8	0.3
98	6.8	88.3	1.4	2.3	0.8	0.4
99	6.6	87.9	1.3	2.8	0.9	0.5
100	7.9	85.6	1.1	4.4	0.7	0.2
Mean	7.40	87.36	1.20	2.94	0.74	0.34
SD	0.67	1.05	0.14	0.88	0.15	0.11
N	5	5	5	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 25 Relative to Start Date

Group 1: Control	Haematological Parameters					
	Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)	Baso (x10E3/ μ L)
16	0.53	4.67	0.06	0.11	0.02	0.01
17	0.47	5.93	0.08	0.16	0.05	0.02
18	0.32	4.34	0.09	0.18	0.03	0.01
19	0.34	5.34	0.10	0.07	0.03	0.01
20	0.41	5.26	0.06	0.11	0.04	0.01
21	0.80	6.73	0.11	0.11	0.06	0.03
22	0.53	4.88	0.05	0.10	0.03	0.01
23	0.30	4.75	0.04	0.09	0.02	0.01
24	0.58	6.52	0.08	0.11	0.05	0.04
25	0.45	4.01	0.06	0.07	0.04	0.01
Mean	0.473	5.243	0.073	0.111	0.037	0.016
SD	0.149	0.904	0.023	0.035	0.013	0.011
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 25 Relative to Start Date

Group 2: 50 Units/kg	Haematological Parameters					
	Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)	Baso (x10E3/ μ L)
41	0.51	4.33	0.06	0.07	0.04	0.02
42	0.25	4.94	0.04	0.09	0.03	0.02
43	0.58	6.20	0.08	0.14	0.05	0.03
44	0.29	4.91	0.09	0.10	0.03	0.01
45	0.66	6.26	0.08	0.11	0.06	0.02
46	0.47	4.17	0.08	0.22	0.03	0.02
47	0.37	5.08	0.04	0.10	0.03	0.02
48	0.49	5.96	0.07	0.16	0.06	0.03
49	0.24	4.44	0.05	0.16	0.01	0.02
50	0.36	4.29	0.04	0.04	0.03	0.02
Mean	0.422	5.058	0.063	0.119	0.037	0.021
SD	0.143	0.809	0.019	0.052	0.016	0.006
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 25 Relative to Start Date

Group 3: 250 Units/kg	Haematological Parameters					
	Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)	Baso (x10E3/ μ L)
61	0.39	5.00	0.07	0.12	0.05	0.01
62	0.55	5.25	0.07	0.08	0.05	0.01
63	0.40	5.13	0.06	0.12	0.02	0.03
64	0.46	5.04	0.09	0.10	0.04	0.02
65	0.32	3.74	0.04	0.13	0.02	0.01
66	0.48	4.99	0.07	0.16	0.03	0.01
67	0.41	5.96	0.06	0.17	0.06	0.03
68	0.36	4.06	0.04	0.09	0.03	0.01
69	0.41	4.12	0.05	0.07	0.02	0.01
70	0.40	3.73	0.06	0.11	0.03	0.01
Mean	0.418	4.702	0.061	0.115	0.035	0.015
SD	0.065	0.743	0.015	0.032	0.014	0.008
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 25 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters					
	Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)	Baso (x10E3/ μ L)
86	0.51	4.99	0.06	0.11	0.05	0.03
87	0.44	4.14	0.05	0.12	0.02	0.01
88	0.53	5.36	0.05	0.14	0.03	0.02
89	0.67	5.78	0.06	0.17	0.06	0.02
90	0.61	6.82	0.08	0.09	0.09	0.02
91	0.44	5.47	0.05	0.11	0.06	0.02
92	0.25	4.05	0.05	0.17	0.03	0.02
93	0.37	4.11	0.10	0.10	0.03	0.02
94	0.56	5.88	0.08	0.12	0.06	0.02
95	0.28	4.13	0.04	0.11	0.03	0.01
Mean	0.466	5.073	0.062	0.124	0.046	0.019
SD	0.137	0.954	0.019	0.028	0.022	0.006
N	10	10	10	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 39 Relative to Start Date

Group 1: Control	Haematological Parameters					
	Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)	Baso (x10E3/ μ L)
26	0.56	7.63	0.09	0.24	0.06	0.03
27	0.71	6.67	0.12	0.16	0.08	0.02
28	0.76	7.51	0.11	0.19	0.05	0.04
29	0.62	7.35	0.07	0.13	0.06	0.03
30	0.70	7.02	0.10	0.18	0.04	0.03
Mean	0.670	7.236	0.098	0.180	0.058	0.030
SD	0.079	0.391	0.019	0.041	0.015	0.007
N	5	5	5	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 39 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters					
	Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)	Baso (x10E3/ μ L)
96	0.67	7.26	0.10	0.19	0.05	0.03
97	0.63	7.20	0.09	0.25	0.07	0.02
98	0.67	8.78	0.14	0.23	0.08	0.04
99	0.71	9.46	0.14	0.31	0.10	0.05
100	0.63	6.80	0.09	0.35	0.06	0.02
Mean	0.662	7.900	0.112	0.266	0.072	0.032
SD	0.033	1.153	0.026	0.064	0.019	0.013
N	5	5	5	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 25 Relative to Start Date

Group 1: Control	Haematological Parameters		
	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
16	49.3	0.96	19.59
17	49.5	0.98	19.69
18	49.4	0.96	19.51
19	48.9	0.95	19.33
20	49.8	0.97	19.44
21	49.7	0.96	19.27
22	49.6	0.97	19.48
23	49.4	0.96	19.41
24	48.6	0.96	19.72
25	48.5	0.96	19.72
Mean	49.27	0.963	19.516
SD	0.45	0.008	0.161
N	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 25 Relative to Start Date

Group 2: 50 Units/kg	Haematological Parameters		
	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
41	49.4	0.98	19.81
42	49.4	0.98	19.76
43	50.9	0.98	19.16
44	49.6	0.97	19.63
45	49.7	0.97	19.56
46	48.9	0.96	19.62
47	49.4	0.95	19.33
48	49.4	0.97	19.73
49	49.3	0.95	19.32
50	49.6	0.96	19.34
Mean	49.56	0.967	19.526
SD	0.52	0.012	0.223
N	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 25 Relative to Start Date

Group 3: 250 Units/kg	Haematological Parameters		
	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
61	49.3	0.95	19.32
62	50.0	0.97	19.35
63	49.4	0.97	19.57
64	51.4	0.99	19.22
65	48.4	0.93	19.29
66	48.9	0.94	19.28
67	49.1	0.97	19.72
68	49.5	0.97	19.68
69	49.4	0.96	19.53
70	49.0	0.96	19.65
Mean	49.44	0.961	19.461
SD	0.81	0.017	0.188
N	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 25 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters		
	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
86	49.1	0.97	19.82
87	49.6	0.96	19.44
88	50.3	0.97	19.28
89	49.8	0.97	19.52
90	49.6	0.96	19.45
91	49.4	0.96	19.51
92	49.2	0.96	19.53
93	49.5	0.94	19.04
94	51.7	0.99	19.20
95	48.8	0.95	19.57
Mean	49.70	0.963	19.436
SD	0.81	0.013	0.217
N	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 39 Relative to Start Date

Group 1: Control	Haematological Parameters		
	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
26	48.1	0.95	19.72
27	48.6	0.95	19.48
28	49.0	0.97	19.74
29	48.5	0.97	19.95
30	48.7	0.95	19.56
Mean	48.58	0.958	19.690
SD	0.33	0.011	0.182
N	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 39 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters		
	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
96	48.2	0.96	19.87
97	49.0	0.97	19.82
98	48.8	0.98	20.07
99	48.5	0.96	19.82
100	48.0	0.95	19.71
Mean	48.50	0.964	19.858
SD	0.41	0.011	0.132
N	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 1: Control	Haematological Parameters		
	TPT (Seconds)	aPTT (Seconds)	TT (Seconds)
16	8.4	24.1	12.8
17	8.3	21.1	13.0
18	8.6	22.0	12.5
19	8.7	23.3	12.5
20	8.2	21.9	13.0
21	8.8	20.6	13.3
22	8.2	22.2	13.3
23	8.4	23.2	12.5
24	8.3	22.0	13.3
25	8.4	23.2	13.2
Mean	8.43	22.36	12.94
SD	0.21	1.08	0.34
N	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 2: 50 Units/kg	Haematological Parameters		
	TPT (Seconds)	aPTT (Seconds)	TT (Seconds)
41	8.1	21.5	12.5
42	9.1	23.2	12.8
43	8.3	22.1	11.6
44	8.6	23.1	12.9
45	8.3	21.1	12.8
46	8.5	23.6	13.3
47	8.4	22.0	12.7
48	9.4	21.0	12.3
49	10.4	23.0	12.0
50	8.7	24.2	12.4
Mean	8.78	22.48	12.53
SD	0.69	1.10	0.49
N	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 3: 250 Units/kg	Haematological Parameters		
	TPT (Seconds)	aPTT (Seconds)	TT (Seconds)
61	9.5	21.8	13.1
62	8.3	21.4	12.7
63	8.3	21.3	13.3
64	9.0	20.2	12.3
65	9.7	30.0	12.5
66	8.8	21.3	12.9
67	8.4	21.1	12.8
68	9.1	21.9	12.2
69	8.6	21.4	12.6
70	8.5	20.9	12.4
Mean	8.82	22.13	12.68
SD	0.50	2.81	0.35
N	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters		
	TPT (Seconds)	aPTT (Seconds)	TT (Seconds)
86	8.5	26.4	13.1
87	8.5	21.5	12.9
88	8.5	20.9	12.8
89	8.4	22.7	12.7
90	10.5	21.8	12.0
91	8.5	22.9	12.9
92	8.5	21.9	13.0
93	8.4	21.7	12.7
94	8.4	18.9	12.6
95	8.5	23.1	12.8
Mean	8.67	22.18	12.75
SD	0.64	1.91	0.30
N	10	10	10

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 44 Relative to Start Date

Group 1: Control	Haematological Parameters		
	TPT (Seconds)	aPTT (Seconds)	TT (Seconds)
26	9.1	24.4	12.8
27	9.2	22.7	12.2
28	8.6	21.7	12.7
29	9.0	21.5	13.2
30	8.6	24.6	12.9
Mean	8.90	22.98	12.76
SD	0.28	1.46	0.36
N	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

Sex: Female Day: 44 Relative to Start Date

Group 4: 500 Units/kg	Haematological Parameters		
	TPT (Seconds)	aPTT (Seconds)	TT (Seconds)
96	8.9	24.4	12.8
97	9.4	21.4	12.5
98	9.0	22.9	13.0
99	8.6	25.4	13.8
100	8.7	22.9	13.0
Mean	8.92	23.40	13.02
SD	0.31	1.54	0.48
N	5	5	5

TABLE 4-2 Haematological Parameters - Individual Data Mouse

<u>Comments and Markers</u>							
<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Subject</u>	<u>Measurement</u>	<u>Type</u>	<u>Marker</u>
	30	4	Male	76	TPT	Replacement	NM
<i>Comment:</i> No measurement possible as not enough sample material available							

TABLE 5-1

Biochemical Parameters - Summary

Mouse

Day: 30 Relative to Start Date

Sex: Male		Biochemical Parameters						
		Albumin	Globulin	Alb./Glob. Ratio	Bilirubin (total) (µmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (µmol/L)	BUN/Creat. Ratio
		(g/L)	(g/L)					
		[a]	[a1]	[a1]	[a2]	[a1]	[a1]	[a1]
Group 1: Control	Mean	28.57	22.03	1.300	3.11	2.393	29.0	313.594
	SD	0.76	1.33	0.070	0.70	0.408	1.9	28.196
	N	10	10	10	10	10	10	10
Group 2: 50 Units/kg	Mean	27.96	22.44	1.255	3.73	2.146	28.8	316.533
	SD	1.67	1.73	0.141	1.23	0.560	1.1	45.966
	N	10	10	10	10	10	10	10
	%Diff	-2.1	1.9	-3.5	19.9	-10.3	-0.7	0.9
Group 3: 250 Units/kg	Mean	28.21	22.49	1.259	3.65	2.287	29.7	310.724
	SD	0.84	1.30	0.093	0.63	0.396	2.7	29.330
	N	10	10	10	10	10	10	10
	%Diff	-1.3	2.1	-3.2	17.4	-4.4	2.4	-0.9
Group 4: 500 Units/kg	Mean	28.35	22.55	1.260	3.49	2.313	28.7	308.041
	SD	0.70	1.17	0.070	0.48	0.352	1.8	22.049
	N	10	10	10	10	10	10	10
	%Diff	-0.8	2.4	-3.1	12.2	-3.3	-1.0	-1.8

[a] - Anova & Dunnett(Rank)

[a1] - Anova & Dunnett

[a2] - Anova & Dunnett(Log)

TABLE 5-1

Biochemical Parameters - Summary

Mouse

Day: 44 Relative to Start Date

Sex: Male		Biochemical Parameters						
		Albumin	Globulin	Alb./Glob. Ratio	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	BUN/Creat. Ratio
		(g/L)	(g/L)					
		[a]	[a]	[a]	[a]	[a]	[a]	[a]
Group 1: Control	Mean	28.72	22.68	1.270	3.34	2.162	32.6	306.046
	SD	0.51	1.33	0.081	0.32	0.179	2.5	32.601
	N	5	5	5	5	5	5	5
Group 4: 500 Units/kg	Mean	28.52	22.48	1.270	3.10	1.954	32.2	322.741
	SD	0.39	0.84	0.061	0.55	0.197	1.6	70.912
	N	5	5	5	5	5	5	5
	%Diff	-0.7	-0.9	0.0	-7.2	-9.6	-1.2	5.5

[a] - Anova & Dunnett

TABLE 5-1

Biochemical Parameters - Summary

Mouse

Day: 30 Relative to Start Date

Sex: Male		Biochemical Parameters						
		Glucose	Protein	Urea	Calcium	Chloride	Potas- sium	Sodium
		(mmol/L)	(total) (g/L)	(in blood) (mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)
		[a]	[a]	[a]	[a1]	[a1]	[a]	[a]
Group 1: Control	Mean	9.965	50.6	9.110	2.239	118.1	3.960	148.1
	SD	2.206	1.8	1.156	0.096	2.1	0.131	1.0
	N	10	10	10	10	10	10	10
Group 2: 50 Units/kg	Mean	8.806	50.4	9.120	2.228	119.0	3.972	148.8
	SD	1.814	1.8	1.391	0.077	1.1	0.232	0.4
	N	10	10	10	10	10	10	10
	%Diff	-11.6	-0.4	0.1	-0.5	0.8	0.3	0.5
Group 3: 250 Units/kg	Mean	10.140	50.7	9.210	2.217	118.2	4.005	148.1
	SD	2.299	1.3	0.997	0.080	0.8	0.243	0.9
	N	10	10	10	10	10	10	10
	%Diff	1.8	0.2	1.1	-1.0	0.1	1.1	0.0
Group 4: 500 Units/kg	Mean	9.783	50.9	8.859	2.211	119.1	4.025	148.5
	SD	1.834	1.4	1.017	0.074	1.9	0.260	1.0
	N	10	10	10	10	10	10	10
	%Diff	-1.8	0.6	-2.8	-1.3	0.8	1.6	0.3

[a] - Anova & Dunnett

[a1] - Anova & Dunnett(Rank)

TABLE 5-1

Biochemical Parameters - Summary

Mouse

Day: 44 Relative to Start Date

Sex: Male		Biochemical Parameters						
		Glucose	Protein	Urea	Calcium	Chloride	Potas- sium	Sodium
		(mmol/L)	(total) (g/L)	(in blood) (mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)
		[a]	[a]	[a]	[a]	[a]	[a]	[a]
Group 1: Control	Mean	10.302	51.4	9.960	2.302	118.8	3.936	149.0
	SD	1.640	1.3	1.155	0.044	0.4	0.252	0.7
	N	5	5	5	5	5	5	5
Group 4: 500 Units/kg	Mean	8.786	51.0	10.420	2.276	118.6	3.956	149.4
	SD	2.066	0.7	2.517	0.054	1.1	0.325	0.9
	N	5	5	5	5	5	5	5
	%Diff	-14.7	-0.8	4.6	-1.1	-0.2	0.5	0.3

[a] - Anova & Dunnett

TABLE 5-1

Biochemical Parameters - Summary

Mouse

Day: 30 Relative to Start Date

Sex: Male		Biochemical Parameters				
		ALAT	aP	ASAT	LDH	CK
		(U/L)	(U/L)	(U/L)	(U/L)	(U/L)
		[a]	[a]	[a1]	[a1]	[a2]
Group 1: Control	Mean	33.7	81.2	87.7	204.5	188.6
	SD	7.5	11.6	27.5	39.3	90.5
	N	10	10	10	10	10
Group 2: 50 Units/kg	Mean	43.5	88.7	133.2	320.5	272.9
	SD	12.8	17.8	74.2	226.2	294.7
	N	10	10	10	10	10
	%Diff	29.1	9.2	51.9	56.7	44.7
Group 3: 250 Units/kg	Mean	38.2	87.2	116.2	277.2	283.9
	SD	11.5	14.8	23.2	62.2	97.3
	N	10	10	10	10	10
	%Diff	13.4	7.4	32.5	35.6	50.5
Group 4: 500 Units/kg	Mean	38.5	83.8	102.5	245.7	240.3
	SD	9.5	20.9	37.4	58.0	182.6
	N	10	10	10	10	10
	%Diff	14.2	3.2	16.9	20.1	27.4

[a] - Anova & Dunnett

[a1] - Anova & Dunnett(Rank)

[a2] - Anova & Dunnett(Log)

TABLE 5-1

Biochemical Parameters - Summary

Mouse

Day: 44 Relative to Start Date

Sex: Male		Biochemical Parameters				
		ALAT	aP	ASAT	LDH	CK
		(U/L)	(U/L)	(U/L)	(U/L)	(U/L)
		[a]	[a]	[a]	[a]	[a]
Group 1: Control	Mean	29.6	80.6	82.8	190.8	150.8
	SD	4.3	13.6	16.8	51.9	83.7
	N	5	5	5	5	5
Group 4: 500 Units/kg	Mean	43.8*	93.2	124.6*	255.0	252.0
	SD	10.0	9.8	27.6	55.9	87.4
	N	5	5	5	5	5
	%Diff	48.0	15.6	50.5	33.6	67.1

[a] - Anova & Dunnett: * = $p \leq 0.05$

TABLE 5-1

Biochemical Parameters - Summary

Mouse

Day: 30 Relative to Start Date

Sex: Female		Biochemical Parameters						
		Albumin	Globulin	Alb./Glob. Ratio	Bilirubin (total) (µmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (µmol/L)	BUN/Creat. Ratio
		(g/L)	(g/L)					
		[a]	[a1]	[a1]	[a2]	[a1]	[a1]	[a]
Group 1: Control	Mean	29.34	20.86	1.414	3.36	1.720	30.0	307.376
	SD	1.06	1.48	0.121	0.77	0.294	3.7	39.540
	N	10	10	10	10	10	10	10
Group 2: 50 Units/kg	Mean	28.18	20.02	1.413	3.54	1.622	28.4	411.988
	SD	2.66	2.12	0.124	0.78	0.296	4.1	245.277
	N	10	10	10	10	10	10	10
Group 3: 250 Units/kg	%Diff	-4.0	-4.0	0.0	5.4	-5.7	-5.3	34.0
	Mean	29.23	21.37	1.374	4.09	1.553	31.6	342.632
	SD	1.12	1.64	0.104	1.59	0.292	2.5	89.937
Group 4: 500 Units/kg	N	10	10	10	10	10	10	10
	%Diff	-0.4	2.4	-2.8	21.7	-9.7	5.3	11.5
	Mean	29.49	21.51	1.377	3.14	1.685	32.0	314.451
	SD	0.87	1.72	0.091	1.03	0.311	2.5	98.328
	N	10	10	10	10	10	10	10
	%Diff	0.5	3.1	-2.6	-6.5	-2.0	6.7	2.3

[a] - Anova & Dunnett(Rank)

[a1] - Anova & Dunnett

[a2] - Anova & Dunnett(Log)

TABLE 5-1

Biochemical Parameters - Summary

Mouse

Day: 44 Relative to Start Date

Sex: Female		Biochemical Parameters						
		Albumin	Globulin	Alb./Glob. Ratio	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	BUN/Creat. Ratio
		(g/L)	(g/L)					
		[a]	[a1]	[a1]	[a1]	[a1]	[a1]	[a1]
Group 1: Control	Mean	28.50	19.10	1.494	4.20	1.374	32.8	332.884
	SD	0.41	0.72	0.054	0.37	0.196	1.1	60.329
	N	5	5	5	5	5	5	5
Group 4: 500 Units/kg	Mean	28.64	18.96	1.518	4.18	1.578	33.4	341.409
	SD	1.32	1.50	0.137	0.94	0.286	2.9	75.379
	N	5	5	5	5	5	5	5
	%Diff	0.5	-0.7	1.6	-0.5	14.8	1.8	2.6

[a] - Anova & Dunnett(Rank)

[a1] - Anova & Dunnett

TABLE 5-1

Biochemical Parameters - Summary

Mouse

Day: 30 Relative to Start Date

Sex: Female		Biochemical Parameters						
		Glucose	Protein	Urea	Calcium	Chloride	Potas- sium	Sodium
		(mmol/L)	(total) (g/L)	(in blood) (mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)
		[a]	[a1]	[a2]	[a1]	[a1]	[a]	[a1]
Group 1: Control	Mean	8.281	50.2	9.215	2.324	119.5	4.031	149.0
	SD	1.164	1.7	1.616	0.031	1.4	0.421	1.3
	N	10	10	10	10	10	10	10
Group 2: 50 Units/kg	Mean	6.607	48.2	10.975	2.258	119.2	4.037	148.3
	SD	2.306	4.4	4.569	0.096	3.1	0.417	1.8
	N	10	10	10	10	10	10	10
Group 3: 250 Units/kg	%Diff	-20.2	-4.0	19.1	-2.8	-0.3	0.1	-0.5
	Mean	7.358	50.6	10.789	2.272	120.0	3.872	149.0
	SD	2.416	2.1	2.657	0.082	2.4	0.300	1.1
Group 4: 500 Units/kg	N	10	10	10	10	10	10	10
	%Diff	-11.1	0.8	17.1	-2.2	0.4	-3.9	0.0
	Mean	8.258	51.0	10.093	2.281	119.1	3.860	148.8
	SD	2.394	2.4	3.317	0.073	1.1	0.472	0.6
	N	10	10	10	10	10	10	10
	%Diff	-0.3	1.6	9.5	-1.9	-0.3	-4.2	-0.1

[a] - Anova & Dunnett

[a1] - Anova & Dunnett(Rank)

[a2] - Anova & Dunnett(Log)

TABLE 5-1

Biochemical Parameters - Summary

Mouse

Day: 44 Relative to Start Date

Sex: Female		Biochemical Parameters						
		Glucose	Protein	Urea	Calcium	Chloride	Potas- sium	Sodium
		(mmol/L)	(total) (g/L)	(in blood) (mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)	(mmol/L)
		[a]	[a1]	[a1]	[a1]	[a1]	[a1]	[a1]
Group 1: Control	Mean	6.726	47.6	10.918	2.192	119.4	3.734	149.0
	SD	0.654	0.9	2.019	0.040	1.7	0.115	1.2
	N	5	5	5	5	5	5	5
Group 4: 500 Units/kg	Mean	7.302	47.6	11.436	2.234	118.0	3.804	148.4
	SD	2.885	2.1	2.874	0.048	1.6	0.145	0.5
	N	5	5	5	5	5	5	5
	%Diff	8.6	0.0	4.7	1.9	-1.2	1.9	-0.4

[a] - Anova & Dunnett(Rank)

[a1] - Anova & Dunnett

TABLE 5-1

Biochemical Parameters - Summary

Mouse

Day: 30 Relative to Start Date

Sex: Female		Biochemical Parameters				
		ALAT	aP	ASAT	LDH	CK
		(U/L)	(U/L)	(U/L)	(U/L)	(U/L)
		[a]	[a1]	[a]	[a]	[a2]
Group 1: Control	Mean	47.0	163.7	203.8	354.8	408.8
	SD	14.8	22.6	143.7	168.6	421.7
	N	10	10	10	10	10
Group 2: 50 Units/kg	Mean	84.9	152.3	682.1	818.8	2612.7
	SD	71.7	26.5	950.5	1006.1	4670.1
	N	10	10	10	10	10
	%Diff	80.6	-7.0	234.7	130.8	539.1
Group 3: 250 Units/kg	Mean	90.4	179.3	749.2	959.5	1877.1
	SD	64.6	31.3	964.8	1145.6	2752.4
	N	10	10	10	10	10
	%Diff	92.3	9.5	267.6	170.4	359.2
Group 4: 500 Units/kg	Mean	49.7	157.4	242.4	399.5	556.3
	SD	21.4	20.5	207.0	291.3	697.6
	N	10	10	10	10	10
	%Diff	5.7	-3.8	18.9	12.6	36.1

[a] - Anova & Dunnett(Rank)

[a1] - Anova & Dunnett

[a2] - Anova & Dunnett(Log)

TABLE 5-1

Biochemical Parameters - Summary

Mouse

Day: 44 Relative to Start Date

Sex: Female		Biochemical Parameters				
		ALAT	aP	ASAT	LDH	CK
		(U/L)	(U/L)	(U/L)	(U/L)	(U/L)
		[a]	[a]	[a]	[a1]	[a]
Group 1: Control	Mean	72.8	156.8	384.0	570.8	1076.6
	SD	10.3	17.3	58.1	99.1	460.2
	N	5	5	5	5	5
Group 4: 500 Units/kg	Mean	59.8	148.4	301.4	558.8	899.8
	SD	25.5	33.4	163.8	416.8	646.4
	N	5	5	5	5	5
	%Diff	-17.9	-5.4	-21.5	-2.1	-16.4

[a] - Anova & Dunnett

[a1] - Anova & Dunnett(Rank)

TABLE 5-1 Biochemical Parameters - Summary Mouse

<u>Comments and Markers</u>					
<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker Comment</u>
44		4	Male	ALAT	* Anova & Dunnett: * = p ≤ 0.05
44		4	Male	ASAT	* Anova & Dunnett: * = p ≤ 0.05

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 1: Control	Biochemical Parameters						
	Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	BUN/Creat. Ratio
1	29.2	22.8	1.28	2.9	2.67	32	340.00
2	29.0	22.0	1.32	2.8	2.58	28	265.00
3	27.9	21.1	1.32	3.0	2.87	26	293.46
4	29.2	20.8	1.40	2.6	1.62	32	330.63
5	28.1	23.9	1.18	4.2	2.31	29	343.10
6	26.9	20.1	1.34	2.6	2.39	29	302.76
7	28.6	23.4	1.22	2.4	2.89	29	286.90
8	29.3	22.7	1.29	3.5	2.51	27	354.44
9	28.5	20.5	1.39	2.7	2.20	29	311.03
10	29.0	23.0	1.26	4.4	1.89	29	308.62
Mean	28.57	22.03	1.300	3.11	2.393	29.0	313.594
SD	0.76	1.33	0.070	0.70	0.408	1.9	28.196
N	10	10	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 2: 50 Units/kg	Biochemical Parameters						
	Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	BUN/Creat. Ratio
31	26.9	22.1	1.22	3.3	2.31	27	307.04
32	29.3	22.7	1.29	2.8	2.30	29	273.10
33	27.1	22.9	1.18	3.2	2.58	28	228.57
34	28.1	18.9	1.49	6.0	1.15	29	373.45
35	27.3	21.7	1.26	5.5	1.75	28	367.86
36	28.5	23.5	1.21	2.9	2.77	31	286.13
37	24.4	25.6	0.95	3.6	2.19	30	362.00
38	30.6	22.4	1.37	2.3	2.65	29	312.07
39	28.8	21.2	1.36	3.1	1.31	28	318.21
40	28.6	23.4	1.22	4.6	2.45	29	336.90
Mean	27.96	22.44	1.255	3.73	2.146	28.8	316.533
SD	1.67	1.73	0.141	1.23	0.560	1.1	45.966
N	10	10	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 3: 250 Units/kg	Biochemical Parameters						
	Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	BUN/Creat. Ratio
51	29.5	22.5	1.31	3.2	2.11	31	303.87
52	27.4	22.6	1.21	3.2	2.20	27	291.48
53	26.6	24.4	1.09	4.9	1.76	34	309.41
54	28.1	23.9	1.18	4.1	2.46	34	290.59
55	29.1	20.9	1.39	3.3	2.32	30	325.00
56	28.0	22.0	1.27	3.9	2.86	29	282.41
57	28.8	22.2	1.30	2.6	2.25	29	307.59
58	28.3	23.7	1.19	3.8	2.73	28	277.50
59	28.5	22.5	1.27	3.6	2.57	26	360.77
60	27.8	20.2	1.38	3.9	1.61	29	358.62
Mean	28.21	22.49	1.259	3.65	2.287	29.7	310.724
SD	0.84	1.30	0.093	0.63	0.396	2.7	29.330
N	10	10	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 4: 500 Units/kg	Biochemical Parameters						
	Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Bilirubin (total) (μmol/L)	Cholest- rol (total) (mmol/L)	Crea- tinine (μmol/L)	BUN/Creat. Ratio
71	28.0	23.0	1.22	3.7	2.49	26	289.23
72	27.9	20.1	1.39	3.4	3.06	28	307.50
73	28.7	22.3	1.29	2.5	2.35	29	333.79
74	28.9	24.1	1.20	3.6	2.31	31	287.42
75	27.7	22.3	1.24	3.3	2.46	27	292.22
76	29.2	21.8	1.34	3.6	1.72	30	332.33
77	27.0	23.0	1.17	3.1	2.22	27	271.48
78	29.0	22.0	1.32	3.9	2.37	28	315.71
79	28.9	24.1	1.20	4.3	2.19	31	318.39
80	28.2	22.8	1.24	3.5	1.96	30	332.33
Mean	28.35	22.55	1.260	3.49	2.313	28.7	308.041
SD	0.70	1.17	0.070	0.48	0.352	1.8	22.049
N	10	10	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Male Day: 44 Relative to Start Date

Group 1: Control	Biochemical Parameters						
	Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Bilirubin (total) (μmol/L)	Cholesterol (total) (mmol/L)	Creatinine (μmol/L)	BUN/Creat. Ratio
11	28.5	21.5	1.33	3.3	2.13	29	324.83
12	28.7	21.3	1.35	3.2	2.17	33	250.91
13	28.1	23.9	1.18	3.1	2.04	32	315.00
14	28.8	24.2	1.19	3.2	2.46	33	333.94
15	29.5	22.5	1.31	3.9	2.01	36	305.56
Mean	28.72	22.68	1.270	3.34	2.162	32.6	306.046
SD	0.51	1.33	0.081	0.32	0.179	2.5	32.601
N	5	5	5	5	5	5	5

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Male Day: 44 Relative to Start Date

Group 4: 500 Units/kg	Biochemical Parameters						
	Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	BUN/Creat. Ratio
81	28.8	23.2	1.24	2.7	2.11	34	337.06
82	28.1	22.9	1.23	3.9	1.75	33	263.03
83	28.1	22.9	1.23	2.5	1.92	31	256.13
84	28.7	22.3	1.29	3.3	1.79	33	431.82
85	28.9	21.1	1.37	3.1	2.20	30	325.67
Mean	28.52	22.48	1.270	3.10	1.954	32.2	322.741
SD	0.39	0.84	0.061	0.55	0.197	1.6	70.912
N	5	5	5	5	5	5	5

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 1: Control	Biochemical Parameters						
	Glucose (mmol/L)	Protein (total) (g/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)
1	13.27	52	10.88	2.32	117	3.93	148
2	9.67	51	7.42	2.25	118	3.95	147
3	9.72	49	7.63	2.29	119	3.81	149
4	10.12	50	10.58	2.11	118	3.70	149
5	8.06	52	9.95	2.13	120	4.00	149
6	13.26	47	8.78	2.35	113	4.03	146
7	9.09	52	8.32	2.37	118	4.10	148
8	5.89	52	9.57	2.25	121	4.12	149
9	10.85	49	9.02	2.12	118	3.91	148
10	9.72	52	8.95	2.20	119	4.05	148
Mean	9.965	50.6	9.110	2.239	118.1	3.960	148.1
SD	2.206	1.8	1.156	0.096	2.1	0.131	1.0
N	10	10	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 2: 50 Units/kg	Biochemical Parameters						
	Glucose (mmol/L)	Protein (total) (g/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)
31	7.91	49	8.29	2.27	119	4.04	149
32	9.11	52	7.92	2.22	119	4.04	149
33	10.71	50	6.40	2.24	118	3.84	148
34	5.51	47	10.83	2.06	117	3.48	148
35	6.27	49	10.30	2.17	120	4.28	149
36	8.72	52	8.87	2.27	118	3.98	149
37	10.06	50	10.86	2.17	120	3.89	149
38	10.49	53	9.05	2.31	120	3.82	149
39	10.64	50	8.91	2.26	120	4.24	149
40	8.64	52	9.77	2.31	119	4.11	149
Mean	8.806	50.4	9.120	2.228	119.0	3.972	148.8
SD	1.814	1.8	1.391	0.077	1.1	0.232	0.4
N	10	10	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 3: 250 Units/kg	Biochemical Parameters						
	Glucose (mmol/L)	Protein (total) (g/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)
51	11.08	52	9.42	2.23	117	3.94	148
52	11.20	50	7.87	2.23	118	3.95	148
53	14.31	51	10.52	2.05	119	4.00	148
54	10.70	52	9.88	2.28	118	4.23	147
55	10.49	50	9.75	2.28	119	3.70	150
56	11.03	50	8.19	2.24	117	4.48	147
57	8.26	51	8.92	2.16	118	3.95	148
58	10.26	52	7.77	2.30	119	3.84	148
59	8.47	51	9.38	2.27	119	4.23	148
60	5.60	48	10.40	2.13	118	3.73	149
Mean	10.140	50.7	9.210	2.217	118.2	4.005	148.1
SD	2.299	1.3	0.997	0.080	0.8	0.243	0.9
N	10	10	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 4: 500 Units/kg	Biochemical Parameters						
	Glucose (mmol/L)	Protein (total) (g/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)
71	12.04	51	7.52	2.30	116	4.05	147
72	13.32	48	8.61	2.27	118	4.55	147
73	8.41	51	9.68	2.21	119	3.98	149
74	9.57	53	8.91	2.30	121	4.08	149
75	8.91	50	7.89	2.24	118	4.09	148
76	8.60	51	9.97	2.10	120	3.74	150
77	7.52	50	7.33	2.11	118	3.90	148
78	9.67	51	8.84	2.24	118	3.84	149
79	8.59	53	9.87	2.20	122	4.32	149
80	11.20	51	9.97	2.14	121	3.70	149
Mean	9.783	50.9	8.859	2.211	119.1	4.025	148.5
SD	1.834	1.4	1.017	0.074	1.9	0.260	1.0
N	10	10	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Male Day: 44 Relative to Start Date

Group 1: Control	Biochemical Parameters						
	Glucose (mmol/L)	Protein (total) (g/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)
11	9.32	50	9.42	2.30	118	4.08	148
12	12.79	50	8.28	2.29	119	3.75	149
13	9.31	52	10.08	2.24	119	3.67	150
14	8.93	53	11.02	2.36	119	4.29	149
15	11.16	52	11.00	2.32	119	3.89	149
Mean	10.302	51.4	9.960	2.302	118.8	3.936	149.0
SD	1.640	1.3	1.155	0.044	0.4	0.252	0.7
N	5	5	5	5	5	5	5

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Male Day: 44 Relative to Start Date

Group 4: 500 Units/kg	Biochemical Parameters						
	Glucose (mmol/L)	Protein (total) (g/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)
81	10.37	52	11.46	2.28	118	3.64	150
82	10.53	51	8.68	2.21	119	3.74	149
83	7.99	51	7.94	2.24	117	3.99	148
84	5.56	51	14.25	2.35	120	4.48	150
85	9.48	50	9.77	2.30	119	3.93	150
Mean	8.786	51.0	10.420	2.276	118.6	3.956	149.4
SD	2.066	0.7	2.517	0.054	1.1	0.325	0.9
N	5	5	5	5	5	5	5

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 1: Control	Biochemical Parameters				
	ALAT (U/L)	aP (U/L)	ASAT (U/L)	LDH (U/L)	CK (U/L)
1	21	90	64	193	149
2	33	66	74	207	223
3	33	89	90	200	156
4	41	97	136	223	248
5	42	83	105	242	162
6	33	60	41	130	29
7	21	77	65	147	115
8	37	91	109	223	259
9	40	77	104	252	361
10	36	82	89	228	184
Mean	33.7	81.2	87.7	204.5	188.6
SD	7.5	11.6	27.5	39.3	90.5
N	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 2: 50 Units/kg	Biochemical Parameters				
	ALAT (U/L)	aP (U/L)	ASAT (U/L)	LDH (U/L)	CK (U/L)
31	44	75	123	259	109
32	57	98	79	231	53
33	32	94	101	212	145
34	62	127	329	715	988
35	64	95	153	315	304
36	33	83	97	222	162
37	35	99	96	261	31
38	36	66	103	167	128
39	31	75	87	74	244
40	41	75	164	749	565
Mean	43.5	88.7	133.2	320.5	272.9
SD	12.8	17.8	74.2	226.2	294.7
N	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 3: 250 Units/kg	Biochemical Parameters				
	ALAT (U/L)	aP (U/L)	ASAT (U/L)	LDH (U/L)	CK (U/L)
51	41	108	123	235	261
52	51	68	122	292	388
53	13	87	133	356	408
54	36	74	110	283	307
55	33	91	92	182	146
56	39	72	111	345	257
57	38	88	98	231	109
58	32	77	84	204	361
59	44	96	124	295	323
60	55	111	165	349	279
Mean	38.2	87.2	116.2	277.2	283.9
SD	11.5	14.8	23.2	62.2	97.3
N	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 4: 500 Units/kg	Biochemical Parameters				
	ALAT (U/L)	aP (U/L)	ASAT (U/L)	LDH (U/L)	CK (U/L)
71	25	69	79	204	166
72	34	32	82	259	221
73	30	93	86	174	95
74	47	88	130	267	218
75	51	82	78	222	95
76	35	107	96	216	139
77	39	93	89	222	134
78	30	84	98	227	347
79	41	91	87	282	282
80	53	99	200	384	706
Mean	38.5	83.8	102.5	245.7	240.3
SD	9.5	20.9	37.4	58.0	182.6
N	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Male Day: 44 Relative to Start Date

Group 1: Control	Biochemical Parameters				
	ALAT	aP	ASAT	LDH	CK
	(U/L)	(U/L)	(U/L)	(U/L)	(U/L)
11	37	102	87	164	60
12	27	77	69	180	147
13	29	74	62	150	92
14	29	66	102	281	275
15	26	84	94	179	180
Mean	29.6	80.6	82.8	190.8	150.8
SD	4.3	13.6	16.8	51.9	83.7
N	5	5	5	5	5

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Male Day: 44 Relative to Start Date

Group 4: 500 Units/kg	Biochemical Parameters				
	ALAT (U/L)	aP (U/L)	ASAT (U/L)	LDH (U/L)	CK (U/L)
81	34	92	90	185	143
82	39	82	141	285	323
83	53	96	116	322	192
84	56	108	162	272	352
85	37	88	114	211	250
Mean	43.8	93.2	124.6	255.0	252.0
SD	10.0	9.8	27.6	55.9	87.4
N	5	5	5	5	5

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 1: Control	Biochemical Parameters						
	Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Bilirubin (total) (μmol/L)	Cholest- rol (total) (mmol/L)	Crea- tinine (μmol/L)	BUN/Creat. Ratio
16	29.6	20.4	1.45	2.9	1.91	30	241.00
17	27.9	21.1	1.32	4.7	1.88	29	259.66
18	30.1	18.9	1.59	3.7	1.54	36	312.78
19	28.2	21.8	1.29	4.4	2.20	27	315.93
20	28.2	22.8	1.24	3.3	1.86	31	271.61
21	29.3	18.7	1.57	3.1	1.33	29	362.41
22	30.6	20.4	1.50	2.1	1.99	23	310.00
23	29.2	19.8	1.47	3.6	1.31	33	323.33
24	29.2	21.8	1.34	3.0	1.54	28	358.21
25	31.1	22.9	1.36	2.8	1.64	34	318.82
Mean	29.34	20.86	1.414	3.36	1.720	30.0	307.376
SD	1.06	1.48	0.121	0.77	0.294	3.7	39.540
N	10	10	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 2: 50 Units/kg	Biochemical Parameters						
	Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	BUN/Creat. Ratio
41	29.7	19.3	1.54	2.6	1.69	32	293.75
42	29.7	17.3	1.72	3.8	1.20	32	434.38
43	26.7	19.3	1.38	3.3	1.74	27	199.26
44	28.9	21.1	1.37	2.7	1.78	31	257.10
45	30.8	22.2	1.39	3.4	1.57	27	358.52
46	29.5	21.5	1.37	2.8	1.79	30	235.67
47	29.8	22.2	1.34	3.2	2.14	30	268.67
48	23.9	17.1	1.40	4.7	1.68	21	912.38
49	23.2	17.8	1.30	4.6	1.12	22	799.55
50	29.6	22.4	1.32	4.3	1.51	32	360.63
Mean	28.18	20.02	1.413	3.54	1.622	28.4	411.988
SD	2.66	2.12	0.124	0.78	0.296	4.1	245.277
N	10	10	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 3: 250 Units/kg	Biochemical Parameters						
	Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	BUN/Creat. Ratio
61	29.1	20.9	1.39	5.0	1.42	34	368.82
62	28.4	20.6	1.38	2.5	2.09	31	242.26
63	29.3	21.7	1.35	2.6	1.64	28	268.21
64	27.4	19.6	1.40	5.7	1.02	30	303.00
65	29.6	19.4	1.53	7.2	1.60	29	547.24
66	28.4	24.6	1.15	3.6	1.62	30	333.00
67	31.6	21.4	1.48	2.9	1.71	34	268.53
68	29.0	20.0	1.45	5.0	1.30	31	425.48
69	30.0	23.0	1.30	2.5	1.76	36	319.17
70	29.5	22.5	1.31	3.9	1.37	33	350.61
Mean	29.23	21.37	1.374	4.09	1.553	31.6	342.632
SD	1.12	1.64	0.104	1.59	0.292	2.5	89.937
N	10	10	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 4: 500 Units/kg	Biochemical Parameters						
	Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	BUN/Creat. Ratio
86	30.4	22.6	1.35	2.6	2.18	28	292.86
87	28.7	21.3	1.35	2.2	2.00	28	247.86
88	30.1	23.9	1.26	2.9	1.69	31	298.39
89	29.0	22.0	1.32	2.6	1.95	33	243.03
90	28.4	18.6	1.53	5.6	1.50	32	579.38
91	30.8	21.2	1.45	2.7	1.60	34	320.29
92	29.3	21.7	1.35	4.0	1.58	34	329.71
93	29.8	20.2	1.48	2.4	1.66	35	315.71
94	28.3	19.7	1.44	3.7	1.05	34	264.71
95	30.1	23.9	1.26	2.7	1.64	31	252.58
Mean	29.49	21.51	1.377	3.14	1.685	32.0	314.451
SD	0.87	1.72	0.091	1.03	0.311	2.5	98.328
N	10	10	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Female Day: 44 Relative to Start Date

Group 1: Control	Biochemical Parameters						
	Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Bilirubin (total) (μmol/L)	Cholesterol (total) (mmol/L)	Creatinine (μmol/L)	BUN/Creat. Ratio
26	28.4	18.6	1.53	4.3	1.13	33	403.33
27	28.7	20.3	1.41	4.1	1.41	33	374.85
28	27.9	19.1	1.46	4.5	1.35	31	325.16
29	29.0	19.0	1.53	4.5	1.67	34	314.41
30	28.5	18.5	1.54	3.6	1.31	33	246.67
Mean	28.50	19.10	1.494	4.20	1.374	32.8	332.884
SD	0.41	0.72	0.054	0.37	0.196	1.1	60.329
N	5	5	5	5	5	5	5

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Female Day: 44 Relative to Start Date

Group 4: 500 Units/kg	Biochemical Parameters						
	Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Bilirubin (total) (μmol/L)	Cholesterol (total) (mmol/L)	Creatinine (μmol/L)	BUN/Creat. Ratio
96	28.9	19.1	1.51	4.8	1.42	31	351.61
97	29.1	16.9	1.72	4.1	1.45	34	455.00
98	29.9	19.1	1.57	5.4	1.32	38	342.89
99	28.9	21.1	1.37	3.1	2.04	33	248.18
100	26.4	18.6	1.42	3.5	1.66	31	309.35
Mean	28.64	18.96	1.518	4.18	1.578	33.4	341.409
SD	1.32	1.50	0.137	0.94	0.286	2.9	75.379
N	5	5	5	5	5	5	5

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 1: Control	Biochemical Parameters						
	Glucose (mmol/L)	Protein (total) (g/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)
16	8.16	50	7.23	2.33	118	4.17	149
17	10.87	49	7.53	2.28	120	4.48	148
18	8.04	49	11.26	2.33	120	3.56	150
19	7.64	50	8.53	2.32	121	4.05	149
20	7.63	51	8.42	2.33	117	4.32	147
21	6.83	48	10.51	2.28	120	3.73	151
22	9.35	51	7.13	2.39	118	4.07	148
23	7.47	49	10.67	2.31	121	3.40	151
24	7.84	51	10.03	2.33	121	4.75	148
25	8.98	54	10.84	2.34	119	3.78	149
Mean	8.281	50.2	9.215	2.324	119.5	4.031	149.0
SD	1.164	1.7	1.616	0.031	1.4	0.421	1.3
N	10	10	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 2: 50 Units/kg	Biochemical Parameters						
	Glucose (mmol/L)	Protein (total) (g/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)
41	6.13	49	9.40	2.32	119	3.27	150
42	5.77	47	13.90	2.24	119	3.43	150
43	8.32	46	5.38	2.30	113	4.31	144
44	9.73	50	7.97	2.28	117	4.25	147
45	6.36	53	9.68	2.31	120	3.75	149
46	7.92	51	7.07	2.27	118	4.00	149
47	7.61	52	8.06	2.32	118	4.34	148
48	3.10	41	19.16	2.16	122	4.42	148
49	2.65	41	17.59	2.03	124	4.41	148
50	8.48	52	11.54	2.35	122	4.19	150
Mean	6.607	48.2	10.975	2.258	119.2	4.037	148.3
SD	2.306	4.4	4.569	0.096	3.1	0.417	1.8
N	10	10	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 3: 250 Units/kg	Biochemical Parameters						
	Glucose (mmol/L)	Protein (total) (g/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)
61	4.36	50	12.54	2.15	122	3.46	149
62	9.78	49	7.51	2.29	117	4.17	148
63	7.66	51	7.51	2.26	117	3.92	148
64	7.56	47	9.09	2.17	118	3.92	148
65	4.11	49	15.87	2.43	123	4.46	148
66	7.06	53	9.99	2.25	122	3.54	150
67	9.58	53	9.13	2.29	121	3.97	150
68	4.71	49	13.19	2.24	123	3.73	151
69	11.22	53	11.49	2.36	118	3.63	149
70	7.54	52	11.57	2.28	119	3.92	149
Mean	7.358	50.6	10.789	2.272	120.0	3.872	149.0
SD	2.416	2.1	2.657	0.082	2.4	0.300	1.1
N	10	10	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 4: 500 Units/kg	Biochemical Parameters						
	Glucose (mmol/L)	Protein (total) (g/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)
86	9.07	53	8.20	2.32	119	3.65	149
87	9.43	50	6.94	2.20	119	4.14	148
88	9.07	54	9.25	2.27	119	4.22	149
89	9.62	51	8.02	2.40	120	4.03	149
90	2.98	47	18.54	2.23	121	4.29	148
91	6.21	52	10.89	2.28	119	2.90	150
92	7.70	51	11.21	2.30	119	3.63	149
93	12.02	50	11.05	2.32	118	3.52	148
94	8.74	48	9.00	2.15	117	3.71	149
95	7.74	54	7.83	2.34	120	4.51	149
Mean	8.258	51.0	10.093	2.281	119.1	3.860	148.8
SD	2.394	2.4	3.317	0.073	1.1	0.472	0.6
N	10	10	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Female Day: 44 Relative to Start Date

Group 1: Control	Biochemical Parameters						
	Glucose (mmol/L)	Protein (total) (g/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)
26	6.94	47	13.31	2.20	119	3.80	149
27	6.71	49	12.37	2.13	118	3.60	147
28	5.80	47	10.08	2.20	120	3.63	150
29	7.61	48	10.69	2.19	122	3.87	150
30	6.57	47	8.14	2.24	118	3.77	149
Mean	6.726	47.6	10.918	2.192	119.4	3.734	149.0
SD	0.654	0.9	2.019	0.040	1.7	0.115	1.2
N	5	5	5	5	5	5	5

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Female Day: 44 Relative to Start Date

Group 4: 500 Units/kg	Biochemical Parameters						
	Glucose (mmol/L)	Protein (total) (g/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)
96	6.68	48	10.90	2.24	118	3.65	148
97	4.00	46	15.47	2.15	120	3.70	149
98	6.54	49	13.03	2.25	119	3.86	148
99	11.93	50	8.19	2.27	117	3.79	149
100	7.36	45	9.59	2.26	116	4.02	148
Mean	7.302	47.6	11.436	2.234	118.0	3.804	148.4
SD	2.885	2.1	2.874	0.048	1.6	0.145	0.5
N	5	5	5	5	5	5	5

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 1: Control	Biochemical Parameters				
	ALAT (U/L)	aP (U/L)	ASAT (U/L)	LDH (U/L)	CK (U/L)
16	38	151	135	235	159
17	34	133	111	304	239
18	58	175	236	387	494
19	42	141	157	338	414
20	32	153	83	202	114
21	77	180	577	759	1522
22	37	141	107	173	129
23	65	186	273	484	565
24	42	178	171	329	170
25	45	199	188	337	282
Mean	47.0	163.7	203.8	354.8	408.8
SD	14.8	22.6	143.7	168.6	421.7
N	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 2: 50 Units/kg	Biochemical Parameters				
	ALAT (U/L)	aP (U/L)	ASAT (U/L)	LDH (U/L)	CK (U/L)
41	51	170	195	300	301
42	114	180	878	909	2408
43	28	130	112	145	44
44	37	131	83	153	84
45	41	182	173	334	369
46	40	131	116	204	296
47	35	142	115	225	290
48	209	143	2725	2908	14323
49	215	120	2088	2417	7254
50	79	194	336	593	758
Mean	84.9	152.3	682.1	818.8	2612.7
SD	71.7	26.5	950.5	1006.1	4670.1
N	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 3: 250 Units/kg	Biochemical Parameters				
	ALAT (U/L)	aP (U/L)	ASAT (U/L)	LDH (U/L)	CK (U/L)
61	80	231	472	821	1247
62	30	130	98	146	173
63	52	184	187	287	322
64	217	169	3006	3834	8772
65	194	213	1961	1998	4559
66	80	170	552	678	1436
67	41	166	138	237	185
68	99	190	626	823	1196
69	39	139	115	216	240
70	72	201	337	555	641
Mean	90.4	179.3	749.2	959.5	1877.1
SD	64.6	31.3	964.8	1145.6	2752.4
N	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 4: 500 Units/kg	Biochemical Parameters				
	ALAT (U/L)	aP (U/L)	ASAT (U/L)	LDH (U/L)	CK (U/L)
86	40	161	101	211	110
87	33	138	99	168	96
88	33	153	103	206	131
89	34	130	90	183	141
90	90	198	590	937	2259
91	60	164	247	416	673
92	84	163	648	913	1239
93	48	146	189	312	311
94	38	180	233	421	453
95	37	141	124	228	150
Mean	49.7	157.4	242.4	399.5	556.3
SD	21.4	20.5	207.0	291.3	697.6
N	10	10	10	10	10

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Female Day: 44 Relative to Start Date

Group 1: Control	Biochemical Parameters				
	ALAT (U/L)	aP (U/L)	ASAT (U/L)	LDH (U/L)	CK (U/L)
26	88	165	412	737	1425
27	67	174	381	571	1671
28	65	160	289	547	957
29	79	157	444	521	763
30	65	128	394	478	567
Mean	72.8	156.8	384.0	570.8	1076.6
SD	10.3	17.3	58.1	99.1	460.2
N	5	5	5	5	5

TABLE 5-2 Biochemical Parameters - Individual Data Mouse

Sex: Female Day: 44 Relative to Start Date

Group 4: 500 Units/kg	Biochemical Parameters				
	ALAT (U/L)	aP (U/L)	ASAT (U/L)	LDH (U/L)	CK (U/L)
96	72	159	316	526	780
97	86	191	500	1247	1989
98	75	163	414	564	897
99	26	117	108	197	459
100	40	112	169	260	374
Mean	59.8	148.4	301.4	558.8	899.8
SD	25.5	33.4	163.8	416.8	646.4
N	5	5	5	5	5

Allogenic APOSEC™		
TABLE 6-2	Urinalysis - Individual Data	Mouse

Animal No.	Colour	spec. Gravity (g/mL)	pH	Microscopy
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male animals

Test day 29

Group 1: Control

(1-5)	SC	1.007	7.8	A++
(6-10)	SC	1.009	8.1	A++
Mean:		1.008	7.95	

Group 2: 50 Units/kg

(31-35)	SC	1.010	7.2	A++
(36-40)	SC	1.010	7.3	
Mean:		1.010	7.25	

Group 3: 250 Units/kg

(51-55)	SC	1.012	7.8	A++
(56-60)	SC	1.012	8.0	A+
Mean:		1.012	7.90	

Group 4: 500 Units/kg

(71-75)	SC	1.011	7.6	A++
(76-80)	SC	1.011	7.8	
Mean:		1.011	7.70	

Test day 43

Group 1: Control

(11-15)	SC	1.003	7.0
Mean:		1.003	7.00

Group 4: 500 Units/kg

(81-85)	SC	1.011	7.6
Mean:		1.011	7.60

Allogenic APOSEC™		
TABLE 6-2	Urinalysis - Individual Data	Mouse

Animal No.	Colour	spec. Gravity (g/mL)	pH	Microscopy
------------	--------	----------------------	----	------------

female animals

Test day 29

Group 1: Control

(16-20)	SC	1.007	6.9
(21-25)	SC	1.009	7.6
Mean:		1.008	7.25

Group 2: 50 Units/kg

(41-45)	SC	1.010	7.3	E+
(46-50)	SC	1.011	7.3	
Mean:		1.011	7.30	

Group 3: 250 Units/kg

(61-65)	SC	1.012	7.4
(66-70)	SC	1.009	7.6
Mean:		1.011	7.50

Group 4: 500 Units/kg

(86-90)	SC	1.007	7.7
(91-95)	SC	1.007	7.5
Mean:		1.007	7.60

Test day 43

Group 1: Control

(26-30)	LC	1.012	7.1
Mean:		1.012	7.10

Group 4: 500 Units/kg

(96-100)	SC	1.014	6.6	E+
Mean:		1.014	6.60	

Allogenic APOSEC™
 TABLE 6-2 Urinalysis - Individual Data Mouse

TD 29

Animal No.	Nitrite		Protein (g/L)				Glucose (mmol/L)					Ketones			
	pos.	neg.	neg.	0.3	1	5	norm.	2.8	5.5	17	55	neg.	+	++	+++
male animals															
Group 1: Control															
(1-5)	x		x				x					x			
(6-10)	x		x				x					x			
Group 2: 50 Units/kg															
(31-35)	x		x				x					x			
(36-40)	x		x				x					x			
Group 3: 250 Units/kg															
(51-55)	x		x				x					x			
(56-60)	x		x				x					x			
Group 4: 500 Units/kg															
(71-75)	x		x				x					x			
(76-80)	x		x				x					x			

TD 43

Animal No.	Nitrite		Protein (g/L)				Glucose (mmol/L)					Ketones			
	pos.	neg.	neg.	0.3	1	5	norm.	2.8	5.5	17	55	neg.	+	++	+++
male animals															
Group 1: Control															
(11-15)		x	x				x					x			
Group 4: 500 Units/kg															
(81-85)	x		x				x					x			

Allogenic APOSEC™
 TABLE 6-2 Urinalysis - Individual Data Mouse

TD 29

Animal No.	Nitrite		Protein (g/L)				Glucose (mmol/L)					Ketones			
	pos.	neg.	neg.	0.3	1	5	norm.	2.8	5.5	17	55	neg.	+	++	+++
female animals															
Group 1: Control															
(16-20)	x		x				x					x			
(21-25)	x		x				x					x			
Group 2: 50 Units/kg															
(41-45)	x		x				x					x			
(46-50)	x		x				x					x			
Group 3: 250 Units/kg															
(61-65)	x		x				x					x			
(66-70)	x		x				x					x			
Group 4: 500 Units/kg															
(86-90)	x		x				x					x			
(91-95)	x		x				x					x			

TD 43

Animal No.	Nitrite		Protein (g/L)				Glucose (mmol/L)					Ketones			
	pos.	neg.	neg.	0.3	1	5	norm.	2.8	5.5	17	55	neg.	+	++	+++
female animals															
Group 1: Control															
(26-30)		x	x				x					x			
Group 4: 500 Units/kg															
(96-100)		x	x				x					x			

Allogenic APOSEC™
 TABLE 6-2 Urinalysis - Individual Data Mouse

TD 29

Animal No.	Urobilinogen ($\mu\text{mol/L}$)					Bilirubin				Haemoglobin (ery/ μL)				
	norm.	17	70	140	200	neg.	+	++	+++	neg.	10	25	50	250
male animals														
Group 1: Control														
(1-5)	x					x				x				
(6-10)	x					x				x				
Group 2: 50 Units/kg														
(31-35)	x					x				x				
(36-40)	x					x				x				
Group 3: 250 Units/kg														
(51-55)	x					x				x				
(56-60)	x					x						x		
Group 4: 500 Units/kg														
(71-75)	x					x				x				
(76-80)	x					x				x				

TD 43

Animal No.	Urobilinogen ($\mu\text{mol/L}$)					Bilirubin				Haemoglobin (ery/ μL)				
	norm.	17	70	140	200	neg.	+	++	+++	neg.	10	25	50	250
male animals														
Group 1: Control														
(11-15)	x					x				x				
Group 4: 500 Units/kg														
(81-85)	x					x				x				

TABLE 6-2

Allogenic APOSEC™
Urinalysis - Individual Data

Mouse

TD 29

Animal No.	Urobilinogen ($\mu\text{mol/L}$)					Bilirubin				Haemoglobin (ery/ μL)				
	norm.	17	70	140	200	neg.	+	++	+++	neg.	10	25	50	250
female animals														
Group 1: Control														
(16-20)	x					x				x				
(21-25)	x					x				x				
Group 2: 50 Units/kg														
(41-45)	x					x				x				
(46-50)	x					x				x				
Group 3: 250 Units/kg														
(61-65)	x					x				x				
(66-70)	x					x				x				
Group 4: 500 Units/kg														
(86-90)	x					x				x				
(91-95)	x					x				x				

TD 43

Animal No.	Urobilinogen ($\mu\text{mol/L}$)					Bilirubin				Haemoglobin (ery/ μL)				
	norm.	17	70	140	200	neg.	+	++	+++	neg.	10	25	50	250
female animals														
Group 1: Control														
(26-30)	x					x							x	
Group 4: 500 Units/kg														
(96-100)	x					x					x			

	Allogenic APOSEC™	
TABLE 6-3	Urine Volume - Individual Data	Mouse

Animal No.	urine volume (mL/cage/6 h)	urine volume (mL/kg b.w./24 h)
male animals		
<u>Test day 29</u>		
Group 1: Control		
(1-5)	3.1	91.5
(6-10)	2.9	86.3
Mean:	3.00	88.90
Group 2: 50 Units/kg		
(31-35)	3.8	112.3
(36-40)	3.2	94.7
Mean:	3.50	103.50
Group 3: 250 Units/kg		
(51-55)	2.6	77.8
(56-60)	4.0	118.3
Mean:	3.30	98.05
Group 4: 500 Units/kg		
(71-75)	6.0	173.5
(76-80)	4.5	135.2
Mean:	5.25	154.35
<u>Test day 43</u>		
Group 1: Control		
(11-15)	1.8	51.9
Mean:	1.80	51.90
Group 4: 500 Units/kg		
(81-85)	3.5	98.2
Mean:	3.50	98.20

	Allogenic APOSEC™	
TABLE 6-3	Urine Volume - Individual Data	Mouse

Animal No.	urine volume (mL/cage/6 h)	urine volume (mL/kg b.w./24 h)
female animals		
<u>Test day 29</u>		
Group 1: Control		
(16-20)	1.9	60.5
(21-25)	2.0	65.6
Mean:	1.95	63.05
Group 2: 50 Units/kg		
(41-45)	3.7	118.0
(46-50)	2.1	73.9
Mean:	2.90	95.95
Group 3: 250 Units/kg		
(61-65)	2.9	96.4
(66-70)	1.5	48.2
Mean:	2.20	72.30
Group 4: 500 Units/kg		
(86-90)	3.8	120.7
(91-95)	4.4	141.9
Mean:	4.10	131.30
<u>Test day 43</u>		
Group 1: Control		
(26-30)	2.5	83.1
Mean:	2.50	83.10
Group 4: 500 Units/kg		
(96-100)	2.0	63.4
Mean:	2.00	63.40

	Allogenic APOSEC™	
TABLE 7	Ophthalmological Examination	Mouse

Animal no.	Predose		Eye# TD 29		TD 43	
	left	right	left	right	left	right

Males

Group 1: Control

(1)	MS	0	0	0	0	-	-
(2)	MS	0	0	0	0	-	-
(3)	MS	0	0	0	0	-	-
(4)	MS	0	0	0	0	-	-
(5)	MS	0	0	0	0	-	-
(6)	MS	0	0	0	0	-	-
(7)	MS	0	0	0	0	-	-
(8)	MS	0	0	0	0	-	-
(9)	MS	0	0	0	0	-	-
(10)	MS	0	0	0	0	-	-
(11)	RP	0	0	0	0	0	0
(12)	RP	0	0	0	0	0	0
(13)	RP	0	0	0	0	0	0
(14)	RP	0	0	0	0	0	0
(15)	RP	0	0	0	0	0	0

Group 2: 50 Units/kg

(31)	MS	0	0	0	0	-	-
(32)	MS	0	0	0	0	-	-
(33)	MS	0	0	0	0	-	-
(34)	MS	0	0	0	0	-	-
(35)	MS	0	0	0	0	-	-
(36)	MS	0	0	0	0	-	-
(37)	MS	0	0	0	0	-	-
(38)	MS	0	0	0	0	-	-
(39)	MS	0	0	0	0	-	-
(40)	MS	0	0	0	0	-	-

MS = main study

RP = recovery period

0 = no pathological findings

= includes: adnexa oculi (i.e. lids, lacrimal apparatus), conjunctiva, cornea, anterior chamber, lens, vitreous body, fundus (retina, optic disc)

TABLE 8	Allogenic APOSEC™ Auditory Examination	Mouse

Animal no.		<u>Predose</u>	Hearing <u>TD 29</u>	<u>TD 43</u>
Males				
Group 1: Control				
(1)	MS	0	0	-
(2)	MS	0	0	-
(3)	MS	0	0	-
(4)	MS	0	0	-
(5)	MS	0	0	-
(6)	MS	0	0	-
(7)	MS	0	0	-
(8)	MS	0	0	-
(9)	MS	0	0	-
(10)	MS	0	0	-
(11)	RP	0	0	0
(12)	RP	0	0	0
(13)	RP	0	0	0
(14)	RP	0	0	0
(15)	RP	0	0	0
Group 2: 50 Units/kg				
(31)	MS	0	0	-
(32)	MS	0	0	-
(33)	MS	0	0	-
(34)	MS	0	0	-
(35)	MS	0	0	-
(36)	MS	0	0	-
(37)	MS	0	0	-
(38)	MS	0	0	-
(39)	MS	0	0	-
(40)	MS	0	0	-

MS = main study
RP = recovery period
0 = no pathological findings

TABLE 8	Allogenic APOSEC™ Auditory Examination	Mouse
1	2	3
4	5	6
7	8	9
10	11	12
13	14	15
16	17	18
19	20	21
22	23	24
25	26	27
28	29	30
31	32	33
34	35	36
37	38	39
40	41	42
43	44	45
46	47	48
49	50	51
52	53	54
55	56	57
58	59	60
61	62	63
64	65	66
67	68	69
70	71	72
73	74	75
76	77	78
79	80	81
82	83	84
85	86	87
88	89	90
91	92	93
94	95	96
97	98	99
100	101	102
103	104	105
106	107	108
109	110	111
112	113	114
115	116	117
118	119	120
121	122	123
124	125	126
127	128	129
130	131	132
133	134	135
136	137	138
139	140	141
142	143	144
145	146	147
148	149	150
151	152	153
154	155	156
157	158	159
160	161	162
163	164	165
166	167	168
169	170	171
172	173	174
175	176	177
178	179	180
181	182	183
184	185	186
187	188	189
190	191	192
193	194	195
196	197	198
199	200	201
202	203	204
205	206	207
208	209	210
211	212	213
214	215	216
217	218	219
220	221	222
223	224	225
226	227	228
229	230	231
232	233	234
235	236	237
238	239	240
241	242	243
244	245	246
247	248	249
250	251	252
253	254	255
256	257	258
259	260	261
262	263	264
265	266	267
268	269	270
271	272	273
274	275	276
277	278	279
280	281	282
283	284	285
286	287	288
289	290	291
292	293	294
295	296	297
298	299	300
301	302	303
304	305	306
307	308	309
310	311	312
313	314	315
316	317	318
319	320	321
322	323	324
325	326	327
328	329	330
331	332	333
334	335	336
337	338	339
340	341	342
343	344	345
346	347	348
349	350	351
352	353	354
355	356	357
358	359	360
361	362	363
364	365	366

Animal no.		<u>Predose</u>	<u>Hearing TD 29</u>	<u>TD 43</u>
Males				
Group 3: 250 Units/kg				
(51)	MS	0	0	-
(52)	MS	0	0	-
(53)	MS	0	0	-
(54)	MS	0	0	-
(55)	MS	0	0	-
(56)	MS	0	0	-
(57)	MS	0	0	-
(58)	MS	0	0	-
(59)	MS	0	0	-
(60)	MS	0	0	-
Group 4: 500 Units/kg				
(71)	MS	0	0	-
(72)	MS	0	0	-
(73)	MS	0	0	-
(74)	MS	0	0	-
(75)	MS	0	0	-
(76)	MS	0	0	-
(77)	MS	0	0	-
(78)	MS	0	0	-
(79)	MS	0	0	-
(80)	MS	0	0	-
(81)	RP	0	0	0
(82)	RP	0	0	0
(83)	RP	0	0	0
(84)	RP	0	0	0
(85)	RP	0	0	0

MS = main study
RP = recovery period
0 = no pathological findings

	Allogenic APOSEC™	
TABLE 8	Auditory Examination	Mouse

Animal no.		<u>Predose</u>	Hearing <u>TD 29</u>	<u>TD 43</u>
Females				
Group 3: 250 Units/kg				
(61)	MS	0	0	-
(62)	MS	0	0	-
(63)	MS	0	0	-
(64)	MS	0	0	-
(65)	MS	0	0	-
(66)	MS	0	0	-
(67)	MS	0	0	-
(68)	MS	0	0	-
(69)	MS	0	0	-
(70)	MS	0	0	-
Group 4: 500 Units/kg				
(86)	MS	0	0	-
(87)	MS	0	0	-
(88)	MS	0	0	-
(89)	MS	0	0	-
(90)	MS	0	0	-
(91)	MS	0	0	-
(92)	MS	0	0	-
(93)	MS	0	0	-
(94)	MS	0	0	-
(95)	MS	0	0	-
(96)	RP	0	0	0
(97)	RP	0	0	0
(98)	RP	0	0	0
(99)	RP	0	0	0
(100)	RP	0	0	0

MS = main study
RP = recovery period
0 = no pathological findings

TABLE 9		Allogenic APOSEC™ Macroscopic <i>Post Mortem</i> Findings		Mouse
Animal no.	Sacrifice / Dead	Affected organs	Findings	

Males

Group 3: 250 Units/kg

terminal sacrifice

(51)	TS / TD 30	—	no pathological findings	
(52)	TS / TD 30	—	no pathological findings	
(53)	TS / TD 30	—	no pathological findings	
(54)	TS / TD 30	—	no pathological findings	
(55)	TS / TD 30	—	no pathological findings	
(56)	TS / TD 30	—	no pathological findings	
(57)	TS / TD 30	—	no pathological findings	
(58)	TS / TD 30	—	no pathological findings	
(59)	TS / TD 30	—	no pathological findings	
(60)	TS / TD 30	—	no pathological findings	

TD test day
TS terminal sacrifice

	Allogenic APOSEC™	
TABLE 9	Macroscopic <i>Post Mortem</i> Findings	Mouse

Animal no.	Sacrifice / Dead	Affected organs	Findings
Males			
<u>Group 4: 500 Units/kg</u>			
terminal sacrifice			
(71)	TS / TD 30	—	no pathological findings
(72)	TS / TD 30	—	no pathological findings
(73)	TS / TD 30	—	no pathological findings
(74)	TS / TD 30	—	no pathological findings
(75)	TS / TD 30	—	no pathological findings
(76)	TS / TD 30	—	no pathological findings
(77)	TS / TD 30	—	no pathological findings
(78)	TS / TD 30	—	no pathological findings
(79)	TS / TD 30	—	no pathological findings
(80)	TS / TD 30	—	no pathological findings
recovery sacrifice			
(81)	RS / TD 44	—	no pathological findings
(82)	RS / TD 44	—	no pathological findings
(83)	RS / TD 44	—	no pathological findings
(84)	RS / TD 44	—	no pathological findings
(85)	RS / TD 44	—	no pathological findings

TD test day

TS terminal sacrifice

RS recovery sacrifice

TABLE 9	Allogenic APOSEC™ Macroscopic <i>Post Mortem</i> Findings	Mouse
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Animal no.	Sacrifice / Dead	Affected organs	Findings
Females			
<u>Group 4: 500 Units/kg</u>			
terminal sacrifice			
(86)	TS / TD 30	—	no pathological findings
(87)	TS / TD 30	—	no pathological findings
(88)	TS / TD 30	—	no pathological findings
(89)	TS / TD 30	—	no pathological findings
(90)	TS / TD 30	—	no pathological findings
(91)	TS / TD 30	—	no pathological findings
(92)	TS / TD 30	—	no pathological findings
(93)	TS / TD 30	—	no pathological findings
(94)	TS / TD 30	—	no pathological findings
(95)	TS / TD 30	—	no pathological findings
recovery sacrifice			
(96)	RS / TD 44	—	no pathological findings
(97)	RS / TD 44	—	no pathological findings
(98)	RS / TD 44	—	no pathological findings
(99)	RS / TD 44	—	no pathological findings
(100)	RS / TD 44	—	no pathological findings

TD test day
TS terminal sacrifice
RS recovery sacrifice

TABLE 10-1

Relative Organ Weights - Summary

Mouse

Day: 30 Relative to Start Date

Sex: Male		Relative Organ Weights						
		Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Epididymis (left) (g/kg b.w.)	Epididymis (right) (g/kg b.w.)	Testis (left) (g/kg b.w.)	Testis (right) (g/kg b.w.)
		[a]	[a]	[a1]	[a1]	[a]	[a1]	[a2]
Group 1: Control	Mean	0.2154	0.2924	20.244	2.415	2.466	4.561	4.604
	SD	0.0993	0.1142	1.486	0.558	0.628	0.502	0.536
	N	10	10	10	10	10	10	10
Group 2: 50 Units/kg	Mean	0.2270	0.1936	21.650	1.867	1.978	4.658	4.416
	SD	0.1401	0.0765	1.992	0.229	0.513	0.488	0.513
	N	10	10	10	10	10	10	10
	%Diff	5.4	-33.8	6.9	-22.7	-19.8	2.1	-4.1
Group 3: 250 Units/kg	Mean	0.2484	0.2746	20.468	2.215	1.829*	4.375	4.516
	SD	0.1675	0.2291	0.932	0.495	0.227	0.662	0.582
	N	10	10	10	10	10	10	10
	%Diff	15.3	-6.1	1.1	-8.3	-25.8	-4.1	-1.9
Group 4: 500 Units/kg	Mean	0.2673	0.2367	20.468	2.502	2.013	4.171	4.453
	SD	0.1197	0.0954	1.059	0.763	0.523	0.695	0.452
	N	10	10	10	10	10	10	10
	%Diff	24.1	-19.0	1.1	3.6	-18.4	-8.6	-3.3

[a] - Anova & Dunnett(Log): * = $p \leq 0.05$

[a1] - Anova & Dunnett(Rank)

[a2] - Anova & Dunnett

TABLE 10-1

Relative Organ Weights - Summary

Mouse

Day: 30 Relative to Start Date

Sex: Male		Relative Organ Weights					
		Heart	Kidney (left)	Kidney (right)	Liver	Spleen	Thymus
		(g/kg b.w.)	(g/kg b.w.)	(g/kg b.w.)	(g/kg b.w.)	(g/kg b.w.)	(g/kg b.w.)
		[a]	[a]	[a]	[a]	[a]	[a1]
Group 1: Control	Mean	7.244	8.161	7.938	50.37	2.589	2.204
	SD	0.694	0.579	0.437	3.25	0.317	0.470
	N	10	10	10	10	10	10
Group 2: 50 Units/kg	Mean	7.569	7.721	8.206	49.96	3.163**	1.711*
	SD	0.770	0.586	0.582	4.10	0.529	0.365
	N	10	10	10	10	10	10
Group 3: 250 Units/kg	%Diff	4.5	-5.4	3.4	-0.8	22.2	-22.4
	Mean	7.547	7.828	7.874	51.36	2.838	2.095
	SD	0.608	0.523	0.349	3.72	0.337	0.439
Group 4: 500 Units/kg	N	10	10	10	10	10	10
	%Diff	4.2	-4.1	-0.8	2.0	9.6	-5.0
	Mean	7.013	7.825	8.058	51.22	3.368**	2.156
	SD	0.678	0.600	0.540	2.57	0.344	0.431
	N	10	10	10	10	10	10
	%Diff	-3.2	-4.1	1.5	1.7	30.1	-2.2

[a] - Anova & Dunnett: ** = $p \leq 0.01$ [a1] - Anova & Dunnett(Log): * = $p \leq 0.05$

TABLE 10-1

Relative Organ Weights - Summary

Mouse

Day: 44 Relative to Start Date

Sex: Male		Relative Organ Weights						
		Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Epididymis (left) (g/kg b.w.)	Epididymis (right) (g/kg b.w.)	Testis (left) (g/kg b.w.)	Testis (right) (g/kg b.w.)
		[a]	[a]	[a]	[a]	[a1]	[a]	[a]
Group 1: Control	Mean	0.1022	0.1481	19.275	2.696	2.129	4.626	4.633
	SD	0.0226	0.0382	0.685	0.790	0.878	0.190	0.344
	N	5	5	5	5	5	5	5
Group 4: 500 Units/kg	Mean	0.1364	0.1084	19.083	2.084	2.078	4.088**	3.909*
	SD	0.0323	0.0501	0.528	0.380	0.637	0.304	0.443
	N	5	5	5	5	5	5	5
	%Diff	33.5	-26.8	-1.0	-22.7	-2.4	-11.6	-15.6

[a] - Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$

[a1] - Anova & Dunnett(Log)

TABLE 10-1

Relative Organ Weights - Summary

Mouse

Day: 44 Relative to Start Date

Sex: Male		Relative Organ Weights					
		Heart	Kidney (left)	Kidney (right)	Liver	Spleen	Thymus
		(g/kg b.w.)	(g/kg b.w.)	(g/kg b.w.)	(g/kg b.w.)	(g/kg b.w.)	(g/kg b.w.)
		[a]	[a]	[a1]	[a]	[a]	[a]
Group 1: Control	Mean	7.400	7.405	7.499	47.23	2.402	1.595
	SD	0.861	0.319	0.683	1.44	0.330	0.111
	N	5	5	5	5	5	5
Group 4: 500 Units/kg	Mean	6.628	7.710	8.001	49.93	2.634	1.722
	SD	0.297	0.531	0.535	2.23	0.376	0.271
	N	5	5	5	5	5	5
	%Diff	-10.4	4.1	6.7	5.7	9.7	7.9

[a] - Anova & Dunnett

[a1] - Anova & Dunnett(Log)

TABLE 10-1

Relative Organ Weights - Summary

Mouse

Day: 30 Relative to Start Date

Sex: Female		Relative Organ Weights					
		Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Ovary (left) (g/kg b.w.)	Ovary (right) (g/kg b.w.)	Heart (g/kg b.w.)
		[a]	[a1]	[a]	[a2]	[a2]	[a]
Group 1: Control	Mean	0.2452	0.2818	23.802	0.3778	0.3050	6.903
	SD	0.1013	0.1091	1.026	0.2484	0.0728	0.589
	N	10	10	10	10	10	10
Group 2: 50 Units/kg	Mean	0.3135	0.2427	24.783	0.3309	0.3270	7.354
	SD	0.1057	0.0624	1.520	0.1262	0.0824	1.299
	N	10	10	10	10	10	10
	%Diff	27.8	-13.9	4.1	-12.4	7.2	6.5
Group 3: 250 Units/kg	Mean	0.2397	0.2218	24.779	0.2498	0.2859	7.933
	SD	0.0433	0.0964	1.311	0.1182	0.1364	1.063
	N	10	10	10	10	10	10
	%Diff	-2.3	-21.3	4.1	-33.9	-6.3	14.9
Group 4: 500 Units/kg	Mean	0.2786	0.2694	23.410	0.2422	0.3253	7.065
	SD	0.0885	0.1481	0.951	0.1213	0.1730	0.896
	N	10	10	10	10	10	10
	%Diff	13.6	-4.4	-1.6	-35.9	6.6	2.3

[a] - Anova & Dunnett

[a1] - Anova & Dunnett(Rank)

[a2] - Anova & Dunnett(Log)

TABLE 10-1

Relative Organ Weights - Summary

Mouse

Day: 30 Relative to Start Date

Sex: Female		Relative Organ Weights					
		Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Uterus (g/kg b.w.)
		[a]	[a1]	[a]	[a]	[a]	[a1]
Group 1: Control	Mean	7.171	7.661	52.71	4.182	3.469	6.579
	SD	0.437	0.448	3.91	0.509	0.536	2.345
	N	10	10	10	10	10	10
Group 2: 50 Units/kg	Mean	7.393	7.929	49.94	4.168	2.951	5.995
	SD	0.434	0.871	5.57	0.953	0.531	1.322
	N	10	10	10	10	10	10
	%Diff	3.1	3.5	-5.2	-0.3	-14.9	-8.9
Group 3: 250 Units/kg	Mean	7.445	7.481	50.94	4.224	3.150	7.481
	SD	0.434	0.550	5.43	0.653	0.426	2.734
	N	10	10	10	10	10	10
	%Diff	3.8	-2.4	-3.4	1.0	-9.2	13.7
Group 4: 500 Units/kg	Mean	7.476	7.493	50.73	4.690	3.141	6.051
	SD	0.688	0.400	5.20	0.887	0.534	1.123
	N	10	10	10	10	10	10
	%Diff	4.3	-2.2	-3.7	12.2	-9.5	-8.0

[a] - Anova & Dunnett

[a1] - Anova & Dunnett(Log)

TABLE 10-1

Relative Organ Weights - Summary

Mouse

Day: 44 Relative to Start Date

Sex: Female		Relative Organ Weights					
		Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Ovary (left) (g/kg b.w.)	Ovary (right) (g/kg b.w.)	Heart (g/kg b.w.)
		[a]	[a1]	[a1]	[a1]	[a1]	[a1]
Group 1: Control	Mean	0.3220	0.3348	25.084	0.3328	0.2524	7.938
	SD	0.0332	0.1294	1.739	0.1147	0.0632	0.813
	N	5	5	5	5	5	5
Group 4: 500 Units/kg	Mean	0.2706	0.2695	23.327	0.3265	0.2603	7.796
	SD	0.1258	0.0563	1.228	0.0637	0.0608	0.435
	N	5	5	5	5	5	5
	%Diff	-16.0	-19.5	-7.0	-1.9	3.1	-1.8

[a] - Anova & Dunnett(Rank)

[a1] - Anova & Dunnett

TABLE 10-1

Relative Organ Weights - Summary

Mouse

Day: 44 Relative to Start Date

Sex: Female		Relative Organ Weights					
		Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Uterus (g/kg b.w.)
		[a]	[a]	[a]	[a]	[a]	[a]
Group 1: Control	Mean	7.574	7.699	52.82	3.677	2.358	7.264
	SD	0.809	0.435	3.87	0.491	0.375	2.068
	N	5	5	5	5	5	5
Group 4: 500 Units/kg	Mean	6.941	7.263	51.97	4.215	2.480	5.335
	SD	0.333	0.483	3.96	0.475	0.549	1.046
	N	5	5	5	5	5	5
	%Diff	-8.4	-5.7	-1.6	14.6	5.2	-26.6

[a] - Anova & Dunnett

TABLE 10-1

Relative Organ Weights - Summary

Mouse

<u>Comments and Markers</u>						
<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker</u>	<u>Comment</u>
	30	3	Male	Epididymis (right)	*	Anova & Dunnett(Log): * = $p \leq 0.05$
	30	2	Male	Spleen	**	Anova & Dunnett: ** = $p \leq 0.01$
	30	2	Male	Thymus	*	Anova & Dunnett(Log): * = $p \leq 0.05$
	30	4	Male	Spleen	**	Anova & Dunnett: ** = $p \leq 0.01$

TABLE 10-1

Relative Organ Weights - Summary

Mouse

<u>Comments and Markers</u>						
<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker</u>	<u>Comment</u>
44		4	Male	Testis (left)	**	Anova & Dunnett: ** = $p \leq 0.01$
44		4	Male	Testis (right)	*	Anova & Dunnett: * = $p \leq 0.05$

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 1: Control	Relative Organ Weights						
	Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Epididymis (left) (g/kg b.w.)	Epididymis (right) (g/kg b.w.)	Testis (left) (g/kg b.w.)	Testis (right) (g/kg b.w.)
1	0.192	0.288	19.71	2.24	2.96	4.81	4.81
2	0.365	0.313	21.88	3.22	2.51	4.69	4.69
3	0.180	0.360	19.37	2.58	2.05	4.50	4.95
4	0.152	0.253	21.21	2.38	1.98	5.05	4.55
5	0.143	0.143	20.95	3.41	2.32	4.76	4.76
6	0.163	0.327	17.55	1.78	1.67	3.27	3.27
7	0.093	0.140	18.60	1.68	3.76	4.65	4.19
8	0.394	0.443	20.69	2.08	1.91	4.93	4.93
9	0.187	0.467	20.09	2.54	2.96	4.67	5.14
10	0.286	0.190	22.38	2.23	2.54	4.29	4.76
Mean	0.2154	0.2924	20.244	2.415	2.466	4.561	4.604
SD	0.0993	0.1142	1.486	0.558	0.628	0.502	0.536
N	10	10	10	10	10	10	10

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 2: 50 Units/kg	Relative Organ Weights						
	Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Epididymis (left) (g/kg b.w.)	Epididymis (right) (g/kg b.w.)	Testis (left) (g/kg b.w.)	Testis (right) (g/kg b.w.)
31	0.050	0.099	21.29	1.70	2.31	4.95	4.95
32	0.341	0.195	20.00	1.88	3.00	5.37	5.37
33	0.097	0.145	27.05	1.85	1.89	3.86	3.86
34	0.051	0.202	22.22	1.80	2.38	4.55	4.04
35	0.190	0.142	20.85	1.94	1.64	4.27	4.74
36	0.146	0.097	21.36	1.80	2.34	4.85	4.37
37	0.240	0.288	20.67	1.71	1.73	4.81	4.33
38	0.376	0.329	21.13	1.77	1.62	5.16	4.69
39	0.400	0.200	20.50	2.48	1.45	4.00	4.00
40	0.381	0.238	21.43	1.73	1.43	4.76	3.81
Mean	0.2270	0.1936	21.650	1.867	1.978	4.658	4.416
SD	0.1401	0.0765	1.992	0.229	0.513	0.488	0.513
N	10	10	10	10	10	10	10

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 3: 250 Units/kg	Relative Organ Weights						
	Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Epididymis (left) (g/kg b.w.)	Epididymis (right) (g/kg b.w.)	Testis (left) (g/kg b.w.)	Testis (right) (g/kg b.w.)
51	0.647	0.259	19.40	2.02	1.53	4.31	4.31
52	0.093	0.187	19.63	2.46	1.96	4.67	5.14
53	0.217	0.109	22.28	1.90	1.94	4.89	4.89
54	0.231	0.880	19.91	1.81	1.89	5.09	5.09
55	0.148	0.394	20.69	1.88	1.84	4.93	4.93
56	0.150	0.250	20.50	1.69	2.10	4.00	4.00
57	0.147	0.147	20.10	2.50	1.75	4.90	4.90
58	0.411	0.228	19.63	2.20	1.70	4.11	4.57
59	0.147	0.098	21.57	2.31	1.44	2.94	3.43
60	0.293	0.195	20.98	3.38	2.13	3.90	3.90
Mean	0.2484	0.2746	20.468	2.215	1.829	4.375	4.516
SD	0.1675	0.2291	0.932	0.495	0.227	0.662	0.582
N	10	10	10	10	10	10	10

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 4: 500 Units/kg	Relative Organ Weights						
	Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Epididymis (left) (g/kg b.w.)	Epididymis (right) (g/kg b.w.)	Testis (left) (g/kg b.w.)	Testis (right) (g/kg b.w.)
71	0.133	0.356	19.56	2.18	1.76	4.00	4.44
72	0.282	0.141	19.72	1.57	1.83	3.76	4.23
73	0.388	0.291	20.39	3.14	2.67	4.37	4.37
74	0.141	0.141	19.72	1.43	1.89	4.23	4.69
75	0.271	0.317	19.91	3.95	1.40	4.52	4.98
76	0.204	0.204	22.45	2.32	2.03	5.10	5.10
77	0.377	0.142	20.28	2.43	2.29	4.25	4.25
78	0.179	0.179	19.64	2.44	3.07	4.46	4.46
79	0.495	0.396	20.79	2.33	1.63	2.48	3.47
80	0.202	0.202	22.22	3.23	1.57	4.55	4.55
Mean	0.2673	0.2367	20.468	2.502	2.013	4.171	4.453
SD	0.1197	0.0954	1.059	0.763	0.523	0.695	0.452
N	10	10	10	10	10	10	10

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 1: Control	Relative Organ Weights					
	Heart (g/kg b.w.)	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)
1	8.65	7.69	7.69	48.1	2.40	1.92
2	7.29	7.81	7.81	46.9	2.60	2.92
3	6.76	9.01	8.11	54.1	2.25	1.98
4	7.58	7.58	7.58	50.5	2.53	1.57
5	6.67	9.05	8.57	47.6	2.86	1.86
6	6.94	8.16	7.76	57.1	3.27	2.00
7	6.51	7.44	7.44	51.2	2.33	2.74
8	7.88	7.88	8.37	49.3	2.46	2.86
9	6.54	8.41	7.48	51.4	2.34	2.24
10	7.62	8.57	8.57	47.6	2.86	1.95
Mean	7.244	8.161	7.938	50.37	2.589	2.204
SD	0.694	0.579	0.437	3.25	0.317	0.470
N	10	10	10	10	10	10

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 2: 50 Units/kg	Relative Organ Weights					
	Heart (g/kg b.w.)	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)
31	7.43	7.92	8.42	54.5	3.96	1.68
32	8.29	7.32	7.80	48.8	2.93	1.85
33	7.73	7.73	7.25	53.1	2.90	1.35
34	8.08	8.59	9.09	40.4	4.04	1.62
35	8.06	8.53	9.00	52.1	3.32	1.33
36	5.83	6.80	7.77	53.4	2.91	1.46
37	7.21	8.17	8.65	48.1	2.40	2.40
38	8.45	7.51	7.98	51.6	2.82	2.11
39	7.00	7.50	8.00	50.0	3.50	1.35
40	7.62	7.14	8.10	47.6	2.86	1.95
Mean	7.569	7.721	8.206	49.96	3.163	1.711
SD	0.770	0.586	0.582	4.10	0.529	0.365
N	10	10	10	10	10	10

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 3: 250 Units/kg	Relative Organ Weights					
	Heart (g/kg b.w.)	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)
51	8.19	7.76	8.19	56.0	2.59	1.77
52	7.94	7.48	7.94	51.4	2.34	2.76
53	8.70	7.07	7.61	48.9	2.72	2.07
54	7.87	7.41	7.87	46.3	3.24	2.31
55	6.90	7.88	7.39	49.3	2.46	2.17
56	7.00	8.00	8.00	50.0	3.00	1.90
57	7.35	7.35	8.33	53.9	2.94	1.32
58	6.85	8.22	7.76	50.2	2.74	2.74
59	7.35	8.33	7.35	49.0	2.94	2.11
60	7.32	8.78	8.29	58.5	3.41	1.80
Mean	7.547	7.828	7.874	51.36	2.838	2.095
SD	0.608	0.523	0.349	3.72	0.337	0.439
N	10	10	10	10	10	10

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 4: 500 Units/kg	Relative Organ Weights					
	Heart (g/kg b.w.)	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)
71	6.22	7.56	7.56	48.9	3.11	2.18
72	8.45	7.98	7.51	51.6	3.76	1.69
73	7.28	8.25	7.77	48.5	3.88	3.11
74	7.04	7.04	7.51	51.6	3.29	1.92
75	7.24	7.69	8.14	49.8	3.62	2.40
76	6.63	8.16	8.67	51.0	3.57	1.99
77	7.08	8.96	8.49	56.6	2.83	2.55
78	6.70	7.59	8.93	49.1	3.13	1.83
79	7.43	6.93	8.42	54.5	3.47	2.13
80	6.06	8.08	7.58	50.5	3.03	1.77
Mean	7.013	7.825	8.058	51.22	3.368	2.156
SD	0.678	0.600	0.540	2.57	0.344	0.431
N	10	10	10	10	10	10

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 1: Control	Relative Organ Weights					
	Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Ovary (left) (g/kg b.w.)	Ovary (right) (g/kg b.w.)	Heart (g/kg b.w.)
16	0.164	0.219	24.04	0.273	0.328	6.56
17	0.104	0.207	22.80	0.155	0.207	6.74
18	0.223	0.335	25.14	0.279	0.279	7.26
19	0.272	0.326	25.00	0.163	0.217	7.61
20	0.156	0.208	22.40	0.156	0.260	6.77
21	0.223	0.168	25.14	0.335	0.279	6.70
22	0.361	0.515	22.68	0.567	0.309	6.19
23	0.447	0.335	23.46	0.726	0.391	7.82
24	0.220	0.165	23.63	0.275	0.440	6.04
25	0.282	0.339	23.73	0.847	0.339	7.34
Mean	0.2452	0.2818	23.802	0.3778	0.3050	6.903
SD	0.1013	0.1091	1.026	0.2484	0.0728	0.589
N	10	10	10	10	10	10

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 2: 50 Units/kg	Relative Organ Weights					
	Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Ovary (left) (g/kg b.w.)	Ovary (right) (g/kg b.w.)	Heart (g/kg b.w.)
41	0.270	0.270	25.41	0.324	0.378	6.49
42	0.508	0.226	24.29	0.339	0.339	6.78
43	0.211	0.211	23.16	0.316	0.316	7.89
44	0.167	0.222	24.44	0.222	0.278	8.33
45	0.426	0.372	24.47	0.319	0.479	10.11
46	0.422	0.301	25.30	0.361	0.301	6.02
47	0.272	0.217	22.83	0.163	0.326	7.07
48	0.292	0.234	25.15	0.585	0.234	6.43
49	0.270	0.135	28.38	0.203	0.203	6.08
50	0.298	0.238	24.40	0.476	0.417	8.33
Mean	0.3135	0.2427	24.783	0.3309	0.3270	7.354
SD	0.1057	0.0624	1.520	0.1262	0.0824	1.299
N	10	10	10	10	10	10

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 3: 250 Units/kg	Relative Organ Weights					
	Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Ovary (left) (g/kg b.w.)	Ovary (right) (g/kg b.w.)	Heart (g/kg b.w.)
61	0.248	0.124	26.09	0.248	0.186	8.70
62	0.201	0.201	22.61	0.352	0.553	8.04
63	0.231	0.231	24.86	0.116	0.231	8.09
64	0.282	0.226	25.42	0.113	0.113	10.17
65	0.299	0.479	26.95	0.419	0.419	7.19
66	0.219	0.219	25.14	0.109	0.164	7.10
67	0.220	0.220	23.63	0.385	0.220	7.14
68	0.240	0.180	25.15	0.299	0.359	7.78
69	0.162	0.162	23.24	0.162	0.378	8.65
70	0.294	0.176	24.71	0.294	0.235	6.47
Mean	0.2397	0.2218	24.779	0.2498	0.2859	7.933
SD	0.0433	0.0964	1.311	0.1182	0.1364	1.063
N	10	10	10	10	10	10

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 4: 500 Units/kg	Relative Organ Weights					
	Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Ovary (left) (g/kg b.w.)	Ovary (right) (g/kg b.w.)	Heart (g/kg b.w.)
86	0.263	0.263	23.68	0.263	0.158	5.79
87	0.263	0.158	22.63	0.158	0.158	6.84
88	0.165	0.165	23.08	0.275	0.385	8.24
89	0.311	0.207	22.80	0.207	0.207	6.22
90	0.176	0.235	25.29	0.353	0.294	7.65
91	0.447	0.279	23.46	0.503	0.447	6.15
92	0.393	0.674	24.16	0.112	0.730	7.30
93	0.215	0.215	23.12	0.108	0.376	7.53
94	0.279	0.223	24.02	0.279	0.279	8.38
95	0.273	0.273	21.86	0.164	0.219	6.56
Mean	0.2786	0.2694	23.410	0.2422	0.3253	7.065
SD	0.0885	0.1481	0.951	0.1213	0.1730	0.896
N	10	10	10	10	10	10

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 1: Control	Relative Organ Weights					
	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Uterus (g/kg b.w.)
16	7.10	8.20	49.2	3.28	2.90	5.04
17	6.22	7.77	51.8	4.66	3.47	7.54
18	7.82	7.82	55.9	3.91	4.19	3.89
19	7.61	7.61	59.8	4.35	3.59	9.89
20	7.29	6.77	52.1	4.17	3.44	7.46
21	7.26	7.82	50.3	4.47	2.74	10.52
22	7.22	7.22	46.4	3.61	4.33	4.48
23	7.26	7.82	55.9	3.91	3.85	4.47
24	7.14	8.24	54.9	4.95	3.02	5.09
25	6.78	7.34	50.8	4.52	3.16	7.41
Mean	7.171	7.661	52.71	4.182	3.469	6.579
SD	0.437	0.448	3.91	0.509	0.536	2.345
N	10	10	10	10	10	10

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 2: 50 Units/kg	Relative Organ Weights					
	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Uterus (g/kg b.w.)
41	7.03	7.57	54.1	3.78	3.89	5.55
42	7.91	7.91	56.5	3.39	2.99	4.67
43	7.89	10.00	42.1	5.79	2.63	8.32
44	7.78	7.22	55.6	4.44	2.67	4.52
45	7.45	8.51	53.2	5.32	3.56	6.12
46	7.23	7.83	48.2	4.82	3.55	6.09
47	7.07	8.15	48.9	4.35	2.39	5.16
48	7.60	7.60	46.8	3.51	2.51	4.79
49	7.43	6.76	40.5	2.70	2.50	7.05
50	6.55	7.74	53.6	3.57	2.80	7.70
Mean	7.393	7.929	49.94	4.168	2.951	5.995
SD	0.434	0.871	5.57	0.953	0.531	1.322
N	10	10	10	10	10	10

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 3: 250 Units/kg	Relative Organ Weights					
	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Uterus (g/kg b.w.)
61	8.07	8.07	49.7	3.11	2.67	13.94
62	7.04	7.54	50.3	4.52	3.07	8.13
63	6.94	6.94	52.0	4.05	3.93	5.34
64	7.91	7.91	39.5	5.08	2.99	4.82
65	7.78	7.78	47.9	3.59	2.46	6.19
66	7.10	7.65	60.1	4.92	3.55	8.46
67	7.14	8.24	54.9	4.40	3.30	7.74
68	7.78	6.59	47.9	3.59	2.93	9.20
69	7.03	7.03	54.1	4.86	3.24	5.47
70	7.65	7.06	52.9	4.12	3.35	5.52
Mean	7.445	7.481	50.94	4.224	3.150	7.481
SD	0.434	0.550	5.43	0.653	0.426	2.734
N	10	10	10	10	10	10

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 4: 500 Units/kg	Relative Organ Weights					
	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Uterus (g/kg b.w.)
86	8.95	7.37	52.6	4.74	3.63	6.25
87	7.37	6.84	57.9	5.26	2.84	7.75
88	6.59	7.14	54.9	5.49	3.19	4.97
89	7.77	7.25	51.8	4.66	2.75	8.22
90	7.06	7.65	47.1	3.53	2.24	5.05
91	7.82	7.26	50.3	3.91	3.97	5.60
92	6.74	7.87	50.6	3.93	3.65	5.94
93	6.99	7.53	48.4	3.76	2.69	5.54
94	7.82	7.82	39.1	6.15	3.02	6.15
95	7.65	8.20	54.6	5.46	3.44	5.03
Mean	7.476	7.493	50.73	4.690	3.141	6.051
SD	0.688	0.400	5.20	0.887	0.534	1.123
N	10	10	10	10	10	10

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Male Day: 44 Relative to Start Date

Group 1: Control	Relative Organ Weights						
	Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Epididymis (left) (g/kg b.w.)	Epididymis (right) (g/kg b.w.)	Testis (left) (g/kg b.w.)	Testis (right) (g/kg b.w.)
11	0.097	0.146	20.39	3.40	1.94	4.37	4.85
12	0.088	0.177	19.03	1.77	1.33	4.87	4.42
13	0.142	0.190	19.43	2.37	1.90	4.74	4.74
14	0.091	0.136	18.64	3.64	3.64	4.55	5.00
15	0.092	0.092	18.89	2.30	1.84	4.61	4.15
Mean	0.1022	0.1481	19.275	2.696	2.129	4.626	4.633
SD	0.0226	0.0382	0.685	0.790	0.878	0.190	0.344
N	5	5	5	5	5	5	5

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Male Day: 44 Relative to Start Date

Group 4: 500 Units/kg	Relative Organ Weights						
	Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Epididymis (left) (g/kg b.w.)	Epididymis (right) (g/kg b.w.)	Testis (left) (g/kg b.w.)	Testis (right) (g/kg b.w.)
81	0.180	0.090	18.47	2.25	2.25	3.60	3.60
82	0.089	0.089	18.75	2.23	1.79	4.02	3.57
83	0.140	0.140	19.53	2.33	1.86	4.19	4.65
84	0.132	0.176	18.94	2.20	3.08	4.41	3.96
85	0.141	0.047	19.72	1.41	1.41	4.23	3.76
Mean	0.1364	0.1084	19.083	2.084	2.078	4.088	3.909
SD	0.0323	0.0501	0.528	0.380	0.637	0.304	0.443
N	5	5	5	5	5	5	5

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Male Day: 44 Relative to Start Date

Group 1: Control	Relative Organ Weights					
	Heart (g/kg b.w.)	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)
11	7.28	7.28	7.28	48.5	2.43	1.70
12	7.96	7.52	7.08	48.7	2.65	1.42
13	7.58	7.58	7.58	47.4	1.90	1.66
14	8.18	7.73	8.64	45.5	2.73	1.64
15	5.99	6.91	6.91	46.1	2.30	1.57
Mean	7.400	7.405	7.499	47.23	2.402	1.595
SD	0.861	0.319	0.683	1.44	0.330	0.111
N	5	5	5	5	5	5

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Male Day: 44 Relative to Start Date

Group 4: 500 Units/kg	Relative Organ Weights					
	Heart (g/kg b.w.)	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)
81	6.76	8.11	7.66	49.5	3.15	1.71
82	6.25	7.59	7.59	49.1	2.68	1.38
83	6.51	7.44	7.91	51.2	2.79	1.81
84	7.05	8.37	7.93	52.9	2.20	1.59
85	6.57	7.04	8.92	46.9	2.35	2.11
Mean	6.628	7.710	8.001	49.93	2.634	1.722
SD	0.297	0.531	0.535	2.23	0.376	0.271
N	5	5	5	5	5	5

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Female Day: 44 Relative to Start Date

Group 1: Control	Relative Organ Weights					
	Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Ovary (left) (g/kg b.w.)	Ovary (right) (g/kg b.w.)	Heart (g/kg b.w.)
26	0.284	0.227	23.30	0.455	0.341	8.52
27	0.357	0.417	27.98	0.298	0.179	8.33
28	0.341	0.227	24.43	0.455	0.227	6.82
29	0.289	0.520	24.86	0.231	0.289	8.67
30	0.339	0.282	24.86	0.226	0.226	7.34
Mean	0.3220	0.3348	25.084	0.3328	0.2524	7.938
SD	0.0332	0.1294	1.739	0.1147	0.0632	0.813
N	5	5	5	5	5	5

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Female Day: 44 Relative to Start Date

Group 4: 500 Units/kg	Relative Organ Weights					
	Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Ovary (left) (g/kg b.w.)	Ovary (right) (g/kg b.w.)	Heart (g/kg b.w.)
96	0.442	0.276	24.86	0.387	0.331	7.73
97	0.227	0.227	23.86	0.398	0.284	7.39
98	0.158	0.263	22.63	0.316	0.263	7.37
99	0.361	0.361	21.65	0.258	0.258	8.25
100	0.165	0.220	23.63	0.275	0.165	8.24
Mean	0.2706	0.2695	23.327	0.3265	0.2603	7.796
SD	0.1258	0.0563	1.228	0.0637	0.0608	0.435
N	5	5	5	5	5	5

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Female Day: 44 Relative to Start Date

Group 1: Control	Relative Organ Weights					
	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Uterus (g/kg b.w.)
26	7.95	7.95	51.1	3.41	2.05	6.25
27	6.55	7.74	47.6	3.57	2.44	9.52
28	8.52	7.95	56.8	4.55	2.84	9.09
29	6.94	6.94	52.0	3.47	2.54	6.94
30	7.91	7.91	56.5	3.39	1.92	4.52
Mean	7.574	7.699	52.82	3.677	2.358	7.264
SD	0.809	0.435	3.87	0.491	0.375	2.068
N	5	5	5	5	5	5

TABLE 10-2 Relative Organ Weights - Individual Data Mouse

Sex: Female Day: 44 Relative to Start Date

Group 4: 500 Units/kg	Relative Organ Weights					
	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Uterus (g/kg b.w.)
96	7.18	7.73	55.2	4.42	3.37	4.97
97	7.39	6.82	45.5	3.41	2.39	6.25
98	6.84	7.37	52.6	4.21	2.21	4.74
99	6.70	6.70	51.5	4.64	1.91	4.12
100	6.59	7.69	54.9	4.40	2.53	6.59
Mean	6.941	7.263	51.97	4.215	2.480	5.335
SD	0.333	0.483	3.96	0.475	0.549	1.046
N	5	5	5	5	5	5

TABLE 11-1

Absolute Organ Weights - Summary

Mouse

Day: 30 Relative to Start Date

Sex: Male		Absolute Organ Weights						
		Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Epididymis (left) (g)	Epididymis (right) (g)	Testis (left) (g)	Testis (right) (g)
		[a]	[a]	[a1]	[a1]	[a]	[a1]	[a2]
Group 1: Control	Mean	0.0045	0.0062	0.427	0.051	0.052	0.096	0.097
	SD	0.0019	0.0025	0.019	0.011	0.013	0.007	0.009
	N	10	10	10	10	10	10	10
Group 2: 50 Units/kg	Mean	0.0047	0.0040	0.446	0.038*	0.041*	0.096	0.091
	SD	0.0029	0.0016	0.042	0.004	0.010	0.011	0.011
	N	10	10	10	10	10	10	10
	%Diff	4.4	-35.5	4.4	-24.3	-21.9	0.0	-6.2
Group 3: 250 Units/kg	Mean	0.0053	0.0058	0.425	0.046	0.038*	0.091	0.094
	SD	0.0040	0.0050	0.014	0.011	0.004	0.014	0.013
	N	10	10	10	10	10	10	10
	%Diff	17.8	-6.5	-0.5	-9.2	-27.1	-5.2	-3.1
Group 4: 500 Units/kg	Mean	0.0056	0.0050	0.431	0.053	0.043	0.088	0.094
	SD	0.0024	0.0021	0.010	0.016	0.012	0.015	0.011
	N	10	10	10	10	10	10	10
	%Diff	24.4	-19.4	0.9	3.9	-18.2	-8.3	-3.1

[a] - Anova & Dunnett(Log): * = $p \leq 0.05$ [a1] - Anova & Dunnett(Rank): * = $p \leq 0.05$

[a2] - Anova & Dunnett

TABLE 11-1

Absolute Organ Weights - Summary

Mouse

Day: 30 Relative to Start Date

Sex: Male		Absolute Organ Weights					
		Heart	Kidney (left)	Kidney (right)	Liver	Spleen	Thymus
		(g)	(g)	(g)	(g)	(g)	(g)
		[a]	[a]	[a]	[a1]	[a1]	[a]
Group 1: Control	Mean	0.153	0.173	0.168	1.07	0.055	0.0465
	SD	0.014	0.019	0.014	0.14	0.010	0.0092
	N	10	10	10	10	10	10
Group 2: 50 Units/kg	Mean	0.156	0.159	0.169	1.03	0.065*	0.0353*
	SD	0.017	0.012	0.012	0.09	0.010	0.0079
	N	10	10	10	10	10	10
	%Diff	2.0	-8.1	0.6	-3.7	18.2	-24.1
Group 3: 250 Units/kg	Mean	0.157	0.163	0.164	1.07	0.059	0.0437
	SD	0.016	0.016	0.014	0.12	0.007	0.0102
	N	10	10	10	10	10	10
	%Diff	2.6	-5.8	-2.4	0.0	7.3	-6.0
Group 4: 500 Units/kg	Mean	0.148	0.165	0.170	1.08	0.071**	0.0455
	SD	0.016	0.014	0.014	0.06	0.007	0.0093
	N	10	10	10	10	10	10
	%Diff	-3.3	-4.6	1.2	0.9	29.1	-2.2

[a] - Anova & Dunnett: * = $p \leq 0.05$ [a1] - Anova & Dunnett(Log): * = $p \leq 0.05$; ** = $p \leq 0.01$

TABLE 11-1

Absolute Organ Weights - Summary

Mouse

Day: 44 Relative to Start Date

Sex: Male		Absolute Organ Weights						
		Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Epididymis (left) (g)	Epididymis (right) (g)	Testis (left) (g)	Testis (right) (g)
		[a]	[a]	[a]	[a]	[a1]	[a2]	[a]
Group 1: Control	Mean	0.0022	0.0032	0.416	0.058	0.046	0.100	0.100
	SD	0.0004	0.0008	0.009	0.016	0.019	0.007	0.007
	N	5	5	5	5	5	5	5
Group 4: 500 Units/kg	Mean	0.0030	0.0024	0.420	0.046	0.046	0.090	0.086*
	SD	0.0007	0.0011	0.007	0.009	0.015	0.007	0.009
	N	5	5	5	5	5	5	5
	%Diff	36.4	-25.0	1.0	-20.7	0.0	-10.0	-14.0

[a] - Anova & Dunnett: * = $p \leq 0.05$

[a1] - Anova & Dunnett(Log)

[a2] - Anova & Dunnett(Rank)

TABLE 11-1

Absolute Organ Weights - Summary

Mouse

Day: 44 Relative to Start Date

Sex: Male		Absolute Organ Weights					
		Heart	Kidney (left)	Kidney (right)	Liver	Spleen	Thymus
		(g)	(g)	(g)	(g)	(g)	(g)
		[a]	[a]	[a1]	[a]	[a]	[a1]
Group 1: Control	Mean	0.160	0.160	0.162	1.02	0.052	0.0344
	SD	0.021	0.010	0.016	0.04	0.008	0.0015
	N	5	5	5	5	5	5
Group 4: 500 Units/kg	Mean	0.146	0.170	0.176	1.10	0.058	0.0378
	SD	0.009	0.016	0.009	0.07	0.008	0.0051
	N	5	5	5	5	5	5
	%Diff	-8.8	6.3	8.6	7.8	11.5	9.9

[a] - Anova & Dunnett

[a1] - Anova & Dunnett(Log)

TABLE 11-1

Absolute Organ Weights - Summary

Mouse

Day: 30 Relative to Start Date

Sex: Female		Absolute Organ Weights					
		Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Ovary (left) (g)	Ovary (right) (g)	Heart (g)
		[a]	[a1]	[a2]	[a1]	[a]	[a1]
Group 1: Control	Mean	0.0045	0.0052	0.438	0.0069	0.0056	0.127
	SD	0.0018	0.0021	0.013	0.0044	0.0013	0.009
	N	10	10	10	10	10	10
Group 2: 50 Units/kg	Mean	0.0055	0.0043	0.434	0.0058	0.0058	0.130
	SD	0.0019	0.0013	0.019	0.0021	0.0017	0.029
	N	10	10	10	10	10	10
	%Diff	22.2	-17.3	-0.9	-15.9	3.6	2.4
Group 3: 250 Units/kg	Mean	0.0042	0.0039	0.436	0.0044	0.0051	0.140
	SD	0.0006	0.0016	0.015	0.0021	0.0027	0.021
	N	10	10	10	10	10	10
	%Diff	-6.7	-25.0	-0.5	-36.2	-8.9	10.2
Group 4: 500 Units/kg	Mean	0.0051	0.0049	0.428	0.0044	0.0059	0.129
	SD	0.0016	0.0026	0.013	0.0021	0.0030	0.014
	N	10	10	10	10	10	10
	%Diff	13.3	-5.8	-2.3	-36.2	5.4	1.6

[a] - Anova & Dunnett(Log)

[a1] - Anova & Dunnett(Rank)

[a2] - Anova & Dunnett

TABLE 11-1

Absolute Organ Weights - Summary

Mouse

Day: 30 Relative to Start Date

Sex: Female		Absolute Organ Weights					
		Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Spleen (g)	Thymus (g)	Uterus (g)
		[a]	[a]	[a1]	[a1]	[a1]	[a1]
Group 1: Control	Mean	0.132	0.141	0.97	0.077	0.0640	0.121
	SD	0.008	0.007	0.07	0.009	0.0108	0.043
	N	10	10	10	10	10	10
Group 2: 50 Units/kg	Mean	0.130	0.140	0.88	0.074	0.0520	0.105
	SD	0.013	0.024	0.13	0.021	0.0110	0.024
	N	10	10	10	10	10	10
	%Diff	-1.5	-0.7	-9.3	-3.9	-18.8	-13.2
Group 3: 250 Units/kg	Mean	0.131	0.132	0.90	0.075	0.0557	0.131
	SD	0.006	0.013	0.12	0.015	0.0090	0.044
	N	10	10	10	10	10	10
	%Diff	-0.8	-6.4	-7.2	-2.6	-13.0	8.3
Group 4: 500 Units/kg	Mean	0.137	0.137	0.93	0.086	0.0575	0.111
	SD	0.016	0.007	0.12	0.017	0.0099	0.024
	N	10	10	10	10	10	10
	%Diff	3.8	-2.8	-4.1	11.7	-10.2	-8.2

[a] - Anova & Dunnett(Rank)

[a1] - Anova & Dunnett

TABLE 11-1

Absolute Organ Weights - Summary

Mouse

Day: 44 Relative to Start Date

Sex: Female		Absolute Organ Weights					
		Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Ovary (left) (g)	Ovary (right) (g)	Heart (g)
		[a]	[a1]	[a1]	[a1]	[a1]	[a1]
Group 1: Control	Mean	0.0056	0.0058	0.436	0.0058	0.0044	0.138
	SD	0.0005	0.0022	0.022	0.0020	0.0011	0.013
	N	5	5	5	5	5	5
Group 4: 500 Units/kg	Mean	0.0050	0.0050	0.430	0.0060	0.0048	0.144
	SD	0.0023	0.0012	0.012	0.0010	0.0011	0.011
	N	5	5	5	5	5	5
	%Diff	-10.7	-13.8	-1.4	3.4	9.1	4.3

[a] - Anova & Dunnett(Rank)

[a1] - Anova & Dunnett

TABLE 11-1

Absolute Organ Weights - Summary

Mouse

Day: 44 Relative to Start Date

Sex: Female		Absolute Organ Weights					
		Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Spleen (g)	Thymus (g)	Uterus (g)
		[a]	[a]	[a]	[a1]	[a1]	[a1]
Group 1: Control	Mean	0.132	0.134	0.92	0.064	0.0410	0.126
	SD	0.016	0.009	0.08	0.009	0.0064	0.034
	N	5	5	5	5	5	5
Group 4: 500 Units/kg	Mean	0.128	0.134	0.96	0.078	0.0456	0.098
	SD	0.004	0.009	0.09	0.011	0.0092	0.016
	N	5	5	5	5	5	5
	%Diff	-3.0	0.0	4.3	21.9	11.2	-22.2

[a] - Anova & Dunnett(Rank)

[a1] - Anova & Dunnett

TABLE 11-1

Absolute Organ Weights - Summary

Mouse

<u>Comments and Markers</u>					
<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker</u> <u>Comment</u>
	30	2	Male	Epididymis - Left	* Anova & Dunnett(Rank): * = $p \leq 0.05$
	30	2	Male	Epididymis - Right	* Anova & Dunnett(Log): * = $p \leq 0.05$
	30	3	Male	Epididymis - Right	* Anova & Dunnett(Log): * = $p \leq 0.05$
	30	2	Male	Spleen Weight	* Anova & Dunnett(Log): * = $p \leq 0.05$
	30	2	Male	Thymus Weight	* Anova & Dunnett: * = $p \leq 0.05$
	30	4	Male	Spleen Weight	** Anova & Dunnett(Log): ** = $p \leq 0.01$

TABLE 11-1 Absolute Organ Weights - Summary Mouse

<u>Comments and Markers</u>						
<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker</u>	<u>Comment</u>
44		4	Male	Testis - Right	*	Anova & Dunnett: * = p ≤ 0.05

TABLE 11-2

Absolute Organ Weights - Individual Data

Mouse

Sex: Male Day: 30 Relative to Start Date

Group 1: Control	Absolute Organ Weights						
	Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Epididymis (left) (g)	Epididymis (right) (g)	Testis (left) (g)	Testis (right) (g)
1	0.004	0.006	0.41	0.05	0.06	0.10	0.10
2	0.007	0.006	0.42	0.06	0.05	0.09	0.09
3	0.004	0.008	0.43	0.06	0.05	0.10	0.11
4	0.003	0.005	0.42	0.05	0.04	0.10	0.09
5	0.003	0.003	0.44	0.07	0.05	0.10	0.10
6	0.004	0.008	0.43	0.04	0.04	0.08	0.08
7	0.002	0.003	0.40	0.04	0.08	0.10	0.09
8	0.008	0.009	0.42	0.04	0.04	0.10	0.10
9	0.004	0.010	0.43	0.05	0.06	0.10	0.11
10	0.006	0.004	0.47	0.05	0.05	0.09	0.10
Mean	0.0045	0.0062	0.427	0.051	0.052	0.096	0.097
SD	0.0019	0.0025	0.019	0.011	0.013	0.007	0.009
N	10	10	10	10	10	10	10

TABLE 11-2 Absolute Organ Weights - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 2: 50 Units/kg	Absolute Organ Weights						
	Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Epididymis (left) (g)	Epididymis (right) (g)	Testis (left) (g)	Testis (right) (g)
31	0.001	0.002	0.43	0.03	0.05	0.10	0.10
32	0.007	0.004	0.41	0.04	0.06	0.11	0.11
33	0.002	0.003	0.56	0.04	0.04	0.08	0.08
34	0.001	0.004	0.44	0.04	0.05	0.09	0.08
35	0.004	0.003	0.44	0.04	0.03	0.09	0.10
36	0.003	0.002	0.44	0.04	0.05	0.10	0.09
37	0.005	0.006	0.43	0.04	0.04	0.10	0.09
38	0.008	0.007	0.45	0.04	0.03	0.11	0.10
39	0.008	0.004	0.41	0.05	0.03	0.08	0.08
40	0.008	0.005	0.45	0.04	0.03	0.10	0.08
Mean	0.0047	0.0040	0.446	0.038	0.041	0.096	0.091
SD	0.0029	0.0016	0.042	0.004	0.010	0.011	0.011
N	10	10	10	10	10	10	10

TABLE 11-2 Absolute Organ Weights - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 3: 250 Units/kg	Absolute Organ Weights						
	Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Epididymis (left) (g)	Epididymis (right) (g)	Testis (left) (g)	Testis (right) (g)
51	0.015	0.006	0.45	0.05	0.04	0.10	0.10
52	0.002	0.004	0.42	0.05	0.04	0.10	0.11
53	0.004	0.002	0.41	0.03	0.04	0.09	0.09
54	0.005	0.019	0.43	0.04	0.04	0.11	0.11
55	0.003	0.008	0.42	0.04	0.04	0.10	0.10
56	0.003	0.005	0.41	0.03	0.04	0.08	0.08
57	0.003	0.003	0.41	0.05	0.04	0.10	0.10
58	0.009	0.005	0.43	0.05	0.04	0.09	0.10
59	0.003	0.002	0.44	0.05	0.03	0.06	0.07
60	0.006	0.004	0.43	0.07	0.04	0.08	0.08
Mean	0.0053	0.0058	0.425	0.046	0.038	0.091	0.094
SD	0.0040	0.0050	0.014	0.011	0.004	0.014	0.013
N	10	10	10	10	10	10	10

TABLE 11-2 Absolute Organ Weights - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 4: 500 Units/kg	Absolute Organ Weights						
	Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Epididymis (left) (g)	Epididymis (right) (g)	Testis (left) (g)	Testis (right) (g)
71	0.003	0.008	0.44	0.05	0.04	0.09	0.10
72	0.006	0.003	0.42	0.03	0.04	0.08	0.09
73	0.008	0.006	0.42	0.06	0.06	0.09	0.09
74	0.003	0.003	0.42	0.03	0.04	0.09	0.10
75	0.006	0.007	0.44	0.09	0.03	0.10	0.11
76	0.004	0.004	0.44	0.05	0.04	0.10	0.10
77	0.008	0.003	0.43	0.05	0.05	0.09	0.09
78	0.004	0.004	0.44	0.05	0.07	0.10	0.10
79	0.010	0.008	0.42	0.05	0.03	0.05	0.07
80	0.004	0.004	0.44	0.06	0.03	0.09	0.09
Mean	0.0056	0.0050	0.431	0.053	0.043	0.088	0.094
SD	0.0024	0.0021	0.010	0.016	0.012	0.015	0.011
N	10	10	10	10	10	10	10

TABLE 11-2 Absolute Organ Weights - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 1: Control	Absolute Organ Weights					
	Heart (g)	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Spleen (g)	Thymus (g)
1	0.18	0.16	0.16	1.0	0.05	0.040
2	0.14	0.15	0.15	0.9	0.05	0.056
3	0.15	0.20	0.18	1.2	0.05	0.044
4	0.15	0.15	0.15	1.0	0.05	0.031
5	0.14	0.19	0.18	1.0	0.06	0.039
6	0.17	0.20	0.19	1.4	0.08	0.049
7	0.14	0.16	0.16	1.1	0.05	0.059
8	0.16	0.16	0.17	1.0	0.05	0.058
9	0.14	0.18	0.16	1.1	0.05	0.048
10	0.16	0.18	0.18	1.0	0.06	0.041
Mean	0.153	0.173	0.168	1.07	0.055	0.0465
SD	0.014	0.019	0.014	0.14	0.010	0.0092
N	10	10	10	10	10	10

TABLE 11-2 Absolute Organ Weights - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 2: 50 Units/kg	Absolute Organ Weights					
	Heart (g)	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Spleen (g)	Thymus (g)
31	0.15	0.16	0.17	1.1	0.08	0.034
32	0.17	0.15	0.16	1.0	0.06	0.038
33	0.16	0.16	0.15	1.1	0.06	0.028
34	0.16	0.17	0.18	0.8	0.08	0.032
35	0.17	0.18	0.19	1.1	0.07	0.028
36	0.12	0.14	0.16	1.1	0.06	0.030
37	0.15	0.17	0.18	1.0	0.05	0.050
38	0.18	0.16	0.17	1.1	0.06	0.045
39	0.14	0.15	0.16	1.0	0.07	0.027
40	0.16	0.15	0.17	1.0	0.06	0.041
Mean	0.156	0.159	0.169	1.03	0.065	0.0353
SD	0.017	0.012	0.012	0.09	0.010	0.0079
N	10	10	10	10	10	10

TABLE 11-2 Absolute Organ Weights - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 3: 250 Units/kg	Absolute Organ Weights					
	Heart (g)	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Spleen (g)	Thymus (g)
51	0.19	0.18	0.19	1.3	0.06	0.041
52	0.17	0.16	0.17	1.1	0.05	0.059
53	0.16	0.13	0.14	0.9	0.05	0.038
54	0.17	0.16	0.17	1.0	0.07	0.050
55	0.14	0.16	0.15	1.0	0.05	0.044
56	0.14	0.16	0.16	1.0	0.06	0.038
57	0.15	0.15	0.17	1.1	0.06	0.027
58	0.15	0.18	0.17	1.1	0.06	0.060
59	0.15	0.17	0.15	1.0	0.06	0.043
60	0.15	0.18	0.17	1.2	0.07	0.037
Mean	0.157	0.163	0.164	1.07	0.059	0.0437
SD	0.016	0.016	0.014	0.12	0.007	0.0102
N	10	10	10	10	10	10

TABLE 11-2 Absolute Organ Weights - Individual Data Mouse

Sex: Male Day: 30 Relative to Start Date

Group 4: 500 Units/kg	Absolute Organ Weights					
	Heart (g)	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Spleen (g)	Thymus (g)
71	0.14	0.17	0.17	1.1	0.07	0.049
72	0.18	0.17	0.16	1.1	0.08	0.036
73	0.15	0.17	0.16	1.0	0.08	0.064
74	0.15	0.15	0.16	1.1	0.07	0.041
75	0.16	0.17	0.18	1.1	0.08	0.053
76	0.13	0.16	0.17	1.0	0.07	0.039
77	0.15	0.19	0.18	1.2	0.06	0.054
78	0.15	0.17	0.20	1.1	0.07	0.041
79	0.15	0.14	0.17	1.1	0.07	0.043
80	0.12	0.16	0.15	1.0	0.06	0.035
Mean	0.148	0.165	0.170	1.08	0.071	0.0455
SD	0.016	0.014	0.014	0.06	0.007	0.0093
N	10	10	10	10	10	10

TABLE 11-2 Absolute Organ Weights - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 1: Control	Absolute Organ Weights					
	Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Ovary (left) (g)	Ovary (right) (g)	Heart (g)
16	0.003	0.004	0.44	0.005	0.006	0.12
17	0.002	0.004	0.44	0.003	0.004	0.13
18	0.004	0.006	0.45	0.005	0.005	0.13
19	0.005	0.006	0.46	0.003	0.004	0.14
20	0.003	0.004	0.43	0.003	0.005	0.13
21	0.004	0.003	0.45	0.006	0.005	0.12
22	0.007	0.010	0.44	0.011	0.006	0.12
23	0.008	0.006	0.42	0.013	0.007	0.14
24	0.004	0.003	0.43	0.005	0.008	0.11
25	0.005	0.006	0.42	0.015	0.006	0.13
Mean	0.0045	0.0052	0.438	0.0069	0.0056	0.127
SD	0.0018	0.0021	0.013	0.0044	0.0013	0.009
N	10	10	10	10	10	10

TABLE 11-2

Absolute Organ Weights - Individual Data

Mouse

Sex: Female Day: 30 Relative to Start Date

Group 2: 50 Units/kg	Absolute Organ Weights					
	Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Ovary (left) (g)	Ovary (right) (g)	Heart (g)
41	0.005	0.005	0.47	0.006	0.007	0.12
42	0.009	0.004	0.43	0.006	0.006	0.12
43	0.004	0.004	0.44	0.006	0.006	0.15
44	0.003	0.004	0.44	0.004	0.005	0.15
45	0.008	0.007	0.46	0.006	0.009	0.19
46	0.007	0.005	0.42	0.006	0.005	0.10
47	0.005	0.004	0.42	0.003	0.006	0.13
48	0.005	0.004	0.43	0.010	0.004	0.11
49	0.004	0.002	0.42	0.003	0.003	0.09
50	0.005	0.004	0.41	0.008	0.007	0.14
Mean	0.0055	0.0043	0.434	0.0058	0.0058	0.130
SD	0.0019	0.0013	0.019	0.0021	0.0017	0.029
N	10	10	10	10	10	10

TABLE 11-2 Absolute Organ Weights - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 3: 250 Units/kg	Absolute Organ Weights					
	Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Ovary (left) (g)	Ovary (right) (g)	Heart (g)
61	0.004	0.002	0.42	0.004	0.003	0.14
62	0.004	0.004	0.45	0.007	0.011	0.16
63	0.004	0.004	0.43	0.002 <	0.004	0.14
64	0.005	0.004	0.45	0.002 <	0.002 <	0.18
65	0.005	0.008	0.45	0.007	0.007	0.12
66	0.004	0.004	0.46	0.002 <	0.003	0.13
67	0.004	0.004	0.43	0.007	0.004	0.13
68	0.004	0.003	0.42	0.005	0.006	0.13
69	0.003	0.003	0.43	0.003	0.007	0.16
70	0.005	0.003	0.42	0.005	0.004	0.11
Mean	0.0042	0.0039	0.436	0.0044	0.0051	0.140
SD	0.0006	0.0016	0.015	0.0021	0.0027	0.021
N	10	10	10	10	10	10

< = Out of range

TABLE 11-2

Absolute Organ Weights - Individual Data

Mouse

Sex: Female Day: 30 Relative to Start Date

Group 4: 500 Units/kg	Absolute Organ Weights					
	Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Ovary (left) (g)	Ovary (right) (g)	Heart (g)
86	0.005	0.005	0.45	0.005	0.003	0.11
87	0.005	0.003	0.43	0.003	0.003	0.13
88	0.003	0.003	0.42	0.005	0.007	0.15
89	0.006	0.004	0.44	0.004	0.004	0.12
90	0.003	0.004	0.43	0.006	0.005	0.13
91	0.008	0.005	0.42	0.009	0.008	0.11
92	0.007	0.012	0.43	0.002 <	0.013	0.13
93	0.004	0.004	0.43	0.002 <	0.007	0.14
94	0.005	0.004	0.43	0.005	0.005	0.15
95	0.005	0.005	0.40	0.003	0.004	0.12
Mean	0.0051	0.0049	0.428	0.0044	0.0059	0.129
SD	0.0016	0.0026	0.013	0.0021	0.0030	0.014
N	10	10	10	10	10	10

< = Out of range

TABLE 11-2

Absolute Organ Weights - Individual Data

Mouse

Sex: Female Day: 30 Relative to Start Date

Group 1: Control	Absolute Organ Weights					
	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Spleen (g)	Thymus (g)	Uterus (g)
16	0.13	0.15	0.9	0.06	0.053	0.09
17	0.12	0.15	1.0	0.09	0.067	0.15
18	0.14	0.14	1.0	0.07	0.075	0.07
19	0.14	0.14	1.1	0.08	0.066	0.18
20	0.14	0.13	1.0	0.08	0.066	0.14
21	0.13	0.14	0.9	0.08	0.049	0.19
22	0.14	0.14	0.9	0.07	0.084	0.09
23	0.13	0.14	1.0	0.07	0.069	0.08
24	0.13	0.15	1.0	0.09	0.055	0.09
25	0.12	0.13	0.9	0.08	0.056	0.13
Mean	0.132	0.141	0.97	0.077	0.0640	0.121
SD	0.008	0.007	0.07	0.009	0.0108	0.043
N	10	10	10	10	10	10

TABLE 11-2

Absolute Organ Weights - Individual Data

Mouse

Sex: Female Day: 30 Relative to Start Date

Group 2: 50 Units/kg	Absolute Organ Weights					
	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Spleen (g)	Thymus (g)	Uterus (g)
41	0.13	0.14	1.0	0.07	0.072	0.10
42	0.14	0.14	1.0	0.06	0.053	0.08
43	0.15	0.19	0.8	0.11	0.050	0.16
44	0.14	0.13	1.0	0.08	0.048	0.08
45	0.14	0.16	1.0	0.10	0.067	0.12
46	0.12	0.13	0.8	0.08	0.059	0.10
47	0.13	0.15	0.9	0.08	0.044	0.09
48	0.13	0.13	0.8	0.06	0.043	0.08
49	0.11	0.10	0.6	0.04	0.037	0.10
50	0.11	0.13	0.9	0.06	0.047	0.13
Mean	0.130	0.140	0.88	0.074	0.0520	0.105
SD	0.013	0.024	0.13	0.021	0.0110	0.024
N	10	10	10	10	10	10

TABLE 11-2

Absolute Organ Weights - Individual Data

Mouse

Sex: Female Day: 30 Relative to Start Date

Group 3: 250 Units/kg	Absolute Organ Weights					
	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Spleen (g)	Thymus (g)	Uterus (g)
61	0.13	0.13	0.8	0.05	0.043	0.22
62	0.14	0.15	1.0	0.09	0.061	0.16
63	0.12	0.12	0.9	0.07	0.068	0.09
64	0.14	0.14	0.7	0.09	0.053	0.09
65	0.13	0.13	0.8	0.06	0.041	0.10
66	0.13	0.14	1.1	0.09	0.065	0.15
67	0.13	0.15	1.0	0.08	0.060	0.14
68	0.13	0.11	0.8	0.06	0.049	0.15
69	0.13	0.13	1.0	0.09	0.060	0.10
70	0.13	0.12	0.9	0.07	0.057	0.09
Mean	0.131	0.132	0.90	0.075	0.0557	0.131
SD	0.006	0.013	0.12	0.015	0.0090	0.044
N	10	10	10	10	10	10

TABLE 11-2 Absolute Organ Weights - Individual Data Mouse

Sex: Female Day: 30 Relative to Start Date

Group 4: 500 Units/kg	Absolute Organ Weights					
	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Spleen (g)	Thymus (g)	Uterus (g)
86	0.17	0.14	1.0	0.09	0.069	0.12
87	0.14	0.13	1.1	0.10	0.054	0.15
88	0.12	0.13	1.0	0.10	0.058	0.09
89	0.15	0.14	1.0	0.09	0.053	0.16
90	0.12	0.13	0.8	0.06	0.038	0.09
91	0.14	0.13	0.9	0.07	0.071	0.10
92	0.12	0.14	0.9	0.07	0.065	0.11
93	0.13	0.14	0.9	0.07	0.050	0.10
94	0.14	0.14	0.7	0.11	0.054	0.11
95	0.14	0.15	1.0	0.10	0.063	0.09
Mean	0.137	0.137	0.93	0.086	0.0575	0.111
SD	0.016	0.007	0.12	0.017	0.0099	0.024
N	10	10	10	10	10	10

TABLE 11-2 Absolute Organ Weights - Individual Data Mouse

Sex: Male Day: 44 Relative to Start Date

Group 1: Control	Absolute Organ Weights						
	Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Epididymis (left) (g)	Epididymis (right) (g)	Testis (left) (g)	Testis (right) (g)
11	0.002	0.003	0.42	0.07	0.04	0.09	0.10
12	0.002	0.004	0.43	0.04	0.03	0.11	0.10
13	0.003	0.004	0.41	0.05	0.04	0.10	0.10
14	0.002	0.003	0.41	0.08	0.08	0.10	0.11
15	0.002	0.002	0.41	0.05	0.04	0.10	0.09
Mean	0.0022	0.0032	0.416	0.058	0.046	0.100	0.100
SD	0.0004	0.0008	0.009	0.016	0.019	0.007	0.007
N	5	5	5	5	5	5	5

TABLE 11-2 Absolute Organ Weights - Individual Data Mouse

Sex: Male Day: 44 Relative to Start Date

Group 4: 500 Units/kg	Absolute Organ Weights						
	Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Epididymis (left) (g)	Epididymis (right) (g)	Testis (left) (g)	Testis (right) (g)
81	0.004	0.002	0.41	0.05	0.05	0.08	0.08
82	0.002	0.002	0.42	0.05	0.04	0.09	0.08
83	0.003	0.003	0.42	0.05	0.04	0.09	0.10
84	0.003	0.004	0.43	0.05	0.07	0.10	0.09
85	0.003	0.001	0.42	0.03	0.03	0.09	0.08
Mean	0.0030	0.0024	0.420	0.046	0.046	0.090	0.086
SD	0.0007	0.0011	0.007	0.009	0.015	0.007	0.009
N	5	5	5	5	5	5	5

TABLE 11-2

Absolute Organ Weights - Individual Data

Mouse

Sex: Male Day: 44 Relative to Start Date

Group 1: Control	Absolute Organ Weights					
	Heart (g)	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Spleen (g)	Thymus (g)
11	0.15	0.15	0.15	1.0	0.05	0.035
12	0.18	0.17	0.16	1.1	0.06	0.032
13	0.16	0.16	0.16	1.0	0.04	0.035
14	0.18	0.17	0.19	1.0	0.06	0.036
15	0.13	0.15	0.15	1.0	0.05	0.034
Mean	0.160	0.160	0.162	1.02	0.052	0.0344
SD	0.021	0.010	0.016	0.04	0.008	0.0015
N	5	5	5	5	5	5

TABLE 11-2 Absolute Organ Weights - Individual Data Mouse

Sex: Male Day: 44 Relative to Start Date

Group 4: 500 Units/kg	Absolute Organ Weights					
	Heart (g)	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Spleen (g)	Thymus (g)
81	0.15	0.18	0.17	1.1	0.07	0.038
82	0.14	0.17	0.17	1.1	0.06	0.031
83	0.14	0.16	0.17	1.1	0.06	0.039
84	0.16	0.19	0.18	1.2	0.05	0.036
85	0.14	0.15	0.19	1.0	0.05	0.045
Mean	0.146	0.170	0.176	1.10	0.058	0.0378
SD	0.009	0.016	0.009	0.07	0.008	0.0051
N	5	5	5	5	5	5

TABLE 11-2

Absolute Organ Weights - Individual Data

Mouse

Sex: Female Day: 44 Relative to Start Date

Group 1: Control	Absolute Organ Weights					
	Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Ovary (left) (g)	Ovary (right) (g)	Heart (g)
26	0.005	0.004	0.41	0.008	0.006	0.15
27	0.006	0.007	0.47	0.005	0.003	0.14
28	0.006	0.004	0.43	0.008	0.004	0.12
29	0.005	0.009	0.43	0.004	0.005	0.15
30	0.006	0.005	0.44	0.004	0.004	0.13
Mean	0.0056	0.0058	0.436	0.0058	0.0044	0.138
SD	0.0005	0.0022	0.022	0.0020	0.0011	0.013
N	5	5	5	5	5	5

TABLE 11-2

Absolute Organ Weights - Individual Data

Mouse

Sex: Female Day: 44 Relative to Start Date

Group 4: 500 Units/kg	Absolute Organ Weights					
	Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Ovary (left) (g)	Ovary (right) (g)	Heart (g)
96	0.008	0.005	0.45	0.007	0.006	0.14
97	0.004	0.004	0.42	0.007	0.005	0.13
98	0.003	0.005	0.43	0.006	0.005	0.14
99	0.007	0.007	0.42	0.005	0.005	0.16
100	0.003	0.004	0.43	0.005	0.003	0.15
Mean	0.0050	0.0050	0.430	0.0060	0.0048	0.144
SD	0.0023	0.0012	0.012	0.0010	0.0011	0.011
N	5	5	5	5	5	5

TABLE 11-2

Absolute Organ Weights - Individual Data

Mouse

Sex: Female Day: 44 Relative to Start Date

Group 1: Control	Absolute Organ Weights					
	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Spleen (g)	Thymus (g)	Uterus (g)
26	0.14	0.14	0.9	0.06	0.036	0.11
27	0.11	0.13	0.8	0.06	0.041	0.16
28	0.15	0.14	1.0	0.08	0.050	0.16
29	0.12	0.12	0.9	0.06	0.044	0.12
30	0.14	0.14	1.0	0.06	0.034	0.08
Mean	0.132	0.134	0.92	0.064	0.0410	0.126
SD	0.016	0.009	0.08	0.009	0.0064	0.034
N	5	5	5	5	5	5

TABLE 11-2 Absolute Organ Weights - Individual Data Mouse

Sex: Female Day: 44 Relative to Start Date

Group 4: 500 Units/kg	Absolute Organ Weights					
	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Spleen (g)	Thymus (g)	Uterus (g)
96	0.13	0.14	1.0	0.08	0.061	0.09
97	0.13	0.12	0.8	0.06	0.042	0.11
98	0.13	0.14	1.0	0.08	0.042	0.09
99	0.13	0.13	1.0	0.09	0.037	0.08
100	0.12	0.14	1.0	0.08	0.046	0.12
Mean	0.128	0.134	0.96	0.078	0.0456	0.098
SD	0.004	0.009	0.09	0.011	0.0092	0.016
N	5	5	5	5	5	5

TABLE 11-2

Absolute Organ Weights - Individual Data

Mouse

<u>Comments and Markers</u>							
<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Subject</u>	<u>Measurement</u>	<u>Type</u>	<u>Marker</u>
30	30	3	Female	63	Ovary Weight - Left	Out of Range	<
30	30	3	Female	64	Ovary Weight - Left	Out of Range	<
30	30	3	Female	64	Ovary Weight - Right	Out of Range	<
30	30	3	Female	66	Ovary Weight - Left	Out of Range	<
30	30	4	Female	92	Ovary Weight - Left	Out of Range	<
30	30	4	Female	93	Ovary Weight - Left	Out of Range	<

TABLE 12-1 Allogenic APOSEC™
Bone Marrow - Summary Mouse

	Myeloids (in %)	Erythroids (in %)	Myeloid/Erythroid ratio	Chi ² -Test
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Males

Terminal sacrifice (test day 30)Group 1: Control

Mean:	75.40	24.60	3.372 : 1	-
SD:	6.99	6.99		

Group 2: 50 Units/kg

Mean:	72.30	27.70	2.734 : 1	ns
SD:	5.36	5.36	-	

Group 3: 250 Units/kg

Mean:	71.30	28.70	2.546 : 1	ns
SD:	4.02	4.02	-	

Group 4: 500 Units/kg

Mean:	71.90	28.10	2.648 : 1	ns
SD:	5.03	5.03	-	

Recovery sacrifice (test day 44)Group 1: Control

Mean:	68.50	31.50	2.195 : 1	-
SD:	-	-	-	

Group 4: 500 Units/kg

Mean:	56.60	43.40	1.326 : 1	ns
SD:	4.83	4.83	-	

ns = not significant

** p ≤ 0.01 (Chi-square test)

TABLE 12-1 Allogenic APOSEC™
Bone Marrow - Summary Mouse

	Myeloids (in %)	Erythroids (in %)	Myeloid/Erythroid ratio	Chi ² -Test
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Females

Terminal sacrifice (test day 30)

Group 1: Control

Mean:	66.60	33.40	2.048 : 1	-
SD:	4.57	4.57	-	

Group 2: 50 Units/kg

Mean:	66.20	33.80	1.974 : 1	ns
SD:	2.46	2.46	-	

Group 3: 250 Units/kg

Mean:	71.40	28.60	2.558 : 1	ns
SD:	4.23	4.23	-	

Group 4: 500 Units/kg

Mean:	65.80	34.20	1.946 : 1	ns
SD:	3.13	3.13	-	

Recovery sacrifice (test day 44)

Group 1: Control

Mean:	72.00	28.00	2.744 : 1	-
SD:	7.09	7.09	-	

Group 4: 500 Units/kg

Mean:	65.10	34.90	1.924 : 1	ns
SD:	5.35	5.35	-	

ns = not significant

** $p \leq 0.01$ (Chi-square test)

TABLE 12-2 Allogenic APOSEC™
Bone Marrow - Individual Data Mouse

	Myeloids (in %)	Erythroids (in %)	Myeloid/Erythroid ratio	Chi ² -Test (p-value)
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Males

Terminal sacrifice (test day 30)Group 1: Control

(1)	84.5	15.5	5.45 : 1	
(2)	80.0	20.0	4.00 : 1	
(3)	75.0	25.0	3.00 : 1	
(4)	70.0	30.0	2.33 : 1	
(5)	67.5	32.5	2.08 : 1	
Mean:	75.40	24.60	3.372 : 1	-
SD:	6.99	6.99	-	

Group 2: 50 Units/kg

(31)	80.0	20.0	4.00 : 1	
(32)	68.0	32.0	2.13 : 1	
(33)	73.0	27.0	2.70 : 1	
(34)	66.5	33.5	1.99 : 1	
(35)	74.0	26.0	2.85 : 1	
Mean:	72.30	27.70	2.734 : 1	0.571
SD:	5.36	5.36	-	

** $p \leq 0.01$ (Chi-square test)

TABLE 12-2 Allogenic APOSEC™
Bone Marrow - Individual Data Mouse

	Myeloids (in %)	Erythroids (in %)	Myeloid/Erythroid ratio	Chi ² -Test (p-value)
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Males

Terminal sacrifice (test day 30)Group 3: 250 Units/kg

(51)	71.5	28.5	2.51 : 1	
(52)	69.5	30.5	2.28 : 1	
(53)	66.5	33.5	1.99 : 1	
(54)	77.5	22.5	3.44 : 1	
(55)	71.5	28.5	2.51 : 1	
Mean:	71.30	28.70	2.546 : 1	0.431
SD:	4.02	4.02	-	

Group 4: 500 Units/kg

(71)	64.0	36.0	1.78 : 1	
(72)	72.5	27.5	2.64 : 1	
(73)	73.0	27.0	2.70 : 1	
(74)	72.0	28.0	2.57 : 1	
(75)	78.0	22.0	3.55 : 1	
Mean:	71.90	28.10	2.648 : 1	0.571
SD:	5.03	5.03	-	

** $p \leq 0.01$ (Chi-square test)

TABLE 12-2 Allogenic APOSEC™
Bone Marrow - Individual Data Mouse

	Myeloids (in %)	Erythroids (in %)	Myeloid/Erythroid ratio	Chi ² -Test (p-value)
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Males

Recovery sacrifice (test day 44)Group 1: Control

(11)	71.0	29.0	2.45 : 1	
(12) [#]	N/A	N/A		
(13) [#]	N/A	N/A		
(14) [#]	N/A	N/A		
(15)	66.0	34.0	1.94 : 1	
Mean:	68.50	31.50	2.195 : 1	-
SD:	-	-	-	

Group 4: 500 Units/kg

(81)	60.0	40.0	1.50 : 1	
(82)	55.0	45.0	1.22 : 1	
(83)	54.0	46.0	1.17 : 1	
(84)	51.0	49.0	1.04 : 1	
(85)	63.0	37.0	1.70 : 1	
Mean:	56.60	43.40	1.326 : 1	0.017
SD:	4.83	4.83	-	

** $p \leq 0.01$ (Chi-square test)

[#] No evaluation possible due to insufficient staining

TABLE 12-2 Allogenic APOSEC™
Bone Marrow - Individual Data Mouse

	Myeloids (in %)	Erythroids (in %)	Myeloid/Erythroid ratio	Chi ² -Test (p-value)
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Females

Terminal sacrifice (test day 30)

Group 1: Control

(16)	63.5	36.5	1.74 : 1	
(17)	68.0	32.0	2.13 : 1	
(18)	64.5	35.5	1.82 : 1	
(19)	63.0	37.0	1.70 : 1	
(20)	74.0	26.0	2.85 : 1	
Mean:	66.60	33.40	2.048 : 1	-
SD:	4.57	4.57	-	

Group 2: 50 Units/kg

(41)	63.5	36.5	1.74 : 1	
(42)	65.0	35.0	1.86 : 1	
(43)	68.0	32.0	2.13 : 1	
(44)	69.5	30.5	2.28 : 1	
(45)	65.0	35.0	1.86 : 1	
Mean:	66.20	33.80	1.974 : 1	0.916
SD:	2.46	2.46	-	

** $p \leq 0.01$ (Chi-square test)

TABLE 12-2 Allogenic APOSEC™
Bone Marrow - Individual Data Mouse

	Myeloids (in %)	Erythroids (in %)	Myeloid/Erythroid ratio	Chi ² -Test (p-value)
--	--------------------	----------------------	----------------------------	-------------------------------------

Females

Terminal sacrifice (test day 30)

Group 3: 250 Units/kg

(61)	74.5	25.5	2.92 : 1	
(62)	69.0	31.0	2.23 : 1	
(63)	65.5	34.5	1.90 : 1	
(64)	72.0	28.0	2.57 : 1	
(65)	76.0	24.0	3.17 : 1	
Mean:	71.40	28.60	2.558 : 1	0.449
SD:	4.23	4.23	-	

Group 4: 500 Units/kg

(86)	64.0	36.0	1.78 : 1	
(87)	67.5	32.5	2.08 : 1	
(88)	63.0	37.0	1.70 : 1	
(89)	64.0	36.0	1.78 : 1	
(90)	70.5	29.5	2.39 : 1	
Mean:	65.80	34.20	1.946 : 1	0.916
SD:	3.13	3.13	-	

** $p \leq 0.01$ (Chi-square test)

TABLE 12-2 Allogenic APOSEC™
Bone Marrow - Individual Data Mouse

	Myeloids (in %)	Erythroids (in %)	Myeloid/Erythroid ratio	Chi ² -Test (p-value)
--	--------------------	----------------------	----------------------------	-------------------------------------

Females

Recovery sacrifice (test day 44)

Group 1: Control

(26)	61.5	38.5	1.60 : 1	
(27)	75.5	24.5	3.08 : 1	
(28)	76.5	23.5	3.26 : 1	
(29)	78.5	21.5	3.65 : 1	
(30)	68.0	32.0	2.13 : 1	
Mean:	72.00	28.00	2.744 : 1	-
SD:	7.09	7.09	-	

Group 4: 500 Units/kg

(96)	64.0	36.0	1.78 : 1	
(97)	63.5	36.5	1.74 : 1	
(98)	67.5	32.5	2.08 : 1	
(99)	58.0	42.0	1.38 : 1	
(100)	72.5	27.5	2.64 : 1	
Mean:	65.10	34.90	1.924 : 1	0.162
SD:	5.35	5.35	-	

** $p \leq 0.01$ (Chi-square test)

9. APPENDICES

A P P E N D I X 1

Certificates of Analysis



ÖSTERREICHISCHES ROTES KREUZ

ROTES KREUZ

Aus Liebe zum Menschen.

CERTIFICATE OF ANALYSIS

Manufacturer: Österreichisches Rotes Kreuz, Landesverband Oberösterreich, Blutzentrale Linz
Krankenhausstraße 7, 4010 Linz, Austria

Name: APOSEC™

Filling size: 100 mL glass bottle with 20 mL lyophilised APOSEC™

Batch-No: 399049

Man. Date: 29.06.2016

Valid for: Non-clinical trials

TEST	SPECIFICATION	RESULTS
Endotoxine	< 0,25 EU/mL	< 0,25 EU/mL
Mycoplasma	negative	negative
LEAD CYTOKINES		
EGF	51-214 pg/mL	110,248 pg/mL
TGF-β	3580-10354 pg/mL	5286,6 pg/mL
IL-8	300-4829 pg/mL	1618,75 pg/mL
POTENCY ASSAYS		
Inhibition of Platelet Aggregation	determined	---
STERILITY		
Endproduct	sterile	sterile

The above lot was manufactured according to Austrian Medicinal Product Act (AMG) and GMP regulations. All donations were tested negative for HIV, HCV, HBV, HAV, HEV, Parvo B19 and syphilis. This human investigational medicinal product is only intended for toxicological studies and not for human use. During this developmental phase the formal approval of the Qualified Person is not mandatory.

24.10.16

Date / Signature (Head of quality control)

Dateiname und Pfad: lbz-srv-
file03\complexrights\5Dok\Vorabedokumente\Produktion\Gewebebank\Formulare APOSEC
allogenEXT-Certificate of Analysis.docx

Version: 2.0, gültig
ab 28.09.2016

Seite 1 von 1

LANDESVERBAND OBERÖSTERREICH, BLUTZENTRALE LINZ, 4017 Linz, Krankenhausstr. 7
BLUT- und GEWEBEBANK, AMBULATORIUM, LABORATORIUM, GENETISCHE DIAGNOSTIK
TELEFON: 0732/777000-0, TELEFAX: 0732/777000-12, EMAIL: blutzentrale@o.roteskruz.at, INTERNET: <http://www.roteskruz.at/ooe>
BANKVERBINDUNG: ALLGEMEINE SPARKASSE, KTO.NR.: 1200-750130, BLZ: 20320, IBAN: AT142032001200750130, BIC: ASPKAT2LXXX
UID-NR.: ATU 23006707, EORI-Nummer: ATEOS1000010552, DVR: 0078883, ZVR-NR.: 534696372
ERFÜLLUNGORT UND AUSSCHLIESSLICHER GERICHTSSTAND IST LINZ



ÖSTERREICHISCHES ROTES KREUZ

GEMEINNÜTZIGER VEREIN

Aus Liebe zum Menschen.

CERTIFICATE OF ANALYSIS

Manufacturer: Österreichisches Rotes Kreuz, Landesverband Oberösterreich, Blutzentrale Linz
Krankenhausstraße 7, 4010 Linz, Austria

Name: APOSEC™

Filling size: 100 mL glass bottle with 20 mL lyophilised APOSEC™

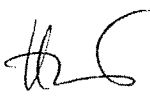
Batch-No: 399050

Man. Date: 01.07.2016

Valid for: Non-clinical trials

TEST	SPECIFICATION	RESULTS
Endotoxine	< 0,25 EU/mL	< 0,25 EU/mL
Mycoplasma	negative	negative
LEAD CYTOKINES		
EGF	51-214 pg/mL	104,886 pg/mL
TGF-β	3580-10354 pg/mL	3881,9 pg/mL
IL-8	300-4829 pg/mL	1160,97 pg/mL
POTENCY ASSAYS		
Inhibition of Platelet Aggregation	determined	---
STERILITY		
Endproduct	sterile	sterile

The above lot was manufactured according to Austrian Medicinal Product Act (AMG) and GMP regulations. All donations were tested negative for HIV, HCV, HBV, HAV, HEV, Parvo B19 and syphilis. This human investigational medicinal product is only intended for toxicological studies and not for human use. During this developmental phase the formal approval of the Qualified Person is not mandatory.

24.10.16 

Date / Signature (Head of quality control)

Dateiname und Pfad: lhbz-srv-
file03\complexrights\1\0ko\Vorgabedokumente\Produktion\Gewebebank\Formulare APOSEC
allogen\EXT-Certificate of Analysis.docx

Version: 2.0, gültig
ab 28.09.2016

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LANDESVERBAND OBERÖSTERREICH, BLUTZENTRALE LINZ, 4017 Linz, Krankenhausstr. 7
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TELEFON: 0732/777000-0, TELEFAX: 0732/777000-12, EMAIL: blutzentrale@o.roteskreuz.at, INTERNET: <http://www.roteskreuz.at/ooo>
BANKVERBINDUNG: ALLGEMEINE SPARKASSE, KTO.NR.: 1200750130, BLZ: 20320, IBAN: AT142032001200750130, BIC: ASPKAT2LXXX
UID-NR.: ATU 23006707, EORI-Nummer: ATEOS1000010552, DVR: 0078883, ZVR-NR.: 534696372
ERFÜLLUNGORT UND AUSSCHLIESSLICHER RICHTSSTAND IST LINZ



ÖSTERREICHISCHES ROTES KREUZ

*Aus Liebe zum Menschen.***CERTIFICATE OF ANALYSIS**

Manufacturer: Österreichisches Rotes Kreuz, Landesverband Oberösterreich, Blutzentrale Linz
Krankenhausstraße 7, 4010 Linz, Austria

Name: APOSEC™

Filling size: 100 mL glass bottle with 20 mL lyophilised APOSEC™

Batch-No: 399051

Man. Date: 15.06.2016

Valid for: Non-clinical trials

TEST	SPECIFICATION	RESULTS
Endotoxine	< 0,25 EU/mL	< 0,25 EU/mL
Mycoplasma	negative	negative
LEAD CYTOKINES		
EGF	51-214 pg/mL	133,68 pg/mL
TGF-β	3580-10354 pg/mL	4402,9 pg/mL
IL-8	300-4829 pg/mL	1555,63 pg/mL
STERILITY		
Endproduct	sterile	sterile

The above lot was manufactured according to Austrian Medicinal Product Act (AMG) and GMP regulations. All donations were tested negative for HIV, HCV, HBV, HAV, HEV, Parvo B19 and syphilis. This human investigational medicinal product is only intended for toxicological studies and not for human use. During this developmental phase the formal approval of the Qualified Person is not mandatory.

10. MAI 2017

Date / Signature (Head of quality control)



ÖSTERREICHISCHES ROTES KREUZ

ÖBERÖSTERREICH

*Aus Liebe zum Menschen.***CERTIFICATE OF ANALYSIS**

Manufacturer: Österreichisches Rotes Kreuz, Landesverband Oberösterreich, Blutzentrale Linz
Krankenhausstraße 7, 4010 Linz, Austria
Name: APOSEC™
Filling size: 100 mL glass bottle with 20 mL lyophilised APOSEC™
Batch-No: 399053
Man. Date: 15.07.2016
Valid for: Non-clinical trials

TEST	SPECIFICATION	RESULTS
Endotoxine	< 0,25 EU/mL	< 0,25 EU/mL
Mycoplasma	negative	negative
LEAD CYTOKINES		
EGF	51-214 pg/mL	98,075 pg/mL
TGF-β	3580-10354 pg/mL	4222,1 pg/mL
IL-8	300-4829 pg/mL	1072,73 pg/mL
POTENCY ASSAYS		
Inhibition of Platelet Aggregation	determined	---
STERILITY		
Endproduct	sterile	sterile

The above lot was manufactured according to Austrian Medicinal Product Act (AMG) and GMP regulations. All donations were tested negative for HIV, HCV, HBV, HAV, HEV, Parvo B19 and syphilis. This human investigational medicinal product is only intended for toxicological studies and not for human use. During this developmental phase the formal approval of the Qualified Person is not mandatory.

24.10.16

Date / Signature (Head of quality control)

Dateiname und Pfad:
I:\Blutzentrale\KomplexeBerechtigungen\Doko\Vorgabedokumente\Produktion\Gewebebank\For
mulare APOSEC allogent\EXT-Certificate of Analysis.docx

Version: 2.0, gültig
ab 28.09.2016

Seite 1 von 1

LANDESVERBAND OBERÖSTERREICH, BLUTZENTRALE LINZ, 4017 Linz, Krankenhausstr. 7
BLUT- und GEWEBEBANK, AMBULATORIUM, LABORATORIUM, GENETISCHE DIAGNOSTIK.
TELEFON: 0732/777000-0, TELEFAX: 0732/777000-12, EMAIL: blutzentrale@e.rotekruz.at, INTERNET: <http://www.rotekruz.at/ooe>
BANKVERBINDUNG: ALLGEMEINE SPARKASSE, KTO.NR.: 1200750130, BLZ: 20320, IBAN: AT142032001200750130, BIC: ASFKAT2LXXX
UID-NR.: ATU 23006707, EORI-Nummer: ATEOST00010552, DVR: 0078883, ZVR-NR.: 534696372
ERFÜLLUNGORT UND AUSSCHLIESSLICHER GERICHTSSTAND IST LINZ



ÖSTERREICHISCHES ROTES KREUZ

*Aus Liebe zum Menschen.***CERTIFICATE OF ANALYSIS**

Manufacturer: Österreichisches Rotes Kreuz, Landesverband Oberösterreich, Blutzentrale Linz
Krankenhausstraße 7, 4010 Linz, Austria
Name: APOSEC™
Filling size: 100 mL glass bottle with 20 mL lyophilised APOSEC™
Batch-No: 399057
Man. Date: 29.06.2016
Valid for: Non-clinical trials

TEST	SPECIFICATION	RESULTS
Endotoxine	< 0,25 EU/mL	< 0,25 EU/mL
Mycoplasma	negative	negative
LEAD CYTOKINES		
EGF	51-214 pg/mL	121,06 pg/mL
TGF-β	3580-10354 pg/mL	4303,4 pg/mL
IL-8	300-4829 pg/mL	1572,14 pg/mL
STERILITY		
Endproduct	sterile	sterile

The above lot was manufactured according to Austrian Medicinal Product Act (AMG) and GMP regulations. All donations were tested negative for HIV, HCV, HBV, HAV, HEV, Parvo B19 and syphilis. This human investigational medicinal product is only intended for toxicological studies and not for human use. During this developmental phase the formal approval of the Qualified Person is not mandatory.

10. MAI 2017

Date / Signature (Head of quality control)

A P P E N D I X 2

Composition of the Diet, Limitation for Contaminants in the Diet, Drinking Water and Bedding Material

Composition of the diet**Standard Diet for Rats and Mice****ssniff® R/M-H V1530-1534**

(ssniff Spezialdiäten GmbH, 59494 Soest, Germany)

Ingredients

(average % content in the diet)

Dry substance	87.7
Crude protein	19.0
Crude fat	3.3
Crude fibres	4.9
Crude ash	6.4
N-free extracts	54.1
Starch	36.5
Sugar	4.7

Metabolizable Energy

(MJ/kg)

Gross energy	16.3
Metabolizable energy	12.8

Minerals

(average % content in the diet)

Calcium	1.00
Phosphorus	0.70
Sodium	0.24
Magnesium	0.22
Potassium	0.91

Amino Acids

(average % content in the diet)

Lysine	1.00
Methionine	0.30
Met + Cys	0.65
Glycine	0.80
Leucine	1.30
Isoleucine	0.76
Arginine	1.14
Phenylalanine	0.85
Tryptophan	0.25
Histidine	0.44
Phe + Tyr	1.43
Aspartic acid	1.61
Glutamic acid	3.90
Valine	0.88
Threonine	0.68
Proline	1.25
Alanine	0.79
Serine	0.89

Trace Elements

(average content in mg per 1 000 g of the diet)

Iron	179
Zinc	94
Manganese	69
Copper	16
Iodine	2.2
Cobalt	2.1
Selenium	0.3

Vitamins

(additive per 1 000 g of diet)

Vitamin A	15000 IU
Vitamin D ₃	1000 IU
Vitamin E	110 mg
Vitamin B ₁	18 mg
Vitamin B ₂	23 mg
Vitamin B ₆	21 mg
Vitamin B ₁₂	100 µg
Biotin	525 µg
Pantothenic acid	43 mg
Choline chloride	2990 mg
Folic acid	7 mg
Nicotinic acid	135 mg
Vitamin K ₃	5 mg
Inositol	100 mg

Fatty Acids

(%)

C 14:0	0.01
C 16:0	0.47
C 16:1	0.01
C 18:0	0.08
C 18:1	0.62
C 18:2	1.80
C 18:3	0.23
C 20:0	0.01
C 20:1	0.02
C 20:5	-
C 22:6	-

Limitation for contaminants in the diet (ppb)

	min.	max.
Aflatoxin (B ₁ , B ₂ , G ₁ , G ₂), total		5.0
Lindane		20.0
Heptachlor		20.0
Malathion		2500
DDT (Total)		100.0
Dieldrin		20.0
Cadmium		160.0
Arsenic		1000
Lead		1500
Mercury		100.0
Selenium	100	600.0
PCB		50.0

Limitation for contaminants in the bedding material [mg/kg]

	max.
Aflatoxin (B ₁)	0.01
Chlordane	0.05
Endrine	0.02
Fluorine	150.00
Lindane	0.10
Heptachlor and epoxide	0.03
DDT, DDE, DDD	0.05
Dieldrin and aldrin	0.02
Arsenic	2.00
Lead	5.00
Mercury	0.10
Nitrite (Na-Nitrite)	15.00
HCB	0.03

Limitation for contaminants in the drinking water [mg/L]

	max.
Iron	0.200
Manganese	0.050
Ammonium	0.50
Chloride	250
Arsenic	0.010
Lead	0.01
Cadmium	0.0030
Chromium	0.050
Cyanide	0.050
Fluoride	1.5
Nickel	0.020
Nitrite	0.50
Nitrate	50
Mercury	0.0010
Vinylchloride	0.00050
Acrylamide	0.00010
Benzene	0.0010
Boron	1.0
Bromate	0.010
Selenium	0.010
Antimony	0.0050
Copper	2.0
Aluminium	0.200
Sodium	200
Sulphate	250
Uranium	0.010

Polycyclic aromatic hydrocarbons

- Benzo-(b)-fluoranthene		
- Benzo-(k)-fluoranthene		
- Benzo-(ghi)-perylene		
- Indeno-(1,2,3-cd)-pyrene	total	0.00010
- Benzo-(a)-pyrene		0.000010

Chlorinated organic compounds

Trihalogenemethane including

Trichloromethane,
Bromodichloromethane,
Dibromochloromethane and
Tribromomethane

total 0.050

- 1,2-Dichloroethane	0.0030
- Tetrachloroethene and Trichloroethene	0.010
- Epichlorohydrine	0.00010

Organic chemical compounds used as

pesticides and biocides including

their toxic metabolites

maximum of 0.00010/substance

except for

- Aldrin	0.000030
- Dieldrin	0.000030
- Heptachlor	0.000030
- Heptachloroepoxide	0.000030

maximum total of 0.00050

Tritium [Bq/L]

100

pH between 6.5 and 9.5

A P P E N D I X 3

Phase Report on Histopathology
(performed by Global Pathology Support, The Netherlands)



Global Pathology Support

TOXICOLOGIC PATHOLOGY

FINAL

Benoordenhoutseweg 23
2596 BA The Hague
The Netherlands
Telephone: +31 (0)70 314 2404
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E-mail: Bob.Thoolen@gpstoxpath.com
www.gpstoxpath.com

FINAL PATHOLOGIST'S REPORT

**4-Week Toxicity Study of
Allogenic APOSEC™
by Intravenous Slow Bolus Administration
Three Times Weekly to Mice**

- Multi-Site Study -

- PATHOLOGY ASSESSMENT -

Test Site Reference number: 457

LPT Study no. 34946

Issue date report: 29 November, 2017

Author: R.J.M.M. Thoolen



Test Site Reference no. 457 / LPT Study no. 34946

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Test Site Reference no. 457 / LPT Study no. 34946

1. STUDY INFORMATION SHEET

Test Facility:

LPT Laboratory of Pharmacology
and Toxicology GmbH & Co. KG
Redderweg 8
21147 Hamburg
Germany
+49 (0)40 70 20 20 (Tel.)
+49 (0)40 70 20 22 60 (Fax)

Study Director:

Dr. phil. Jost Leuschner
LPT Laboratory of Pharmacology
and Toxicology GmbH & Co. KG
Redderweg 8
21147 Hamburg
Germany
LPT@LPT-Hamburg.de

Test site and Principal Investigator for Histopathology:

Dr. R.J.M.M. Thoolen
Global Pathology Support
Benoordenhoutseweg 23
2596 BA The Hague
The Netherlands
+31 (0)70 314 2404 (Tel.)
Bob.Thoolen@gpstoxpath.com

Test site Quality Assurance:

N. Tirtodikromo
Global Pathology Support
Benoordenhoutseweg 23
2596 BA The Hague
The Netherlands
+31 (0)70 314 2404 (Tel.)
suzy.tirtodikromo@gpstoxpath.com



Test Site Reference no. 457 / LPT Study no. 34946

Test site study identification:

457

Histopathological assessment period:

04 September, 2017 – 27 November, 2017.

Guidelines:

This study phase is performed in compliance with the OECD Principles of Good Laboratory Practice (as revised in 1997), OECD Environmental Health and Safety Publications, ENV/MC/CHEM(98)17, Paris 1998 and subsequent consensus documents.

The OECD Principles of Good Laboratory Practice are accepted by Regulatory Authorities throughout the European Community, United States of America (FDA and EPA) and Japan (MHLW, MAFF and METI).



Test Site Reference no. 457 / LPT Study no. 34946

1.1 GLP COMPLIANCE

GLP Compliance Statement

With respect to the following study phase, which is a part of LPT study 34946:

Test Site Reference number: 457

**4-Week Toxicity Study of
Allogenic APOSEC™
by Intravenous Slow Bolus Administration
Three Times Weekly to Mice**

- Multi-Site Study -

- PATHOLOGY ASSESSMENT -

as conducted by and performed at Global Pathology Support, The Hague, The Netherlands.

I the undersigned, declare this phase report constitutes a true and faithful account of the procedures adopted and the histopathology results obtained in this delegated part of the study.

This delegated part of the study described in this phase report was conducted in compliance with the OECD Principles of Good Laboratory Practice (as revised in 1997), OECD Environmental Health and Safety Publications, ENV/MC/CHEM(98)17, Paris 1998 and subsequent consensus documents.

The OECD Principles of Good Laboratory Practice are accepted by Regulatory Authorities throughout the European Community, United States of America (FDA and EPA) and Japan (MHLW, MAFF and METI).

Macroscopic observations and histological preparation were performed under the responsibility of LPT.

I, the undersigned consider the presented data to be valid.

Signature:

Date:

R.J.M.M. Thoolen

Principal Investigator Pathology /
Managing Director Global Pathology Support



Test Site Reference no. 457 / LPT Study no. 34946

1.2 QUALITY ASSURANCE

This Quality Assurance Statement concerns Global Pathology Support study phase:

Test Site Reference number: 457

**4-Week Toxicity Study of
Allogenic APOSEC™
by Intravenous Slow Bolus Administration
Three Times Weekly to Mice**

- Multi-Site Study -

- PATHOLOGY ASSESSMENT -

which is a part of LPT study 34946.

In compliance with the OECD Principles of Good Laboratory Practices the performance of this part of the study has been monitored by the Global Pathology Support Unit by means of study based auditing of pre-defined critical phases.

All observations were reported in writing to the Principal Investigator, Test Site Management and to the Study Director, Leading QA and Test Facility Management. The specifications of the inspections performed are presented below:

Type of audit	Phase(s) of the study inspected	Date(s) of audit	Date(s) reported to Principal Investigator / Test Site Management	Date(s) reported to Study Director, Leading QA and Test Facility Management
Study plan	Pre-study phase	26 and 27-Nov-2017	27-Nov-2017	27-Nov-2017
Experimental phase	Histopathology phase	27-Nov-2017	27-Nov-2017	27-Nov-2017
Raw data & Draft Report	Reporting phase	28-Nov-2017	29-Nov-2017	29-Nov-2017

This part of the report has been audited by the Quality Assurance Unit of Global Pathology Support. It represents an accurate description of the performance of the study phase. The data reported are an accurate reflection of the raw data produced during the performance of this part of the study.

Signature:

Date:

N. Tirtodikromo
Quality Assurance Manager



Test Site Reference no. 457 / LPT Study no. 34946

2. ANIMAL ALLOCATION AND ANIMAL TREATMENT SCHEME

Group	APOSEC™ dose, i.v. [Units/kg]	No. and sex of animals MS + RP	Animal no.	
			MS	RP
1	0 (0.9% NaCl solution)	10 + 5 m 10 + 5 f	1 - 10 16 - 25	11 - 15 26 - 30
2	50 (low dose)	10 m 10 f	31 - 40 41 - 50	none
3	250 (intermediate dose)	10 m 10 f	51 - 60 61 - 70	none
4	500 (high dose)	10 + 5 m 10 + 5 f	71 - 80 86 - 95	81 - 85 96 - 100

MS: Main study
 RP: Recovery period
 m: male
 f: female
 i.v.: intravenous

3. METHODS

3.1 Necropsy

Necropsy was performed by LPT.

On test day 30 (approx. 24 hours after the last administration), the main study animals were dissected following a randomisation scheme. Necropsy of all animals allocated to the recovery period were performed on test day 44.

Immediately after blood withdrawal for laboratory examinations, the animals were sacrificed under inhalation anesthesia (isoflurane), weighed, dissected and inspected macroscopically under the direction of a pathologist.



Test Site Reference no. 457 / LPT Study no. 34946

The following organs or parts of organs of all animals were fixed in 7% buffered formalin. The eyes were fixed in Davidson's solution and the testicle in modified Davidson's solution for optimum fixation.

Adrenal gland (2)	Oesophagus
Aorta abdominalis	Ovary (2)
Bone (<i>os femoris with joint</i>)	Pancreas
Bone marrow (<i>os femoris/sternum</i>)	Pituitary
Brain (<i>cerebrum, cerebellum, brain stem</i>)	Prostate
Epididymis (2)	Salivary glands (<i>mandibular, parotid, sublingual</i>)
Eye with optic nerve and harderian gland (2)	Seminal vesicle
Gall bladder	Skin (<i>left flank</i>)
Gross lesions observed	Spinal cord (<i>3 sections</i>)
Heart (<i>left and right ventricle, septum</i>)	Spleen
Injection site(s)	Stomach
Intestine, large (<i>caecum, colon, rectum</i>)	Testicle (2)
Intestine, small (<i>duodenum, jejunum, ileum, Swiss roll method</i>)	Thymus
Kidney and ureter (2)	Thyroid (2) (<i>incl. parathyroids</i>)
Liver (<i>2 lobes</i>)	Tissue masses or tumours (<i>including regional lymph nodes</i>)
Lungs (<i>with mainstem bronchi and bronchioles</i>)	Tongue (<i>incl. base</i>)
Lymph node (<i>1, cervical</i>)	Trachea (<i>incl. larynx</i>)
Lymph node (<i>1, mesenteric</i>)	Urinary bladder
Mammary gland (<i>inguinal</i>)	Uterus (<i>incl. cervix and oviducts</i>)
Muscle (<i>skeletal, leg</i>)	Vagina
Nerve (<i>sciatic</i>)	

The afore-listed organs of all animals of groups 1 and 4 were examined histopathologically after preparation of hematoxylin-eosin stained paraffin sections.

In addition, frozen sections of the heart, liver and one kidney were made, stained with Oil Red O, and examined histopathologically.

3.2 Macroscopic post-mortem examination

For all animals, a complete macroscopic post-mortem examination, weighing of organs and statistical analysis of organ weights were performed by LPT.

Full details of the test protocol are available in LPT Study Plan 34946 and Study Plan Amendment(s). In-life and laboratory results are available in LPT Report 34946.



Test Site Reference no. 457 / LPT Study no. 34946

3.3 Histotechnology

During dissection fresh bone marrow was obtained from the os femoris (3 air-dried smears/animal) of 5 main study animals/sex/group and all recovery animals and stained according to PAPPENHEIM.

3.4 Histopathology

The pathologist followed methods for evaluation and reporting according to the test site Standard Operating Procedures. The computerized system used for pathology is Provantis 9.3.1.0. The nomenclature used is an in-house nomenclature with consideration and/or reference to INHAND/WHO/IARC/STP/RITA nomenclatures for non-proliferative and proliferative lesions.

4. LOCATION OF STUDY RECORDS

The following data and materials will be sent to LPT to archive: one signed final pathology report, all slides, dispatch list(s) and a copy of the electronic records made by the pathologist as captured by the appropriate software after completion of the histopathology phase of the study.

All raw data and relevant documentation and one signed final pathology report will be maintained in the document retrieval system at the test site and according to the test site Standard Operating Procedures archived under Test Site Reference no. 457 by Global Pathology Support. Duration of archiving at the test site (Global Pathology Support archive, room 4) will be for 3 years. Thereafter, the data will be transferred to LPT.

5. DEVIATIONS FROM PROTOCOL

There were no deviations from protocol during the study for histopathology.



Test Site Reference no. 457 / LPT Study no. 34946

6. RESULTS

6.1 Mortality

All rats survived until the scheduled necropsy.

6.2 Macroscopic observations

Macroscopic post-mortem examination did not reveal differences between the control and treated groups that could be attributed to the test item.

6.3 Microscopic observations

Histopathological assessment of organs of mice did not reveal significant changes of animals of group 4 when compared to the controls.

All microscopic observations were considered either coincidental or to be within the normal background alterations which may be seen in untreated mice of this age and strain.

7. DISCUSSION & CONCLUSIONS ABOUT AUTOPSY & HISTOPATHOLOGY FINDINGS

All animals survived until scheduled necropsy and occasional macroscopic findings did not reveal any test item-related changes.

After histopathological assessment of all group 1 and 4 animals in both sexes, no significant and toxicologically relevant test item-related effects could be observed.

Both macroscopic and/or microscopic changes observed were all considered to be normal background alterations which may be seen in untreated mice of this age and strain.



8. GROSS PATHOLOGY (MAIN GROUPS 1 TO 4)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 GROSS PATHOLOGY SUMMARY - MAIN GROUPS
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Group:	Male				Female			
		Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
	Number of Animals:	10	10	10	10	10	10	10	10
	Number of Completed Animals:	10	10	10	10	10	10	10	10
adrenal gland (2)									
	Submitted	10	10	10	10	10	10	10	10
	No abnormalities detected	10	10	10	10	10	10	10	10
aorta abdominalis									
	Submitted	10	10	10	10	10	10	10	10
	No abnormalities detected	10	10	10	10	10	10	10	10
bone (os femoris with joint)									
	Submitted	10	10	10	10	10	10	10	10
	No abnormalities detected	10	10	10	10	10	10	10	10
bone marrow (os femoris/sternum)									
	Submitted	10	10	10	10	10	10	10	10
	No abnormalities detected	10	10	10	10	10	10	10	10
brain (cerebrum, cerebellum, brain stem)									
	Submitted	10	10	10	10	10	10	10	10
	No abnormalities detected	10	9	10	10	10	10	10	10
	soft consistency	0	1	0	0	0	0	0	0
caecum									
	Submitted	10	10	10	10	10	10	10	10
	No abnormalities detected	10	10	10	10	10	10	10	10
colon									
	Submitted	10	10	10	10	10	10	10	10
	No abnormalities detected	10	10	10	10	10	10	10	10
duodenum									
	Submitted	10	10	10	10	10	10	10	10
	No abnormalities detected	10	10	10	10	10	10	10	10
epididymis (2)									
	Submitted	10	10	10	10	.	.	.	.
	No abnormalities detected	10	10	10	10	.	.	.	.
eye with optic nerve and hardierian gland (2)									
	Submitted	10	10	10	10	10	10	10	10
	No abnormalities detected	10	10	10	10	10	10	10	10
gall bladder									
	Submitted	10	10	10	10	10	10	10	10



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 GROSS PATHOLOGY SUMMARY - MAIN GROUPS
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male				Female			
	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
Group:								
Number of Animals:	10	10	10	10	10	10	10	10
Number of Completed Animals:	10	10	10	10	10	10	10	10
gall bladder (Continued...)								
No abnormalities detected	10	10	10	10	10	10	10	10
heart (left and right ventricle, septum)								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
ileum								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
injection site(s)								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
jejunum								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
kidney (2)								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
liver (2 lobes)								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
lungs (with mainstem bronchi and bronchioles)								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
lymph node (1, cervical)								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
lymph node (1, mesenteric)								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
mammary gland (inguinal)								
Submitted	.	.	.	.	10	10	10	10
No abnormalities detected	.	.	.	.	10	10	10	10



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 GROSS PATHOLOGY SUMMARY - MAIN GROUPS
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male				Female			
Group:	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
Number of Animals:	10	10	10	10	10	10	10	10
Number of Completed Animals:	10	10	10	10	10	10	10	10
muscle (skeletal, leg)								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
nerve (sciatic)								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
oesophagus								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
ovary (2)								
Submitted	.	.	.	.	10	10	10	10
No abnormalities detected	.	.	.	.	10	10	10	10
pancreas								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
pituitary								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
prostate								
Submitted	10	10	10	10	.	.	.	.
No abnormalities detected	10	10	10	10	.	.	.	.
rectum								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
salivary glands (mandibular, parotid, sublingual)								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
seminal vesicle								
Submitted	10	10	10	10	.	.	.	.
No abnormalities detected	10	10	10	10	.	.	.	.
skin (left flank)								
Submitted	10	10	10	10	10	10	10	10



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 GROSS PATHOLOGY SUMMARY - MAIN GROUPS
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male				Female			
	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
Group:								
Number of Animals:	10	10	10	10	10	10	10	10
Number of Completed Animals:	10	10	10	10	10	10	10	10
skin (left flank) (Continued...)								
No abnormalities detected	10	10	10	10	10	10	10	10
spinal cord (3 sections)								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
spleen								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
stomach								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
testicle (2)								
Submitted	10	10	10	10	.	.	.	.
No abnormalities detected	10	10	10	10	.	.	.	.
thymus								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
thyroid (2) (incl. parathyroids)								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
tissue masses or tumours (including regional lymph nodes)								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
tongue (incl. base)								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
trachea (incl. larynx)								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10
ureter (2)								
Submitted	10	10	10	10	10	10	10	10
No abnormalities detected	10	10	10	10	10	10	10	10



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 GROSS PATHOLOGY SUMMARY - MAIN GROUPS
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Group:	Male				Female			
		Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
Number of Animals:		10	10	10	10	10	10	10	10
Number of Completed Animals:		10	10	10	10	10	10	10	10
urinary bladder									
Submitted		10	10	10	10	10	10	10	10
No abnormalities detected		10	10	10	10	10	10	10	10
uterus (incl. cervix and oviducts)									
Submitted		.	.	.	.	10	10	10	10
No abnormalities detected		.	.	.	.	10	10	10	10
vagina									
Submitted		.	.	.	.	10	10	10	10
No abnormalities detected		.	.	.	.	10	10	10	10



9. GROSS PATHOLOGY (RECOVERY GROUPS)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 GROSS PATHOLOGY SUMMARY - RECOVERY GROUPS
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Group:				
Number of Animals:	5	5	5	5
Number of Completed Animals:	5	5	5	5
adrenal gland (2)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
aorta abdominalis				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
bone (os femoris with joint)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
bone marrow (os femoris/sternum)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
brain (cerebrum, cerebellum, brain stem)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
caecum				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
colon				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
duodenum				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
epididymis (2)				
Submitted	5	5	.	.
No abnormalities detected	5	5	.	.
eye with optic nerve and harderian gland (2)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
gall bladder				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 GROSS PATHOLOGY SUMMARY - RECOVERY GROUPS
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Group:				
Number of Animals:	5	5	5	5
Number of Completed Animals:	5	5	5	5
heart (left and right ventricle, septum)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
ileum				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
injection site(s)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
jejunum				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
kidney (2)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
liver (2 lobes)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
lungs (with mainstem bronchi and bronchioles)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
lymph node (1, cervical)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
lymph node (1, mesenteric)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
mammary gland (inguinal)				
Submitted	.	.	5	5
No abnormalities detected	.	.	5	5
muscle (skeletal, leg)				
Submitted	5	5	5	5



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 GROSS PATHOLOGY SUMMARY - RECOVERY GROUPS
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
Group:	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Number of Animals:	5	5	5	5
Number of Completed Animals:	5	5	5	5
muscle (skeletal, leg) (Continued...)				
No abnormalities detected	5	5	5	5
nerve (sciatic)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
oesophagus				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
ovary (2)				
Submitted	.	.	5	5
No abnormalities detected	.	.	5	5
pancreas				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
pituitary				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
prostate				
Submitted	5	5	.	.
No abnormalities detected	5	5	.	.
rectum				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
salivary glands (mandibular, parotid, sublingual)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
seminal vesicle				
Submitted	5	5	.	.
No abnormalities detected	5	5	.	.
skin (left flank)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 GROSS PATHOLOGY SUMMARY - RECOVERY GROUPS
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Group:				
Number of Animals:	5	5	5	5
Number of Completed Animals:	5	5	5	5
spinal cord (3 sections)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
spleen				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
stomach				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
testicle (2)				
Submitted	5	5	.	.
No abnormalities detected	5	5	.	.
thymus				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
thyroid (2) (incl. parathyroids)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
tissue masses or tumours (including regional lymph nodes)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
tongue (incl. base)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
trachea (incl. larynx)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
ureter (2)				
Submitted	5	5	5	5
No abnormalities detected	5	5	5	5
urinary bladder				
Submitted	5	5	5	5



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Intergroup Comparison of Pathology Observations
GROSS PATHOLOGY SUMMARY - RECOVERY GROUPS
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Group:				
Number of Animals:	5	5	5	5
Number of Completed Animals:	5	5	5	5
urinary bladder (Continued...)				
No abnormalities detected	5	5	5	5
uterus (incl. cervix and oviducts)				
Submitted	.	.	5	5
No abnormalities detected	.	.	5	5
vagina				
Submitted	.	.	5	5
No abnormalities detected	.	.	5	5



10. HISTOPATHOLOGY (GROUPS 1 AND 4)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 HISTOPATHOLOGY SUMMARY - MAIN GROUPS 1 & 4
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
	Gr. 1	Gr. 4	Gr. 1	Gr. 4
Group:				
Number of Animals:	10	10	10	10
Number of Completed Animals:	10	10	10	10
adrenal gland (2)				
Examined	10	10	10	10
No abnormalities detected	9	9	9	6
accessory (adrenal) cortical nodule(s); unilateral	1	1	0	1
.... one	1	1	0	1
cortex(zona glomerulosa); subcapsular cell hyperplasia; unilateral	1	0	0	3
.... marginal	1	0	0	3
cortex(zona glomerulosa); subcapsular cell hyperplasia; bilateral	0	0	1	0
.... marginal	0	0	1	0
aorta abdominalis				
Examined	10	10	10	10
No abnormalities detected	9	9	10	9
absent	1	1	0	1
bone (os femoris with joint)				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
bone marrow (os femoris/sternum)				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
brain (cerebrum, cerebellum, brain stem)				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
caecum				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
colon				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
duodenum				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10

General Footnote: [Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance]



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 HISTOPATHOLOGY SUMMARY - MAIN GROUPS 1 & 4
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
	Gr. 1	Gr. 4	Gr. 1	Gr. 4
Group:				
Number of Animals:	10	10	10	10
Number of Completed Animals:	10	10	10	10
epididymis (2)				
Examined	10	10	.	.
No abnormalities detected	8	9	.	.
mononuclear inflammatory cell infiltrate; right	1	0	.	.
.... slight	1	0	.	.
pigment deposition; right, focal	1	0	.	.
.... slight	1	0	.	.
sperm granuloma(s); left	1	1	.	.
.... one	1	1	.	.
eye with optic nerve and harderian gland (2)				
Examined	10	10	10	10
No abnormalities detected	5	1	10	10
harderian glands; pigment deposition; unilateral	1	0	0	0
.... slight	1	0	0	0
harderian glands; inflammation; acute, unilateral	5	9	0	0
.... slight	0	4	0	0
.... moderate	2	4	0	0
.... marked	3	1	0	0
gall bladder				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
heart (left and right ventricle, septum)				
Examined	10	10	10	10
No abnormalities detected	10	9	10	10
right atrium; inflammation; acute, area	0	1	0	0
.... marked	0	1	0	0
ileum				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
injection site(s)				
Examined	10	10	10	10
No abnormalities detected	0	0	2	0

General Footnote: [Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance]



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 HISTOPATHOLOGY SUMMARY - MAIN GROUPS 1 & 4
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
	Gr. 1	Gr. 4	Gr. 1	Gr. 4
Group:				
Number of Animals:	10	10	10	10
Number of Completed Animals:	10	10	10	10
injection site(s) (Continued...)				
subcutis; acute inflammatory cell infiltrate	10	10	8	10
.... marginal	7	3	5	2
.... slight	3	5	3	6
.... moderate	0	2	0	2
subcutis; granulation tissue	0	2	1	1
.... marginal	0	2	1	1
subcutis; haemorrhage	5	6	4	4
.... marginal	5	4	4	3
.... slight	0	2	0	1
subcutis; necrosis	7	9	5	7
.... marginal	7	7	4	5
.... slight	0	2	1	1
.... moderate	0	0	0	1
subcutis; pigment deposition	2	5	0	0
.... marginal	2	4	0	0
.... slight	0	1	0	0
subcutis; thromb(i)us	0	1	0	0
.... one	0	1	0	0
jejunum				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
kidney (2)				
Examined	10	10	10	10
No abnormalities detected	1	1	6	9
oil red o staining	9	9	4	1
.... marginal	3	3	4	1
.... slight	6	5	0	0
.... moderate	0	1	0	0
liver (2 lobes)				
Examined	10	10	10	10
No abnormalities detected	1	0	0	1

General Footnote: [Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance]



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 HISTOPATHOLOGY SUMMARY - MAIN GROUPS 1 & 4
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
	Gr. 1	Gr. 4	Gr. 1	Gr. 4
Group:				
Number of Animals:	10	10	10	10
Number of Completed Animals:	10	10	10	10
liver (2 lobes) (Continued...)				
fatty change; diffuse	0	1	0	1
.... marginal	0	1	0	1
mixed inflammatory cell infiltrate	0	0	0	1
.... marginal	0	0	0	1
oil red o staining	9	10	10	9
.... marginal	4	4	4	4
.... slight	4	4	6	5
.... moderate	1	2	0	0
lungs (with mainstem bronchi and bronchioles)				
Examined	10	10	10	10
No abnormalities detected	9	6	10	9
perivascular; acute inflammatory cell infiltrate; multifocal	0	1	0	0
.... moderate	0	1	0	0
congestion	1	2	0	0
.... marginal	0	1	0	0
.... slight	0	1	0	0
.... moderate	1	0	0	0
haemorrhage(s)	0	0	0	1
.... one	0	0	0	1
inflammation; acute alveolar/interstitial	0	1	0	0
.... moderate	0	1	0	0
lymph node (1, cervical)				
Examined	10	10	10	10
No abnormalities detected	10	10	9	6
absent	0	0	0	4
sinuses; contain(s) blood	0	0	1	0
lymph node (1, mesenteric)				
Examined	10	10	10	10
No abnormalities detected	9	9	7	8

General Footnote: [Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance]



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 HISTOPATHOLOGY SUMMARY - MAIN GROUPS 1 & 4
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
	Gr. 1	Gr. 4	Gr. 1	Gr. 4
Group:				
Number of Animals:	10	10	10	10
Number of Completed Animals:	10	10	10	10
lymph node (1, mesenteric) (Continued...)				
sinus histiocytosis	1	1	3	2
.... marginal	0	0	0	1
.... slight	1	1	3	1
mammary gland (inguinal)				
Examined	.	.	10	10
No abnormalities detected	.	.	6	3
absent	.	.	4	7
muscle (skeletal, leg)				
Examined	10	10	10	10
No abnormalities detected	9	9	10	10
absent	0	1	0	0
mononuclear inflammatory cell infiltrate; focal	1	0	0	0
.... slight	1	0	0	0
nerve (sciatic)				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
oesophagus				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
ovary (2)				
Examined	.	.	10	10
No abnormalities detected	.	.	10	10
oviducts				
Examined	.	.	10	10
No abnormalities detected	.	.	10	10
pancreas				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
pituitary				
Examined	10	10	10	10
No abnormalities detected	10	10	10	9

General Footnote: [Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance]



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 HISTOPATHOLOGY SUMMARY - MAIN GROUPS 1 & 4
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
	Gr. 1	Gr. 4	Gr. 1	Gr. 4
Group:				
Number of Animals:	10	10	10	10
Number of Completed Animals:	10	10	10	10
pituitary (Continued...)				
absent	0	0	0	1
prostate				
Examined	10	10	.	.
No abnormalities detected	9	10	.	.
mononuclear inflammatory cell infiltrate	1	0	.	.
.... slight	1	0	.	.
rectum				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
salivary glands (mandibular, parotid, sublingual)				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
seminal vesicle				
Examined	10	10	.	.
No abnormalities detected	10	10	.	.
skin (left flank)				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
spinal cord (3 sections)				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
spleen				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
stomach				
Examined	10	10	10	10
No abnormalities detected	9	10	10	10
forestomach; mucosa/submucosa; acute inflammatory cell infiltrate	1	0	0	0
.... slight	1	0	0	0
forestomach; ulceration; focal	1	0	0	0

General Footnote: [Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance]



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 HISTOPATHOLOGY SUMMARY - MAIN GROUPS 1 & 4
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
	Gr. 1	Gr. 4	Gr. 1	Gr. 4
Group:				
Number of Animals:	10	10	10	10
Number of Completed Animals:	10	10	10	10
stomach (Continued...)				
.... marginal	1	0	0	0
testicle (2)				
Examined	10	10	.	.
No abnormalities detected	10	10	.	.
thymus				
Examined	10	10	10	10
No abnormalities detected	0	1	0	1
absent	1	0	1	0
atrophy	9	9	9	9
.... slight	1	0	0	1
.... moderate	8	9	5	7
.... marked	0	0	4	1
cyst(s)	1	0	0	1
.... three	1	0	0	0
.... a few	0	0	0	1
thyroid (2) (incl. parathyroids)				
Examined	10	10	10	10
No abnormalities detected	10	9	9	6
absent	0	1	0	0
associated ectopic thymus	0	0	1	4
tissue masses or tumours (including regional lymph nodes)				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
tongue (incl. base)				
Examined	10	10	10	10
No abnormalities detected	10	9	10	10
absent	0	1	0	0
trachea (incl. larynx)				
Examined	10	10	10	10
No abnormalities detected	10	9	10	10

General Footnote: [Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance]



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 HISTOPATHOLOGY SUMMARY - MAIN GROUPS 1 & 4
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
	Gr. 1	Gr. 4	Gr. 1	Gr. 4
Group:				
Number of Animals:	10	10	10	10
Number of Completed Animals:	10	10	10	10
trachea (incl. larynx) (Continued...)				
absent	0	1	0	0
ureter (2)				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
urinary bladder				
Examined	10	10	10	10
No abnormalities detected	10	10	10	10
uterus (incl. cervix and oviducts)				
Examined	.	.	10	10
No abnormalities detected	.	.	10	10
vagina				
Examined	.	.	10	10
diestrus	.	.	5	5
oestrus	.	.	5	5

General Footnote: [Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance]



11. HISTOPATHOLOGY (RECOVERY GROUPS)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 HISTOPATHOLOGY SUMMARY - RECOVERY GROUPS
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Group:				
Number of Animals:	5	5	5	5
Number of Completed Animals:	5	5	5	5
adrenal gland (2)				
Examined	5	5	5	5
No abnormalities detected	5	5	4	3
accessory (adrenal) cortical nodule(s); unilateral	0	0	1	1
.... one	0	0	1	1
cortex(zona glomerulosa); subcapsular cell hyperplasia; unilateral	0	0	1	1
.... marginal	0	0	0	1
.... slight	0	0	1	0
cortex(zona glomerulosa); subcapsular cell hyperplasia; bilateral	0	0	0	1
.... marginal	0	0	0	1
aorta abdominalis				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
bone (os femoris with joint)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
bone marrow (os femoris/sternum)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
brain (cerebrum, cerebellum, brain stem)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
caecum				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
colon				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
duodenum				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5

General Footnote: [Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance]



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 HISTOPATHOLOGY SUMMARY - RECOVERY GROUPS
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
Group:	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Number of Animals:	5	5	5	5
Number of Completed Animals:	5	5	5	5
epididymis (2)				
Examined	5	5	.	.
No abnormalities detected	5	5	.	.
eye with optic nerve and harderian gland (2)				
Examined	5	5	5	5
No abnormalities detected	3	3	5	5
harderian glands; inflammation; acute, unilateral	2	2	0	0
.... slight	0	1	0	0
.... moderate	1	1	0	0
.... marked	1	0	0	0
gall bladder				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
heart (left and right ventricle, septum)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
ileum				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
injection site(s)				
Examined	5	5	5	5
No abnormalities detected	5	4	4	5
subcutis; mixed inflammatory cell infiltrate	0	0	1	0
.... slight	0	0	1	0
subcutis; perivascular; mononuclear inflammatory cell infiltrate	0	1	0	0
.... slight	0	1	0	0
subcutis; necrosis	0	0	1	0
.... marginal	0	0	1	0
subcutis; thromb(i)us	0	1	1	0
.... one	0	1	1	0

General Footnote: [Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance]



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 HISTOPATHOLOGY SUMMARY - RECOVERY GROUPS
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
Group:	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Number of Animals:	5	5	5	5
Number of Completed Animals:	5	5	5	5
jejunum				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
kidney (2)				
Examined	5	5	5	5
No abnormalities detected	0	0	1	1
medulla; hyaline cast(s); unilateral	0	1	0	0
.... one	0	1	0	0
oil red o staining	5	5	4	4
.... marginal	3	0	3	3
.... slight	2	4	1	1
.... moderate	0	1	0	0
liver (2 lobes)				
Examined	5	5	5	5
fatty change; diffuse	0	0	4	2
.... marginal	0	0	4	2
oil red o staining	5	5	5	5
.... marginal	3	1	0	1
.... slight	2	3	5	3
.... moderate	0	1	0	1
lungs (with mainstem bronchi and bronchioles)				
Examined	5	5	5	5
No abnormalities detected	5	4	5	5
congestion	0	1	0	0
.... slight	0	1	0	0
lymph node (1, cervical)				
Examined	5	5	5	5
No abnormalities detected	4	5	3	3
absent	1	0	1	2
sinus histiocytosis	0	0	1	0
.... marginal	0	0	1	0

General Footnote: [Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance]



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 HISTOPATHOLOGY SUMMARY - RECOVERY GROUPS
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Group:				
Number of Animals:	5	5	5	5
Number of Completed Animals:	5	5	5	5
lymph node (1, mesenteric)				
Examined	5	5	5	5
No abnormalities detected	5	5	3	3
sinus histiocytosis	0	0	2	2
.... marginal	0	0	1	1
.... slight	0	0	1	1
mammary gland (inguinal)				
Examined	.	.	5	5
No abnormalities detected	.	.	3	5
absent	.	.	2	0
muscle (skeletal, leg)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
nerve (sciatic)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
oesophagus				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
ovary (2)				
Examined	.	.	5	5
No abnormalities detected	.	.	5	5
oviducts				
Examined	.	.	5	5
No abnormalities detected	.	.	5	5
pancreas				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
pituitary				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
prostate				
Examined	5	5	.	.

General Footnote: [Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance]



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 HISTOPATHOLOGY SUMMARY - RECOVERY GROUPS
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Group:				
Number of Animals:	5	5	5	5
Number of Completed Animals:	5	5	5	5
prostate (Continued...)				
No abnormalities detected	5	5	.	.
rectum				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
salivary glands (mandibular, parotid, sublingual)				
Examined	5	5	5	5
No abnormalities detected	5	5	4	5
absent	0	0	1	0
seminal vesicle				
Examined	5	5	.	.
No abnormalities detected	5	5	.	.
skin (left flank)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
spinal cord (3 sections)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
spleen				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
stomach				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
testicle (2)				
Examined	5	5	.	.
No abnormalities detected	5	5	.	.
thymus				
Examined	5	5	5	5
atrophy	5	5	5	5
.... moderate	5	5	1	1
.... marked	0	0	4	4

General Footnote: [Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance]



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Intergroup Comparison of Pathology Observations
 HISTOPATHOLOGY SUMMARY - RECOVERY GROUPS
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Removal Reason: ALL	Male		Female	
Group:	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Number of Animals:	5	5	5	5
Number of Completed Animals:	5	5	5	5
thyroid (2) (incl. parathyroids)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
tissue masses or tumours (including regional lymph nodes)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
tongue (incl. base)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
trachea (incl. larynx)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
ureter (2)				
Examined	5	5	5	5
No abnormalities detected	5	5	5	5
urinary bladder				
Examined	5	5	5	5
No abnormalities detected	5	5	5	4
absent	0	0	0	1
uterus (incl. cervix and oviducts)				
Examined	.	.	5	5
No abnormalities detected	.	.	5	5
vagina				
Examined	.	.	5	5
diestrus	.	.	2	1
metestrus	.	.	0	1
oestrus	.	.	3	3

General Footnote: [Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance]



12. INDIVIDUAL ANIMAL PATHOLOGY



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	1	Group:	Group 1	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

adrenal gland (2) : accessory (adrenal) cortical nodule(s); unilateral, one
 adrenal gland (2) : cortex(zona glomerulosa); subcapsular cell hyperplasia; unilateral, marginal
 injection site(s) : subcutis; acute inflammatory cell infiltrate; marginal
 injection site(s) : subcutis; necrosis; marginal
 injection site(s) : subcutis; pigment deposition; marginal : Green-brown pigment.
 kidney (2) : oil red o staining; marginal
 liver (2 lobes) : oil red o staining; slight
 muscle (skeletal, leg) : mononuclear inflammatory cell infiltrate; focal, slight
 thymus : atrophy; moderate
 thyroid (2) (incl. parathyroids) : Parathyroid(s) missing.

Histo Pathology - The following Tissues were Within Normal Limits:

aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	2	Group:	Group 1	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

eye with optic nerve and harderian gland (2) : harderian glands; pigment deposition; unilateral, slight : Green-brown pigment.

eye with optic nerve and harderian gland (2) : harderian glands; inflammation; acute, unilateral, moderate

injection site(s) : subcutis; acute inflammatory cell infiltrate; marginal

kidney (2) : oil red o staining; slight

liver (2 lobes) : oil red o staining; marginal

lungs (with mainstem bronchi and bronchioles) : congestion; moderate

thymus : absent

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	3	Group:	Group 1	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

adrenal gland (2) : One missing.
 injection site(s) : subcutis; acute inflammatory cell infiltrate; marginal
 injection site(s) : subcutis; haemorrhage; marginal
 injection site(s) : subcutis; necrosis; marginal
 kidney (2) : oil red o staining; slight
 liver (2 lobes) : oil red o staining; slight
 pituitary : Pars intermedia missing. Pars nervosa missing.
 thymus : atrophy; slight
 thymus : cyst(s); three
 thyroid (2) (incl. parathyroids) : Parathyroid(s) missing.

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); eye with optic nerve and hardierian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	4	Group:	Group 1	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

injection site(s) : subcutis; acute inflammatory cell infiltrate; marginal

injection site(s) : subcutis; haemorrhage; marginal

kidney (2) : oil red o staining; slight

liver (2 lobes) : oil red o staining; marginal

nerve (sciatic) : Tissue damaged/incomplete precludes further diagnosis.

thymus : atrophy; moderate

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); eye with optic nerve and hardierian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	5	Group:	Group 1	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

aorta abdominalis : absent

eye with optic nerve and harderian gland (2) : One optic nerve missing.

eye with optic nerve and harderian gland (2) : harderian glands; inflammation; acute, unilateral, marked
 injection site(s) : subcutis; acute inflammatory cell infiltrate; slight

kidney (2) : oil red o staining; marginal

liver (2 lobes) : oil red o staining; marginal

lymph node (1, mesenteric) : sinus histiocytosis; slight

salivary glands (mandibular, parotid, sublingual) : Sublingual gland missing.

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon;
 duodenum; epididymis (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph
 node (1, cervical); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid,
 sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or
 tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	6	Group:	Group 1	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

eye with optic nerve and harderian gland (2) : harderian glands; inflammation; acute, unilateral, marked

injection site(s) : subcutis; acute inflammatory cell infiltrate; marginal

injection site(s) : subcutis; necrosis; marginal

thymus : atrophy; moderate

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; kidney (2); liver (2 lobes); lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	7	Group:	Group 1	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

epididymis (2) : mononuclear inflammatory cell infiltrate; right, slight
 epididymis (2) : sperm granuloma(s); left, one
 eye with optic nerve and hardierian gland (2) : hardierian glands; inflammation; acute, unilateral, moderate
 injection site(s) : subcutis; acute inflammatory cell infiltrate; marginal
 injection site(s) : subcutis; haemorrhage; marginal
 injection site(s) : subcutis; necrosis; marginal
 kidney (2) : oil red o staining; marginal
 liver (2 lobes) : oil red o staining; marginal
 stomach : forestomach; mucosa/submucosa; acute inflammatory cell infiltrate; slight
 stomach : forestomach; ulceration; focal, marginal
 thymus : atrophy; moderate
 ureter (2) : One missing.

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	8	Group:	Group 1	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

eye with optic nerve and harderian gland (2) : One optic nerve missing.
 eye with optic nerve and harderian gland (2) : harderian glands; inflammation; acute, unilateral, marked
 injection site(s) : subcutis; acute inflammatory cell infiltrate; marginal
 injection site(s) : subcutis; haemorrhage; marginal
 injection site(s) : subcutis; necrosis; marginal
 kidney (2) : oil red o staining; slight
 liver (2 lobes) : oil red o staining; slight
 thymus : atrophy; moderate
 thyroid (2) (incl. parathyroids) : Parathyroid(s) missing.

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	9	Group:	Group 1	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

eye with optic nerve and harderian gland (2) : One optic nerve missing.

injection site(s) : subcutis; acute inflammatory cell infiltrate; slight

injection site(s) : subcutis; necrosis; marginal

kidney (2) : oil red o staining; slight

liver (2 lobes) : oil red o staining; slight

prostate : mononuclear inflammatory cell infiltrate; slight

thymus : atrophy; moderate

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	10	Group:	Group 1	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

epididymis (2) : pigment deposition; right, focal, slight : Green-brown.

injection site(s) : subcutis; acute inflammatory cell infiltrate; slight

injection site(s) : subcutis; haemorrhage; marginal

injection site(s) : subcutis; necrosis; marginal

injection site(s) : subcutis; pigment deposition; marginal

kidney (2) : oil red o staining; slight

liver (2 lobes) : oil red o staining; moderate

thymus : Parathyroid(s); one missing.

thymus : atrophy; moderate

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and hardierian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	16	Group:	Group 1	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

injection site(s) : subcutis; acute inflammatory cell infiltrate; marginal

injection site(s) : subcutis; necrosis; marginal

liver (2 lobes) : oil red o staining; marginal

mammary gland (inguinal) : absent

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.

vagina : diestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; kidney (2); lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	17	Group:	Group 1	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

injection site(s) : subcutis; acute inflammatory cell infiltrate; slight

injection site(s) : subcutis; granulation tissue; marginal

injection site(s) : subcutis; haemorrhage; marginal

injection site(s) : subcutis; necrosis; slight

liver (2 lobes) : oil red o staining; slight

mammary gland (inguinal) : absent

ovary (2) : One missing.

thymus : atrophy; marked

thyroid (2) (incl. parathyroids) : Parathyroid(s) missing.

vagina : oestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; kidney (2); lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal: 18	Group: Group 1	Sex: Female
Species: Mouse	Strain: C57BL/6	
Study Type: 4-Week Mouse Toxicity Study	Route: Intravenous	
	Dose: 0 Units/kg	
Death Date: 01/08/2017	Removal Reason: Terminal Sacrifice	
Necropsy Date: 01/08/2017	Study Day (Week) of Death: 30 (5)	
		Gross Status: Complete
		Histo Status: Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

injection site(s) : subcutis; acute inflammatory cell infiltrate; marginal

kidney (2) : oil red o staining; marginal

liver (2 lobes) : oil red o staining; slight

pituitary : Pars intermedia missing. Pars nervosa missing.

thymus : atrophy; moderate

vagina : diestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and hardenian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); mammary gland (inguinal); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	19	Group:	Group 1	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

injection site(s) : subcutis; acute inflammatory cell infiltrate; marginal

injection site(s) : subcutis; haemorrhage; marginal

injection site(s) : subcutis; necrosis; marginal

kidney (2) : oil red o staining; marginal

liver (2 lobes) : oil red o staining; slight

lymph node (1, mesenteric) : sinus histiocytosis; slight

thymus : absent

thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.

thyroid (2) (incl. parathyroids) : associated ectopic thymus

vagina : oestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); mammary gland (inguinal); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	20	Group:	Group 1	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

liver (2 lobes) : oil red o staining; marginal
mammary gland (inguinal) : absent
thymus : atrophy; moderate
thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.
vagina : oestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and hardierian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; kidney (2); lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal: 21	Group: Group 1	Sex: Female
Species: Mouse	Strain: C57BL/6	
Study Type: 4-Week Mouse Toxicity Study	Route: Intravenous	
	Dose: 0 Units/kg	
Death Date: 01/08/2017	Removal Reason: Terminal Sacrifice	
Necropsy Date: 01/08/2017	Study Day (Week) of Death: 30 (5)	
	Gross Status: Complete	
	Histo Status: Complete	

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

kidney (2) : oil red o staining; marginal

liver (2 lobes) : oil red o staining; marginal

pituitary : Pars intermedia missing. Pars nervosa missing.

thymus : atrophy; marked

vagina : oestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and hardierian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); mammary gland (inguinal); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	22	Group:	Group 1	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

injection site(s) : subcutis; acute inflammatory cell infiltrate; marginal

injection site(s) : subcutis; haemorrhage; marginal

liver (2 lobes) : oil red o staining; slight

mammary gland (inguinal) : absent

pituitary : Pars nervosa missing.

thymus : atrophy; marked

vagina : diestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; kidney (2); lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	23	Group:	Group 1	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

eye with optic nerve and hardenian gland (2) : One eye damaged/incomplete precludes further diagnosis.

injection site(s) : subcutis; acute inflammatory cell infiltrate; slight

injection site(s) : subcutis; necrosis; marginal

kidney (2) : oil red o staining; marginal

liver (2 lobes) : oil red o staining; slight

lymph node (1, mesenteric) : sinus histiocytosis; slight

pituitary : Pars nervosa missing.

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s) missing.

vagina : diestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and hardenian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); mammary gland (inguinal); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	24	Group:	Group 1	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

injection site(s) : subcutis; acute inflammatory cell infiltrate; slight

injection site(s) : subcutis; haemorrhage; marginal

injection site(s) : subcutis; necrosis; marginal

liver (2 lobes) : oil red o staining; slight

pituitary : Pars nervosa missing.

salivary glands (mandibular, parotid, sublingual) : Parotid gland missing.

thymus : atrophy; marked

thyroid (2) (incl. parathyroids) : Parathyroid(s) missing.

vagina : oestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and hardierian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; kidney (2); lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); mammary gland (inguinal); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	25	Group:	Group 1	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

adrenal gland (2) : cortex(zona glomerulosa); subcapsular cell hyperplasia; bilateral, marginal

eye with optic nerve and hardierian gland (2) : One optic nerve missing.

injection site(s) : subcutis; acute inflammatory cell infiltrate; marginal

liver (2 lobes) : oil red o staining; marginal

lymph node (1, cervical) : sinuses; contain(s) blood

lymph node (1, mesenteric) : sinus histiocytosis; slight

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s) missing.

vagina : diestrus

Histo Pathology - The following Tissues were Within Normal Limits:

aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and hardierian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; kidney (2); lungs (with mainstem bronchi and bronchioles); mammary gland (inguinal); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	31	Group:	Group 2	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	32	Group:	Group 2	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	33	Group:	Group 2	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

brain (cerebrum, cerebellum, brain stem) : soft consistency

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	34	Group:	Group 2	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	35	Group:	Group 2	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	36	Group:	Group 2	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	37	Group:	Group 2	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	38	Group:	Group 2	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	39	Group:	Group 2	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	40	Group:	Group 2	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	41	Group:	Group 2	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	42	Group:	Group 2	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	43	Group:	Group 2	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	44	Group:	Group 2	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	45	Group:	Group 2	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	46	Group:	Group 2	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	47	Group:	Group 2	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	48	Group:	Group 2	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	49	Group:	Group 2	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	50	Group:	Group 2	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	50 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	51	Group:	Group 3	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	52	Group:	Group 3	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	53	Group:	Group 3	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	54	Group:	Group 3	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	55	Group:	Group 3	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	56	Group:	Group 3	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	57	Group:	Group 3	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	58	Group:	Group 3	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	59	Group:	Group 3	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	60	Group:	Group 3	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	61	Group:	Group 3	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	62	Group:	Group 3	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	63	Group:	Group 3	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	64	Group:	Group 3	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	65	Group:	Group 3	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	66	Group:	Group 3	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	67	Group:	Group 3	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	68	Group:	Group 3	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	69	Group:	Group 3	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	70	Group:	Group 3	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	250 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

No observations found

Histo Pathology - The following Tissues were Within Normal Limits:

None



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	71	Group:	Group 4	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

eye with optic nerve and hardierian gland (2) : hardierian glands; inflammation; acute, unilateral, moderate

injection site(s) : subcutis; acute inflammatory cell infiltrate; marginal

injection site(s) : subcutis; haemorrhage; marginal

injection site(s) : subcutis; necrosis; marginal

kidney (2) : oil red o staining; slight

liver (2 lobes) : oil red o staining; slight

pituitary : Pars nervosa missing.

salivary glands (mandibular, parotid, sublingual) : Sublingual gland missing.

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s) missing.

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	72	Group:	Group 4	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

caecum : Artifact.

colon : Artifact.

duodenum : Artifact.

eye with optic nerve and hardierian gland (2) : hardierian glands; inflammation; acute, unilateral, moderate

heart (left and right ventricle, septum) : right atrium; inflammation; acute, area, marked : Inflammation in atrial myocardium and extending into the epicardium of the right ventricle.

ileum : Artifact.

injection site(s) : subcutis; acute inflammatory cell infiltrate; marginal

injection site(s) : subcutis; haemorrhage; slight

injection site(s) : subcutis; necrosis; marginal

injection site(s) : subcutis; pigment deposition; marginal

jejunum : Artifact.

liver (2 lobes) : oil red o staining; marginal

lungs (with mainstem bronchi and bronchioles) : inflammation; acute alveolar/interstitial, moderate : Diffuse inflammation with interstitial oedema and congestion causing thickening of alveolar septa.

rectum : Artifact.

salivary glands (mandibular, parotid, sublingual) : Parotid gland missing.

stomach : Artifact.

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.

ureter (2) : Artifact.

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); gall bladder; ileum; jejunum; kidney (2); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	73	Group:	Group 4	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

eye with optic nerve and harderian gland (2) : harderian glands; inflammation; acute, unilateral, marked

injection site(s) : subcutis; acute inflammatory cell infiltrate; slight

injection site(s) : subcutis; haemorrhage; marginal

injection site(s) : subcutis; necrosis; marginal

injection site(s) : subcutis; pigment deposition; marginal

kidney (2) : oil red o staining; slight

liver (2 lobes) : oil red o staining; slight

lungs (with mainstem bronchi and bronchioles) : congestion; marginal

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	74	Group:	Group 4	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

adrenal gland (2) : accessory (adrenal) cortical nodule(s); unilateral, one
 eye with optic nerve and hardierian gland (2) : hardierian glands; inflammation; acute, unilateral, slight
 injection site(s) : subcutis; acute inflammatory cell infiltrate; slight
 injection site(s) : subcutis; granulation tissue; marginal
 injection site(s) : subcutis; necrosis; marginal
 kidney (2) : oil red o staining; marginal
 liver (2 lobes) : oil red o staining; marginal
 lungs (with mainstem bronchi and bronchioles) : congestion; slight
 thymus : atrophy; moderate
 thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.

Histo Pathology - The following Tissues were Within Normal Limits:

aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon;
 duodenum; epididymis (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lymph node (1, cervical); lymph node (1, mesenteric);
 muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal
 vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including
 regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	75	Group:	Group 4	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

adrenal gland (2) : One incomplete precludes further diagnosis.
 epididymis (2) : sperm granuloma(s); left, one
 eye with optic nerve and hardenian gland (2) : hardenian glands; inflammation; acute, unilateral, moderate
 injection site(s) : subcutis; acute inflammatory cell infiltrate; moderate
 injection site(s) : subcutis; haemorrhage; slight
 injection site(s) : subcutis; necrosis; slight
 injection site(s) : subcutis; pigment deposition; slight
 kidney (2) : oil red o staining; slight
 liver (2 lobes) : fatty change; diffuse, marginal : Microvesicular.
 liver (2 lobes) : oil red o staining; moderate
 muscle (skeletal, leg) : absent
 thymus : atrophy; moderate
 thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.
 tongue (incl. base) : absent

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	76	Group:	Group 4	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

gall bladder : Tissue incomplete; precludes further diagnosis.

injection site(s) : subcutis; acute inflammatory cell infiltrate; marginal

injection site(s) : subcutis; haemorrhage; marginal

kidney (2) : oil red o staining; marginal

liver (2 lobes) : oil red o staining; marginal

lymph node (1, mesenteric) : sinus histiocytosis; slight

salivary glands (mandibular, parotid, sublingual) : Parotid gland missing.

thyroid (2) (incl. parathyroids) : Parathyroid(s) missing.

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thymus; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	77	Group:	Group 4	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

eye with optic nerve and hardierian gland (2) : hardierian glands; inflammation; acute, unilateral, slight

injection site(s) : subcutis; acute inflammatory cell infiltrate; slight

injection site(s) : subcutis; necrosis; marginal

kidney (2) : oil red o staining; moderate

liver (2 lobes) : oil red o staining; moderate

salivary glands (mandibular, parotid, sublingual) : Sublingual gland missing.

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	78	Group:	Group 4	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

adrenal gland (2) : One missing.

eye with optic nerve and hardierian gland (2) : hardierian glands; inflammation; acute, unilateral, moderate

injection site(s) : subcutis; acute inflammatory cell infiltrate; moderate

injection site(s) : subcutis; necrosis; marginal

injection site(s) : subcutis; pigment deposition; marginal

injection site(s) : subcutis; thromb(i)us; one

kidney (2) : oil red o staining; slight

liver (2 lobes) : oil red o staining; slight

lungs (with mainstem bronchi and bronchioles) : perivascular; acute inflammatory cell infiltrate; multifocal, moderate

pituitary : Pars nervosa missing.

salivary glands (mandibular, parotid, sublingual) : Sublingual and parotid gland missing.

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : absent

trachea (incl. larynx) : absent

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	79	Group:	Group 4	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

eye with optic nerve and harderian gland (2) : harderian glands; inflammation; acute, unilateral, slight

injection site(s) : subcutis; acute inflammatory cell infiltrate; slight

injection site(s) : subcutis; haemorrhage; marginal

injection site(s) : subcutis; necrosis; slight

kidney (2) : oil red o staining; slight

liver (2 lobes) : oil red o staining; slight

salivary glands (mandibular, parotid, sublingual) : Parotid gland missing.

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.

ureter (2) : One missing.

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	80	Group:	Group 4	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	25/07/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	25/07/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

aorta abdominalis : absent

eye with optic nerve and harderian gland (2) : harderian glands; inflammation; acute, unilateral, slight

injection site(s) : subcutis; acute inflammatory cell infiltrate; slight

injection site(s) : subcutis; granulation tissue; marginal

injection site(s) : subcutis; necrosis; marginal

injection site(s) : subcutis; pigment deposition; marginal

kidney (2) : oil red o staining; marginal

liver (2 lobes) : oil red o staining; marginal

salivary glands (mandibular, parotid, sublingual) : Sublingual gland missing.

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.

ureter (2) : One missing.

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	86	Group:	Group 4	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

adrenal gland (2) : accessory (adrenal) cortical nodule(s); unilateral, one

injection site(s) : subcutis; acute inflammatory cell infiltrate; slight

injection site(s) : subcutis; haemorrhage; marginal

injection site(s) : subcutis; necrosis; marginal

liver (2 lobes) : oil red o staining; slight

lungs (with mainstem bronchi and bronchioles) : haemorrhage(s); one

mammary gland (inguinal) : absent

ovary (2) : One missing.

pituitary : Pars nervosa missing.

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : associated ectopic thymus

vagina : oestrus

Histo Pathology - The following Tissues were Within Normal Limits:

aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and hardenian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; kidney (2); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	87	Group:	Group 4	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

injection site(s) : subcutis; acute inflammatory cell infiltrate; slight

injection site(s) : subcutis; granulation tissue; marginal

injection site(s) : subcutis; haemorrhage; marginal

injection site(s) : subcutis; necrosis; marginal

liver (2 lobes) : oil red o staining; slight

lymph node (1, cervical) : absent

mammary gland (inguinal) : absent

oviducts : One missing.

salivary glands (mandibular, parotid, sublingual) : Mandibular and parotid gland missing.

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s) missing.

vagina : oestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; kidney (2); lungs (with mainstem bronchi and bronchioles); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	88	Group:	Group 4	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

adrenal gland (2) : cortex(zona glomerulosa); subcapsular cell hyperplasia; unilateral, marginal

injection site(s) : subcutis; acute inflammatory cell infiltrate; moderate

injection site(s) : subcutis; haemorrhage; marginal

injection site(s) : subcutis; necrosis; slight

liver (2 lobes) : mixed inflammatory cell infiltrate; marginal

liver (2 lobes) : oil red o staining; marginal

mammary gland (inguinal) : absent

pituitary : Pars intermedia missing. Pars nervosa missing.

thymus : atrophy; slight

vagina : diestrus

Histo Pathology - The following Tissues were Within Normal Limits:

aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and hardierian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; kidney (2); lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	89	Group:	Group 4	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

aorta abdominalis : absent
 injection site(s) : subcutis; acute inflammatory cell infiltrate; marginal
 lymph node (1, cervical) : absent
 mammary gland (inguinal) : absent
 pituitary : Pars intermedia missing. Pars nervosa missing.
 salivary glands (mandibular, parotid, sublingual) : Mandibular gland missing.
 thymus : atrophy; moderate
 thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.
 vagina : oestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and hardierian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; kidney (2); liver (2 lobes); lungs (with mainstem bronchi and bronchioles); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	90	Group:	Group 4	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

gall bladder : Tissue incomplete; precludes further diagnosis.

injection site(s) : subcutis; acute inflammatory cell infiltrate; slight

injection site(s) : subcutis; necrosis; marginal

liver (2 lobes) : oil red o staining; marginal

lymph node (1, cervical) : absent

lymph node (1, mesenteric) : sinus histiocytosis; slight

mammary gland (inguinal) : absent

pituitary : absent

thyroid (2) (incl. parathyroids) : Parathyroid(s) missing.

vagina : oestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; kidney (2); lungs (with mainstem bronchi and bronchioles); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thymus; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	91	Group:	Group 4	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

injection site(s) : subcutis; acute inflammatory cell infiltrate; slight

injection site(s) : subcutis; necrosis; marginal

kidney (2) : oil red o staining; marginal

liver (2 lobes) : oil red o staining; slight

lymph node (1, cervical) : absent

oviducts : One missing.

thymus : atrophy; moderate

thymus : cyst(s); a few

thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.

thyroid (2) (incl. parathyroids) : associated ectopic thymus

vagina : diestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and hardenian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, mesenteric); mammary gland (inguinal); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	92	Group:	Group 4	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

adrenal gland (2) : cortex(zona glomerulosa); subcapsular cell hyperplasia; unilateral, marginal

injection site(s) : subcutis; acute inflammatory cell infiltrate; marginal

liver (2 lobes) : oil red o staining; marginal

lymph node (1, mesenteric) : sinus histiocytosis; marginal

mammary gland (inguinal) : absent

salivary glands (mandibular, parotid, sublingual) : Parotid gland missing.

thymus : atrophy; marked

vagina : diestrus

Histo Pathology - The following Tissues were Within Normal Limits:

aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and hardenian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; kidney (2); lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	93	Group:	Group 4	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

adrenal gland (2) : cortex(zona glomerulosa); subcapsular cell hyperplasia; unilateral, marginal

injection site(s) : subcutis; acute inflammatory cell infiltrate; slight

injection site(s) : subcutis; necrosis; marginal

liver (2 lobes) : fatty change; diffuse, marginal

liver (2 lobes) : oil red o staining; slight

pituitary : Pars nervosa missing.

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.

urinary bladder : Tissue damaged/incomplete precludes further diagnosis.

vagina : diestrus

Histo Pathology - The following Tissues were Within Normal Limits:

aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; kidney (2); lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); mammary gland (inguinal); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	94	Group:	Group 4	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

injection site(s) : subcutis; acute inflammatory cell infiltrate; moderate

injection site(s) : subcutis; haemorrhage; slight

injection site(s) : subcutis; necrosis; moderate

liver (2 lobes) : oil red o staining; slight

mammary gland (inguinal) : absent

oviducts : One missing.

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.

thyroid (2) (incl. parathyroids) : associated ectopic thymus

vagina : oestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; kidney (2); lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	95	Group:	Group 4	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	01/08/2017	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/08/2017	Study Day (Week) of Death:	30 (5)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

injection site(s) : subcutis; acute inflammatory cell infiltrate; slight

liver (2 lobes) : oil red o staining; marginal

oviducts : One missing.

pituitary : Pars nervosa missing.

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.

thyroid (2) (incl. parathyroids) : associated ectopic thymus

vagina : diestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; kidney (2); lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); mammary gland (inguinal); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	11	Group:	Gr. 1 Rec.	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	08/08/2017	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	08/08/2017	Study Day (Week) of Death:	44 (7)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

kidney (2) : oil red o staining; slight

liver (2 lobes) : oil red o staining; slight

thymus : atrophy; moderate

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	12	Group:	Gr. 1 Rec.	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	08/08/2017	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	08/08/2017	Study Day (Week) of Death:	44 (7)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

eye with optic nerve and harderian gland (2) : harderian glands; inflammation; acute, unilateral, marked

kidney (2) : oil red o staining; marginal

liver (2 lobes) : oil red o staining; marginal

salivary glands (mandibular, parotid, sublingual) : Parotid gland missing.

thymus : atrophy; moderate

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	13	Group:	Gr. 1 Rec.	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	08/08/2017	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	08/08/2017	Study Day (Week) of Death:	44 (7)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

eye with optic nerve and harderian gland (2) : harderian glands; inflammation; acute, unilateral, moderate

kidney (2) : oil red o staining; slight

liver (2 lobes) : oil red o staining; marginal

thymus : atrophy; moderate

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	14	Group:	Gr. 1 Rec.	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	08/08/2017	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	08/08/2017	Study Day (Week) of Death:	44 (7)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

kidney (2) : oil red o staining; marginal

liver (2 lobes) : oil red o staining; marginal

pituitary : Pars nervosa missing.

spinal cord (3 sections) : One section missing.

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); eye with optic nerve and hardierian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	15	Group:	Gr. 1 Rec.	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	08/08/2017	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	08/08/2017	Study Day (Week) of Death:	44 (7)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

kidney (2) : oil red o staining; marginal

liver (2 lobes) : oil red o staining; slight

lymph node (1, cervical) : absent

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s) missing.

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); eye with optic nerve and hardenian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	26	Group:	Gr. 1 Rec.	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	15/08/2017	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	15/08/2017	Study Day (Week) of Death:	44 (7)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

injection site(s) : subcutis; mixed inflammatory cell infiltrate; slight

injection site(s) : subcutis; necrosis; marginal

injection site(s) : subcutis; thromb(ol)us; one

kidney (2) : oil red o staining; marginal

liver (2 lobes) : fatty change; diffuse, marginal

liver (2 lobes) : oil red o staining; slight

lymph node (1, mesenteric) : sinus histiocytosis; marginal

mammary gland (inguinal) : absent

pituitary : Pars intermedia missing. Pars nervosa missing.

thymus : atrophy; marked

thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.

ureter (2) : One missing.

urinary bladder : Tissue incomplete; precludes further diagnosis.

vagina : diestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and hardenian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	27	Group:	Gr. 1 Rec.	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	15/08/2017	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	15/08/2017	Study Day (Week) of Death:	44 (7)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

liver (2 lobes) : oil red o staining; slight

lymph node (1, mesenteric) : sinus histiocytosis; slight

thymus : atrophy; marked

vagina : oestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; kidney (2); lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); mammary gland (inguinal); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	28	Group:	Gr. 1 Rec.	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	15/08/2017	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	15/08/2017	Study Day (Week) of Death:	44 (7)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

adrenal gland (2) : accessory (adrenal) cortical nodule(s); unilateral, one
 adrenal gland (2) : cortex(zona glomerulosa); subcapsular cell hyperplasia; unilateral, slight
 kidney (2) : oil red o staining; marginal
 liver (2 lobes) : fatty change; diffuse, marginal
 liver (2 lobes) : oil red o staining; slight
 lymph node (1, cervical) : absent
 pituitary : Pars intermedia missing. Pars nervosa missing.
 salivary glands (mandibular, parotid, sublingual) : absent
 spinal cord (3 sections) : One section missing.
 thymus : atrophy; moderate
 thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.
 vagina : oestrus

Histo Pathology - The following Tissues were Within Normal Limits:

aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon;
 duodenum; eye with optic nerve and hardenian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; lungs
 (with mainstem bronchi and bronchioles); lymph node (1, mesenteric); mammary gland (inguinal); muscle (skeletal, leg); nerve (sciatic); oesophagus;
 ovary (2); oviducts; pancreas; pituitary; rectum; skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue
 masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and
 oviducts)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal: 29	Group: Gr. 1 Rec.	Sex: Female
Species: Mouse	Strain: C57BL/6	
Study Type: 4-Week Mouse Toxicity Study	Route: Intravenous	
	Dose: 0 Units/kg	
Death Date: 15/08/2017	Removal Reason: Recovery Sacrifice	
Necropsy Date: 15/08/2017	Study Day (Week) of Death: 44 (7)	
	Gross Status: Complete	
	Histo Status: Complete	

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

kidney (2) : oil red o staining; marginal
 liver (2 lobes) : fatty change; diffuse, marginal
 liver (2 lobes) : oil red o staining; slight
 mammary gland (inguinal) : absent
 thymus : atrophy; marked
 vagina : oestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and hardierian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	30	Group:	Gr. 1 Rec.	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	0 Units/kg		
Death Date:	15/08/2017	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	15/08/2017	Study Day (Week) of Death:	44 (7)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

kidney (2) : oil red o staining; slight
liver (2 lobes) : fatty change; diffuse, marginal
liver (2 lobes) : oil red o staining; slight
lymph node (1, cervical) : sinus histiocytosis; marginal
pituitary : Pars nervosa missing.
thymus : atrophy; marked
ureter (2) : One missing.
vagina : diestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and hardierian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, mesenteric); mammary gland (inguinal); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	81	Group:	Gr. 4 Rec.	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	08/08/2017	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	08/08/2017	Study Day (Week) of Death:	44 (7)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

eye with optic nerve and harderian gland (2) : One eye damaged/incomplete precludes further diagnosis.

kidney (2) : oil red o staining; slight

liver (2 lobes) : oil red o staining; slight

salivary glands (mandibular, parotid, sublingual) : Sublingual gland missing.

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s) missing.

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	82	Group:	Gr. 4 Rec.	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	08/08/2017	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	08/08/2017	Study Day (Week) of Death:	44 (7)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

eye with optic nerve and harderian gland (2) : harderian glands; inflammation; acute, unilateral, slight

kidney (2) : oil red o staining; slight

liver (2 lobes) : oil red o staining; slight

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s) missing.

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	83	Group:	Gr. 4 Rec.	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	08/08/2017	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	08/08/2017	Study Day (Week) of Death:	44 (7)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

kidney (2) : medulla; hyaline cast(s); unilateral, one

kidney (2) : oil red o staining; moderate

liver (2 lobes) : oil red o staining; moderate

salivary glands (mandibular, parotid, sublingual) : Parotid gland missing.

thymus : atrophy; moderate

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal: 84	Group: Gr. 4 Rec.	Sex: Male
Species: Mouse	Strain: C57BL/6	
Study Type: 4-Week Mouse Toxicity Study	Route: Intravenous	
	Dose: 500 Units/kg	
Death Date: 08/08/2017	Removal Reason: Recovery Sacrifice	
Necropsy Date: 08/08/2017	Study Day (Week) of Death: 44 (7)	
	Gross Status: Complete	
	Histo Status: Complete	

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

kidney (2) : oil red o staining; slight

liver (2 lobes) : oil red o staining; slight

pituitary : Pars intermedia missing. Pars nervosa missing.

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s) missing.

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); eye with optic nerve and hardenian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	85	Group:	Gr. 4 Rec.	Sex:	Male
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	08/08/2017	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	08/08/2017	Study Day (Week) of Death:	44 (7)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

eye with optic nerve and harderian gland (2) : harderian glands; inflammation; acute, unilateral, moderate

injection site(s) : subcutis; perivascular; mononuclear inflammatory cell infiltrate; slight

injection site(s) : subcutis; thromb(i)us; one

kidney (2) : oil red o staining; slight

liver (2 lobes) : oil red o staining; marginal

lungs (with mainstem bronchi and bronchioles) : congestion; slight

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; epididymis (2); gall bladder; heart (left and right ventricle, septum); ileum; jejunum; lymph node (1, cervical); lymph node (1, mesenteric); muscle (skeletal, leg); nerve (sciatic); oesophagus; pancreas; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	96	Group:	Gr. 4 Rec.	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	15/08/2017	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	15/08/2017	Study Day (Week) of Death:	44 (7)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

adrenal gland (2) : accessory (adrenal) cortical nodule(s); unilateral, one
 adrenal gland (2) : cortex(zona glomerulosa); subcapsular cell hyperplasia; unilateral, marginal
 kidney (2) : oil red o staining; marginal
 liver (2 lobes) : fatty change; diffuse, marginal
 liver (2 lobes) : oil red o staining; moderate
 nerve (sciatic) : Tissue incomplete; precludes further diagnosis.
 salivary glands (mandibular, parotid, sublingual) : Sublingual gland missing.
 thymus : atrophy; marked
 vagina : diestrus

Histo Pathology - The following Tissues were Within Normal Limits:

aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon;
 duodenum; eye with optic nerve and hardenian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; lungs
 (with mainstem bronchi and bronchioles); lymph node (1, cervical); lymph node (1, mesenteric); mammary gland (inguinal); muscle (skeletal, leg);
 nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal
 cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base);
 trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	97	Group:	Gr. 4 Rec.	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	15/08/2017	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	15/08/2017	Study Day (Week) of Death:	44 (7)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

liver (2 lobes) : oil red o staining; marginal

lymph node (1, mesenteric) : sinus histiocytosis; slight

thymus : atrophy; marked

ureter (2) : Tissue damaged/incomplete precludes further diagnosis.

vagina : oestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; kidney (2); lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); mammary gland (inguinal); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	98	Group:	Gr. 4 Rec.	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	15/08/2017	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	15/08/2017	Study Day (Week) of Death:	44 (7)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

adrenal gland (2) : cortex(zona glomerulosa); subcapsular cell hyperplasia; bilateral, marginal

kidney (2) : oil red o staining; slight

liver (2 lobes) : fatty change; diffuse, marginal

liver (2 lobes) : oil red o staining; slight

lymph node (1, mesenteric) : sinus histiocytosis; marginal

salivary glands (mandibular, parotid, sublingual) : Sublingual gland missing.

thymus : atrophy; marked

thyroid (2) (incl. parathyroids) : Parathyroid(s) missing.

urinary bladder : Tissue damaged/incomplete precludes further diagnosis.

vagina : oestrus

Histo Pathology - The following Tissues were Within Normal Limits:

aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, cervical); mammary gland (inguinal); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	99	Group:	Gr. 4 Rec.	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	15/08/2017	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	15/08/2017	Study Day (Week) of Death:	44 (7)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

adrenal gland (2) : One missing.
 eye with optic nerve and harderian gland (2) : One optic nerve missing.
 kidney (2) : oil red o staining; marginal
 liver (2 lobes) : oil red o staining; slight
 lymph node (1, cervical) : absent
 pituitary : Pars intermedia missing. Pars nervosa missing.
 salivary glands (mandibular, parotid, sublingual) : Parotid and sublingual gland missing.
 thymus : atrophy; marked
 thyroid (2) (incl. parathyroids) : Parathyroid(s); one missing.
 urinary bladder : absent
 vagina : metestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, mesenteric); mammary gland (inguinal); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); uterus (incl. cervix and oviducts)



Provantis
 Test Site Reference number: 457 / Study no. 34946
 Pathology - Individual Animal Data
 INDIVIDUAL ANIMAL PATHOLOGY
 34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
 Administration Three Times Weekly to Mice - Multi-Site Study

Animal:	100	Group:	Gr. 4 Rec.	Sex:	Female
Species:	Mouse	Strain:	C57BL/6		
Study Type:	4-Week Mouse Toxicity Study	Route:	Intravenous		
		Dose:	500 Units/kg		
Death Date:	15/08/2017	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	15/08/2017	Study Day (Week) of Death:	44 (7)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histo Pathology Observations [Correlation]:

kidney (2) : oil red o staining; marginal

liver (2 lobes) : oil red o staining; slight

lymph node (1, cervical) : absent

lymph node (1, mesenteric) : Tissue incomplete; precludes further diagnosis.

salivary glands (mandibular, parotid, sublingual) : Parotid gland missing.

thymus : atrophy; moderate

vagina : oestrus

Histo Pathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris/sternum); brain (cerebrum, cerebellum, brain stem); caecum; colon; duodenum; eye with optic nerve and harderian gland (2); gall bladder; heart (left and right ventricle, septum); ileum; injection site(s); jejunum; lungs (with mainstem bronchi and bronchioles); lymph node (1, mesenteric); mammary gland (inguinal); muscle (skeletal, leg); nerve (sciatic); oesophagus; ovary (2); oviducts; pancreas; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; uterus (incl. cervix and oviducts)



Provantis
Test Site Reference number: 457 / Study no. 34946
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
34946 - 4-Week Toxicity Study of Allogenic APOSEC™ by Intravenous Slow Bolus
Administration Three Times Weekly to Mice - Multi-Site Study

Key Page

Codes

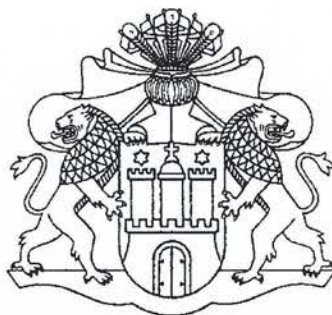
(TGL) = Trackable Gross Lesion, (MPF) = Major Pathological Finding, (?) = Questionable, (E) = Excluded,
(C) = Clinical Observation, (M) = Mass, (G) = Gross Pathology, (H) = Histo Pathology

Group Information

<u>Short Name</u>	<u>Long Name</u>
1	Group 1
2	Group 2
3	Group 3
4	Group 4
1R	Gr. 1 Rec.
4R	Gr. 4 Rec.

A P P E N D I X 4

GLP Certificate of the Test Facility LPT



FREIE UND HANSESTADT HAMBURG
Behörde für Gesundheit und Verbraucherschutz

Gute Laborpraxis / Good Laboratory Practice

GLP – Bescheinigung / Statement of GLP Compliance

(gemäß/according to § 19b (1) Chemikaliengesetz)

Eine GLP-Inspektion zur Überwachung der Einhaltung der GLP-Grundsätze gemäß Chemikaliengesetz bzw. Richtlinie 2004/9/ EG wurde durchgeführt in:

Assessment of conformity with GLP according to Chemikaliengesetz and Directive 2004/9/ EEC at:

☒ Prüfeinrichtung/ Test facility

☐ Prüfstandort/ Test site

LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG

Redderweg 8

21147 Hamburg

(Unverwechselbare Bezeichnung und Adresse/Unequivocal name and address)

Prüfungen nach Kategorien/ Areas of Expertise

(gemäß/according ChemVwV-GLP Nr. 5.3/OECD guidance)

Kategorie 2, 3, 4 und 9 (Sicherheitspharmakologie und Auftragsarchiv)

Datum der Inspektion (Abschluss)

Datum der Inspektion/ Date of Inspection:

07. Juli 2016

Die/Der genannte Prüfeinrichtung /Prüfstandort befindet sich im nationalen GLP-Überwachungsverfahren und wird regelmäßig auf Einhaltung der GLP-Grundsätze überwacht.

Auf der Grundlage des Inspektionsberichtes wird hiermit bestätigt, dass in dieser Prüfeinrichtung/ diesem Prüfstandort die oben genannten Prüfungen unter Einhaltung der GLP-Grundsätze durchgeführt werden können.

The above mentioned test facility/test site is included in the national GLP Compliance Programme and is inspected on a regular basis.

Based on the inspection report it can be confirmed, that this test facility/ test site is able to conduct the aforementioned studies in compliance with the Principles of GLP

Hamburg, den 8. Mai 2017




Dr. Volker Kregel
Direktor des Amtes für Arbeitsschutz

Behörde für Gesundheit und Verbraucherschutz
Marckmannstraße 129b, 20539 Hamburg

LPT Report No. 33201/1

**ACUTE TOXICITY STUDY OF
APOSEC™
BY SINGLE INTRAVENOUS ADMINISTRATION
TO CD RATS**

Sponsor:

APOSCIENCE AG
Mariannengasse 14/9
1090 Vienna
Austria

Study conducted by:

LPT Laboratory of Pharmacology
and Toxicology GmbH & Co. KG
Redderweg 8
21147 Hamburg
Germany

Monitor:

Dr. Silvio Wuschko

Contact person:

Dr. Jost Leuschner

June 09, 2016

This report consists of 37 pages.

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STATEMENT OF COMPLIANCE**ACUTE TOXICITY STUDY OF
APOSEC™
BY SINGLE INTRAVENOUS ADMINISTRATION
TO CD RATS**

The study was performed in compliance with:

- 'Good Laboratory Practice' Regulations of the EC enacted in Germany in the 'Chemikaliengesetz' [Chemicals Act], current edition;
- 'OECD Principles of Good Laboratory Practice' Document Nos. 1, 8 and 13 ENV/MC/CHEM (98) 17, ENV/JM/MONO (99) 24, ENV/JM/MONO (2002) 9, respectively.

These principles are compatible with 'Good Laboratory Practice' regulations specified by regulatory authorities throughout the European Community, the United States (EPA and FDA) and Japan (MHLW, MAFF and METI).

There were no deviations from the 'Good Laboratory Practice' regulations. Raw data obtained during the performance of the study are accurately reflected.



Dr. rer. nat. J. Haferkorn
Study Director

9 Jan 2016

Date

QUALITY ASSURANCE STATEMENT

Based on a quality assurance review, it was concluded that this report accurately reflects the raw data for the study. Methods, procedures and observations are correctly and completely described in the report.

**ACUTE TOXICITY STUDY OF
APOSEC™
BY SINGLE INTRAVENOUS ADMINISTRATION
TO CD RATS**

Study Plan dated March 01, 2016 and 1 Study Plan amendment.

Date of inspection	Criteria	Date of report to the Study Director and the Management
01 Mar 2016	Study Plan	01 Mar 2016
30 Mar 2016	Test item identity, preparation of test item, body weight, administration, animal behaviour, documentation	30 Mar 2016
09 Jun 2016	Final Report	09 Jun 2016

In addition to the detailed study-based inspections series of routine facility inspections were also conducted and reported to the Management.

Approved and submitted by:


Dr. med. vet. habil. K. R. Sultan
Director of Quality Assurance Unit (QAU)


Date

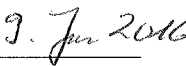
1. SUMMARY

Test system	Acute toxicity by single intravenous administration, in CD rats
Test item	APOSEC™
Vehicle	0.9% aqueous NaCl
Administration volume	2 mL/kg b.w.
Route of administration	Injection into the tail vein
Injection speed	Dose/approx. 2 - 3 minutes
Dose levels	Secretome supernatants from 50 Mio, 250 Mio or 500 Mio cells/kg b.w.
No-effect dose level	Secretome supernatant from 500 Mio cells/kg b.w.
Dose level with first intolerance reactions	> Secretome supernatant from 500 Mio cells/kg b.w.
Lowest lethal dose level	> Secretome supernatant from 500 Mio cells/kg b.w.
LD ₅₀	> Secretome supernatant from 500 Mio cells/kg b.w.
Macroscopic <i>post mortem</i> findings	None

Under the present test conditions, single intravenous administrations of different doses of secretome supernatants (50 Mio, 250 Mio or 500 Mio cells/kg b.w.) did not reveal any signs of toxicity in 5 male and 5 female animals per group, respectively. No animal died prematurely.

All animals gained the expected body weight throughout the whole study period. There were no macroscopic findings during necropsy.


Dr. rer. nat. J. Haferkorn
Study Director


Date

2. GENERAL INFORMATION

2.1 Aim of experiment To establish the toxicity of APOSEC™ following single intravenous administration to CD rats.

2.2 Sponsor / Test Facility / Responsible personnel

Sponsor	APOSCIENCE AG Mariannengasse 14/9 1090 Vienna Austria
Study Monitor	Dr. Silvio Wuschko Phone: + 43 664 885 893 54 E-mail: acc_safety.research@gmx.at
Test Facility	LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG Redderweg 8 21147 Hamburg Germany Phone: + 49 40 70 20 20 Fax: + 49 40 70 20 22 60 E-mail: LPT@LPT-Hamburg.de
Study Director/ Conduct of study	Dr. rer. nat. J. Haferkorn LPT , Redderweg 8 21147 Hamburg Germany
Deputy Study Director	Dr. phil. J. Leuschner
Test Facility Management	Dr. rer. nat. A. Winkler
Animal husbandry	Dipl. Ing. Biotech. F. Kunst
Statistics	Dipl. Biol. J. Köpcke
Veterinarian / Macropathology	Dr. med. vet. M. Wölm / Dipl. vet. med. A. Byk
Quality Assurance Unit (QAU)	Dr. med. vet. habil. K. R. Sultan
Code number of the study in the raw data	33201/1

2.3 Rules and regulations

The study was performed in compliance with:

- Note for Guidance for single dose toxicity (3BS1a) from August 1987, published April 2001 (Directive 75/318/EEC as amended),
- Directive 2003/63/EC amending Directive 2001/83/EC of the European Parliament and of the Council on the Community,
- Safety Guideline ICH M3 (Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, CPMP/ICH286/95 mod. released November 2000),
- FDA Guidance on single dose acute toxicity testing for pharmaceuticals (FDA Guidance, August 1996).

In addition, the 'Good Laboratory Practice' regulations were considered (see the [Statement of Compliance](#) and the enclosed [GLP Certificate of the Test Facility LPT](#)).

Standard Operating
Procedures (SOPs)

All work was carried out according to Standard Operating Procedures which were followed for all stages of the study; they may be inspected in those divisions which were engaged in the examination and in the Quality Assurance Unit (QAU).

Staff safety

The standard safety precautions operating within the department were applied to this study.

2.4 Archive

Archive of data
and specimens

During the study:

In the depot
LPT
Redderweg 8
21147 Hamburg
Germany

After reporting:

The final report will be archived by the Sponsor.

All specimens, written raw data and other documents generated at **LPT** during the course of this study, together with a copy of the final report are stored in the **LPT's** archives.

Duration of storage

According to the periods laid down in the German 'Chemikaliengesetz' [Chemicals Act] at least 15 years.

2.5 Study dates

Start of study

Date of Study Plan	March 01, 2016
Study Plan amendment	No. 1, dated March 29, 2016
Start of the experimental phase	March 04, 2016
Dosing	March 30, 2016

Termination of the study

Termination of the in-life phase	April 13, 2016
Date of the final report	June 09, 2016

2.6 Study Plan deviations

The study was conducted in accordance with the Study Plan and 1 Study Plan amendment agreed upon. There were no major deviations from this Study Plan and the Study Plan amendment. However, the following minor deviations were noted:

- Due to small amount of the test item supplied to **LPT** no retention sample was stored at **LPT**.
- Due to small amount of the test item, concentration 2 was produced by dilution of an aliquot of concentration 3 with 0.9% aqueous NaCl solution (1 + 1, v/v).

These minor deviations did not invalidate the scientific results obtained during this study.

3. TEST ITEM

3.1 Identification of the test item

After receipt at **LPT** the test item was inspected; batch number, amount and characteristics (colour, consistency and form) were determined and compared with information given by the Sponsor. An identification sheet was then filed with the raw data.

Test Item	Parameter	LPT Identification	Sponsor Identification
APOSEC™	colour consistency form	white solid lyophilisate	none solid lyophilisate

No further identification was carried out by **LPT**.

3.2 Description of the test item

Designation	APOSEC™
Batch no.	399033
Receipt no.	60135
Date of receipt	February 24, 2016
Storage conditions	-80°C
Characteristics	Lyophilisate
Stability	No information on stability available to LPT
Retention sample of the test item	Due to small amount of the test item supplied to LPT no retention sample was stored at LPT .

3.3 Preparation of the test item-vehicle mixture

The test item was reconstituted in 0.9% aqueous NaCl solution¹ prior to application.

Concentration 1 / Dose 1:

1 vial reconstitution in 20 mL (standard: after reconstitution secretome supernatant of apoptotic peripheral blood cells from 25 Mio cells/mL)
= secretoma supernatant from 50 Mio cells/kg b.w.

Concentration 2 / Dose 2:

Aliquot from concentration 3 diluted 1 + 1 (v/v) with 0.9% aqueous NaCl solution (concentrated 5x, equivalent to secretome supernatant of apoptotic peripheral blood cells from 125 Mio cells/mL)
= secretoma supernatant from 250 Mio cells/kg b.w.

Concentration 3 / Dose 3:

1 vial reconstitution in 2 mL (concentrated 10x, equivalent to secretome supernatant of apoptotic peripheral blood cells from 250 Mio cells/mL)
= secretoma supernatant from 500 Mio cells/kg b.w.

The reconstituted test item might be frozen at -80°C once for further use.

¹ Batch nos. 154258141 and 154858141; B. Braun Melsungen AG, 34212 Melsungen, Germany

4. METHODS

4.1 Animals / Animal maintenance

Species / Strain/ Stock	Rat (<i>Rattus norvegicus</i>) / CD / Crl: CD(SD)		
Supplier	Charles River Laboratories Research Models and Services Germany GmbH Sandhofer Weg 7 97633 Sulzfeld Germany		
Selection of species	International recommendations		
Number and sex of animals	40 animals (5 males and 5 females per group)		
Body weight (at start of treatment)	Males:	220 - 246 g	
	Females:	184 - 225 g	
Age (at start of treatment)	Males:	Approx. 8 weeks	
	Females:	Approx. 8 weeks	
Identification of animal	By coloured marks and cage label		
Duration of experiment	At least 5 adaptation days 1 test day 2 recovery weeks		

Diet

Commercial diet, ssniff® R/M-H V1534 (ssniff Spezialdiäten GmbH, 59494 Soest, Germany; see [Appendix 3](#): Composition of the diet) served as food. Feed and tap water were available *ad libitum*.

Periodic analysis of the food for contaminants based on EPA/USA² is conducted by LUFA-ITL³ (see [Appendix 3](#): Limitation for contaminants in the diet). Certificates of analysis of the composition and for contaminants were provided by the manufacturer and are QAU archived.

² EPA/USA, Proposed Health Effects Test Standards for Toxic Substances Control Act Test Rules, Federal Register 44, 27334 - 27375, May 1979

³ Landwirtschaftliche Untersuchungs- und Forschungsanstalt, Institut für Tiergesundheit und Lebensmittelqualität GmbH, 24107 Kiel, Germany

Housing

Granulated textured wood (Granulat A2, J. Brandenburg, 49424 Goldenstedt, Germany) was used as bedding material for the cages. The cages were changed and cleaned twice a week.

Periodic analysis of the bedding material for contaminants based on EPA/USA is conducted by LUFA-ITL (see [Appendix 3](#): Limitation for contaminants in the bedding material).

During the 14-day observation period the animals were kept in groups of 2 - 3 animals per sex in MAKROLON cages (type III plus) at a room temperature of $22^{\circ}\text{C} \pm 3^{\circ}\text{C}$ (maximum range) and a relative humidity of $55\% \pm 15\%$ (maximum range). Deviations from the maximum range caused for example during cleaning procedures are dealt with in SOPs.

The rooms were lit (about 150 lux at approx. 1.50 m room height) and darkened for periods of 12 hours each.

Drinking water

Drinking water in bottles was offered *ad libitum*.

Drinking water is examined according to the 'Deutsche Trinkwasserverordnung 2001' [German Regulations on drinking water 2001]⁴ by the Hamburger Wasserwerke, 20539 Hamburg, Germany, at least four times a year (see [Appendix 3](#): Limitation for contaminants in the drinking water).

In addition, drinking water samples taken at **LPT** are analysed by LUFA-ITL once a year for means of bacteriological investigations according to the 'Deutsche Trinkwasserverordnung 2001, Anlage 1' [German Regulations on drinking water 2001, Addendum 1].

⁴ Version from August 02, 2013, revised on November 18, 2015

4.2 Administration

Route of administration	Intravenous injection
Injection speed	Dose/approx. 2 - 3 minutes
Frequency of administration	Single administration
Vehicle	0.9% aqueous NaCl ⁵
Administration volume	2 mL/kg b.w.
Selection of route of administration	The intravenous route is a possible route for human exposure to the test item.

4.3 Groups / Dose levels

Three dose level groups and one vehicle control group were employed. Groups of 10 animals (5 male and 5 female rats) each were examined. The animals were randomised before use.

The following groups were employed:

Group	Test item dose	Number and sex of animals	Animal number
1	0 (Saline control)	5 males 5 females	1 - 5 6 - 10
2	APOSEC™ concentration 1 (low dose) = dose 1	5 males 5 females	11 - 15 16 - 20
3	APOSEC™ concentration 2 (intermediate dose) = dose 2	5 males 5 females	21 - 25 26 - 30
4	APOSEC™ concentration 3 (high dose) = dose 3	5 males 5 females	31 - 35 36 - 40

Dose 1: secretome supernatant from 50 Mio cells/kg b.w.

Dose 2: secretome supernatant from 250 Mio cells/kg b.w.

Dose 3: secretome supernatant from 500 Mio cells/kg b.w.

The dose levels were selected in consultation with the Sponsor based on available data. An orientating experiment employing one female animal per dose was performed (see [Appendix 2](#)).

⁵ Batch nos. 154258141 and 154858141; B. Braun Melsungen AG, 34212 Melsungen, Germany

4.4 Observation

4.4.1 Behaviour

Following administration, observations were made and recorded systematically with individual records being maintained for each animal. Observations were performed before and immediately, 5, 15, 30 and 60 min, as well as 3, 6 and 24 hours after administration. All animals were observed for a period of 14 days.

During the follow-up period (two weeks), changes of skin and fur, eyes and mucous membranes, respiratory and circulatory function, autonomic and central nervous system and somatomotor activity as well as behaviour pattern were observed at least once a day until all symptoms subsided, thereafter each working day. Attention was also paid to possible tremor, convulsions, salivation, diarrhoea, lethargy, sleep and coma.

Observations on deaths were made at least once daily with appropriate actions taken to minimize loss of animals during the study. The time of death would have been recorded as precisely as possible. Individual body weights were recorded before administration of the test item and thereafter in weekly intervals up to the end of the study. Changes in weight were calculated and recorded.

4.4.2 Necropsy

At the end of the experiments all animals were sacrificed, dissected and inspected macroscopically. All gross pathological changes were recorded.

No microscopic examination was carried out as no pathological findings were noted at necropsy.

Necropsy and macroscopic inspection of animals which died prematurely would have been carried out as soon as possible after exitus.

4.5 Statistics

No statistical analysis was performed.

5. RESULTS

Under the present test conditions, single intravenous administrations of different doses of secretome supernatants (50 Mio, 250 Mio or 500 Mio cells/kg b.w.) did not reveal any signs of toxicity in 5 male and 5 female animals per group, respectively. No animal died prematurely.

All animals gained the expected body weight throughout the whole study period. There were no macroscopic findings during necropsy.

Details are listed in [Table 1](#) (Summarized results), [Table 2](#) (Clinical signs), [Table 3](#) (Body weight) and [Table 4](#) (Macroscopic *post mortem* findings).

Acute toxicity study of
APOSEC™
by single intravenous administration to CD rats

TABLE 1 S u m m a r i z e d R e s u l t s

Symptoms/ Criteria	Vehicle control (n = 5)		Dose 1 (n = 5)		Dose 2 (n = 5)		Dose 3 (n = 5)	
	males	females	males	females	males	females	males	females
<u>clinical signs</u>	none	none	none	none	none	none	none	none
<u>mortality</u>								
within 6 h	0	0	0	0	0	0	0	0
within 24 h	0	0	0	0	0	0	0	0
within 7 d	0	0	0	0	0	0	0	0
within 14 d	0	0	0	0	0	0	0	0
<u>mean body weight</u> (in g)								
start	232.0	210.2	238.8	203.8	236.8	206.4	225.0	192.6
after 7 days	288.4 (+24.3)	223.0 (+6.1)	298.6 (+25.0)	230.6 (+13.2)	298.2 (+25.9)	224.2 (+8.6)	287.8 (+27.9)	219.2 (+13.8)
after 14 days	306.8 (+32.4)	238.8 (+13.6)	349.8 (+46.5)	244.8 (+20.2)	348.2 (+46.8)	232.6 (+13.0)	333.6 (+48.2)	227.8 (+18.3)
<u>inhibition of body weight gain</u>	none	none	none	none	none	none	none	none
<u>necropsy findings</u>	none	none	none	none	none	none	none	none

in brackets: body weight gain (%), compared with the start value
h = hours d = days

Dose 1: secretome supernatant from 50 Mio cells/kg b.w.
Dose 2: secretome supernatant from 250 Mio cells/kg b.w.
Dose 3: secretome supernatant from 500 Mio cells/kg b.w.

Acute toxicity study of
APOSEC™
by single intravenous administration to CD rats

TABLE 2 Clinical signs (continued)

Test day	1	1	1	1	1	1	1	2	3	4	5	6	7	8-15
Time after administration	0'	5'	15'	30'	60'	3h	6h							
Animal no./sex	Clinical signs													
<u>Group 2: Dose 1: secretome supernatant from 50 Mio cells/kg b.w.</u>														
11 m	none													
12 m	none													
13 m	none													
14 m	none													
15 m	none													
16 f	none													
17 f	none													
18 f	none													
19 f	none													
20 f	none													

0' = immediately after dosing

' = minute

h = hour

m = male

f = female

Acute toxicity study of
APOSEC™
by single intravenous administration to CD rats

TABLE 2 Clinical signs (continued)

Test day	1	1	1	1	1	1	1	2	3	4	5	6	7	8-15
Time after administration	0'	5'	15'	30'	60'	3h	6h							
Animal no./sex	Clinical signs													
<u>Group 3: Dose 2: secretome supernatant from 250 Mio cells/kg b.w.</u>														
21 m	none													
22 m	none													
23 m	none													
24 m	none													
25 m	none													
26 f	none													
27 f	none													
28 f	none													
29 f	none													
30 f	none													

0' = immediately after dosing

' = minute

h = hour

m = male

f = female

Acute toxicity study of
APOSEC™
by single intravenous administration to CD rats

TABLE 2 Clinical signs (continued)

Test day	1	1	1	1	1	1	1	2	3	4	5	6	7	8-15
Time after administration	0'	5'	15'	30'	60'	3h	6h							
Animal no./sex	Clinical signs													
Group 4: Dose 3: secretome supernatant from 500 Mio cells/kg b.w.														
31 m	none													
32 m	none													
33 m	none													
34 m	none													
35 m	none													
36 f	none													
37 f	none													
38 f	none													
39 f	none													
40 f	none													

0' = immediately after dosing

' = minute

h = hour

m = male

f = female

Acute toxicity study of
APOSEC™
by single intravenous administration to CD rats

TABLE 3 Body weight (continued)

Animal no./ sex	TD 0	TD 8		TD 15		Necropsy/ status
<u>Group 2: Dose 1: secretome supernatant from 50 Mio cells/kg b.w.</u>						
11 m	234	295	(+26.1)	339	(+44.9)	TS
12 m	243	297	(+22.2)	356	(+46.5)	TS
13 m	231	288	(+24.7)	342	(+48.1)	TS
14 m	241	302	(+25.3)	347	(+44.0)	TS
15 m	245	311	(+26.9)	365	(+49.0)	TS
Mean	238.8	298.6	(+25.0)	349.8	(+46.5)	
SD	6.0	8.6		10.7		
16 f	207	230	(+11.1)	252	(+21.7)	TS
17 f	203	231	(+13.8)	240	(+18.2)	TS
18 f	211	234	(+10.9)	241	(+14.2)	TS
19 f	204	236	(+15.7)	252	(+23.5)	TS
20 f	194	222	(+14.4)	239	(+23.2)	TS
Mean	203.8	230.6	(+13.2)	244.8	(+20.2)	
SD	6.3	5.4		6.6		

body weight in g

TD = test day

TD 0 = Test day 1 immediately before dosing

m = male

f = female

SD = standard deviation

TS = terminal sacrifice

in brackets: body weight gain in % compared to the start value

Acute toxicity study of
APOSEC™
by single intravenous administration to CD rats

TABLE 3 Body weight (continued)

Animal no./ sex	TD 0	TD 8		TD 15		Necropsy/ status
<u>Group 3: Dose 2: secretome supernatant from 250 Mio cells/kg b.w.</u>						
21 m	239	303	(+26.8)	357	(+49.4)	TS
22 m	220	261	(+18.6)	289	(+31.4)	TS
23 m	238	303	(+27.3)	358	(+50.4)	TS
24 m	243	311	(+28.0)	359	(+47.7)	TS
25 m	244	313	(+28.3)	378	(+54.9)	TS
Mean	236.8	298.2	(+25.9)	348.2	(+46.8)	
SD	9.7	21.3		34.2		
26 f	205	221	(+7.8)	227	(+10.7)	TS
27 f	198	225	(+13.6)	236	(+19.2)	TS
28 f	225	233	(+3.6)	234	(+4.0)	TS
29 f	207	222	(+7.2)	223	(+7.7)	TS
30 f	197	220	(+11.7)	243	(+23.4)	TS
Mean	206.4	224.2	(+8.6)	232.6	(+13.0)	
SD	11.3	5.3		7.8		

body weight in g

TD = test day

TD 0 = Test day 1 immediately before dosing

m = male

f = female

SD = standard deviation

TS = terminal sacrifice

in brackets: body weight gain in % compared to the start value

Acute toxicity study of
APOSEC™
by single intravenous administration to CD rats

TABLE 3 Body weight (continued)

Animal no./ sex	TD 0	TD 8		TD 15		Necropsy/ status
<u>Group 4: Dose 3: secretome supernatant from 500 Mio cells/kg b.w.</u>						
31 m	220	273	(+24.1)	316	(+43.6)	TS
32 m	220	279	(+26.8)	332	(+50.9)	TS
33 m	226	287	(+27.0)	335	(+48.2)	TS
34 m	230	302	(+31.3)	356	(+54.8)	TS
35 m	229	298	(+30.1)	329	(+43.7)	TS
Mean	225.0	287.8	(+27.9)	333.6	(+48.2)	
SD	4.8	12.3		14.5		
36 f	195	220	(+12.8)	227	(+16.4)	TS
37 f	195	218	(+11.8)	236	(+21.0)	TS
38 f	196	226	(+15.3)	230	(+17.3)	TS
39 f	193	220	(+14.0)	224	(+16.1)	TS
40 f	184	212	(+15.2)	222	(+20.7)	TS
Mean	192.6	219.2	(+13.8)	227.8	(+18.3)	
SD	4.9	5.0		5.5		

body weight in g

TD = test day

TD 0 = Test day 1 immediately before dosing

m = male

f = female

SD = standard deviation

TS = terminal sacrifice

in brackets: body weight gain in % compared to the start value

Acute toxicity study of
APOSEC™
by single intravenous administration to CD rats

TABLE 4 Macroscopic post mortem findings

Animal no./ sex	Affected Organ / Finding
<u>Group 1: 2 mL 0.9% aqueous NaCl/kg b.w.. i.v.</u>	
1 m	no pathological findings
2 m	no pathological findings
3 m	no pathological findings
4 m	no pathological findings
5 m	no pathological findings
6 f	no pathological findings
7 f	no pathological findings
8 f	no pathological findings
9 f	no pathological findings
10 f	no pathological findings

m male
f female

Acute toxicity study of
APOSEC™
by single intravenous administration to CD rats

TABLE 4 Macroscopic post mortem findings (continued)

Animal no./ sex	Affected Organ / Finding
<u>Group 2: Dose 1: secretome supernatant from 50 Mio cells/kg b.w.</u>	
11 m	no pathological findings
12 m	no pathological findings
13 m	no pathological findings
14 m	no pathological findings
15 m	no pathological findings
16 f	no pathological findings
17 f	no pathological findings
18 f	no pathological findings
19 f	no pathological findings
20 f	no pathological findings

m male
f female

Acute toxicity study of
APOSEC™
by single intravenous administration to CD rats

TABLE 4 Macroscopic post mortem findings (continued)

Animal no./ sex	Affected Organ / Finding
<u>Group 3: Dose 2: secretome supernatant from 250 Mio cells/kg b.w.</u>	
21 m	no pathological findings
22 m	no pathological findings
23 m	no pathological findings
24 m	no pathological findings
25 m	no pathological findings
26 f	no pathological findings
27 f	no pathological findings
28 f	no pathological findings
29 f	no pathological findings
30 f	no pathological findings

m male
f female

Acute toxicity study of
APOSEC™
by single intravenous administration to CD rats

TABLE 4 Macroscopic post mortem findings (continued)

Animal no./ sex	Affected Organ / Finding
<u>Group 4: Dose 3: secretome supernatant from 500 Mio cells/kg b.w.</u>	
31 m	no pathological findings
32 m	no pathological findings
33 m	no pathological findings
34 m	no pathological findings
35 m	no pathological findings
36 f	no pathological findings
37 f	no pathological findings
38 f	no pathological findings
39 f	no pathological findings
40 f	no pathological findings

m male
f female

A P P E N D I X 1

Certificate of Analysis



ÖSTERREICHISCHES ROTES KREUZ

OBERÖSTERREICH

*Aus Liebe zum Menschen.***CERTIFICATE OF ANALYSIS**

Manufacturer: Österreichisches Rotes Kreuz, Landesverband Oberösterreich, Blutzentrale Linz
Krankenhausstraße 7, 4010 Linz, Austria

Name: APOSEC™

Filling size: 100 mL glass bottle with 20 mL lyophilised APOSEC™

Batch-No: 399033

Man. Date: 07.01.2016

Valid for: Non-clinical trials

TEST	SPECIFICATION	RESULTS
Endotoxine	< 0,25 EU/mL	< 0,25 EU/mL
Mycoplasma	negative	negative
LEAD CYTOKINES		
EGF	51-214 pg/mL	96,276 pg/mL
TGF-β	3580-10354 pg/mL	3962,1 pg/mL
IL-8	300-4829 pg/mL	1256,21 pg/mL
POTENCY ASSAYS		
NO-Concentration	passed	passed
Platelet Aggregation	> 75% reduction	passed
STERILITY		
Endproduct	sterile	sterile

The above lot was manufactured according to GMP regulations. All donations were tested negative for HIV, HCV, HBV, HAV, HEV, Parvo B19 and syphilis.

Date / Signature

15. Feb. 2016

(Head of quality control)

A P P E N D I X 2

Orientating Preliminary Experiment

Preliminary test
Acute toxicity study of
APOSEC™
by single intravenous administration
to CD rats

Number of animals	2 (1 per dose level)
Sex	Female
Species / Stock / Strain	Rat / CD / Crl: CD(SD)
Body weight	296 - 299 g
Route of administration	Intravenous bolus injection into a tail vein
Administration volume	2 mL/kg b.w.
Injection speed	Dose/approx. 2 - 3 minutes
Dose levels	Secretome supernatant from 333 or 500 Mio cells/kg b.w.
Vehicle	0.9% NaCl solution
Observation period	14 days

Mio Cells [per kg b.w.]	Animals deceased/ employed	Signs of toxicity
333	0/1 female	no signs
500	0/1 female	no signs

A P P E N D I X 3

**Composition of the Diet; Limitation for Contaminants
in the Diet, Drinking Water and Bedding Material**

Composition of the diet**Standard Diet for Rats and Mice****ssniff® R/M-H V1534**

(ssniff Spezialdiäten GmbH, 59494 Soest, Germany)

Ingredients (average % content in the diet)		Amino Acids (average % content in the diet)	
crude protein	19.0	lysine	1.00
crude fat	3.3	methionine	0.30
crude fibres	4.9	Met + Cys	0.65
ash	6.4	glycine	0.80
		leucine	1.30
		isoleucine	0.76
		arginine	1.14
		phenylalanine	0.85
Metabolizable Energy (MJ/kg)	12.8	Phe + Tyr	1.43
		tryptophan	0.25
		histidine	0.44
		aspartic acid	1.61
		glutamic acid	3.90
		valine	0.88
		threonine	0.68
		proline	1.25
		alanine	0.79
		serine	0.89
Minerals (average % content in the diet)		Trace Elements (average content in mg per 1 000 g of diet)	
calcium	1.00	manganese	69
phosphorus	0.70	copper	16
sodium	0.24	zinc	94
magnesium	0.22	iodine	2.2
potassium	0.91	iron	179
		selenium	0.3
		cobalt	2.1
Vitamins (additive per 1 000 g of diet)		Fatty Acids [%]	
vitamin A	15 000 IU	C 14:0	0.01
vitamin D ₃	1 000 IU	C 16:0	0.47
vitamin E	110 mg	C 16:1	0.01
vitamin B ₁	18 mg	C 18:0	0.08
vitamin B ₂	23 mg	C 18:1	0.62
vitamin B ₆	21 mg	C 18:2	1.80
vitamin B ₁₂	100 µg	C 18:3	0.23
biotin	525 µg	C 20:0	0.01
pantothenic acid	43 mg	C 20:1	0.02
choline chloride	2 990 mg	C 20:5	-
folic acid	7 mg	C 22:6	-
nicotinic acid	135 mg		
vitamin K (as menadione)	5 mg		
inositol	100 mg		

Limitation for contaminants in the diet [ppb]

	min.	max.
Aflatoxin (B ₁ , B ₂ , G ₁ , G ₂), total		5
Lindane		20
Heptachlor		20
Malathion		2500
DDT (Total)		100
Dieldrin		20
Cadmium		160
Arsenic		1000
Lead		1500
Mercury		100
Selenium	100	600
PCB		50

Limitation for contaminants in the drinking water [mg/L]

	max.
Iron	0.200
Manganese	0.050
Ammonium	0.50
Chloride	250
Arsenic	0.010
Lead	0.010
Cadmium	0.0030
Chromium	0.050
Cyanide	0.050
Fluoride	1.5
Nickel	0.020
Nitrite	0.50
Nitrate	50
Mercury	0.0010
Vinylchloride	0.00050
Acrylamide	0.00010
Benzene	0.0010
Boron	1.0
Bromate	0.010
Selenium	0.010
Antimony	0.0050
Copper	2.0
Aluminium	0.200
Sodium	200
Sulphate	250
Uranium	0.010

Polycyclic aromatic hydrocarbons

- Benzo-(b)-fluoranthene		
- Benzo-(k)-fluoranthene		
- Benzo-(ghi)-perylene		
- Indeno-(1,2,3-cd)-pyrene	total	0.00010
- Benzo-(a)-pyrene		0.000010

		max.
Chlorinated organic compounds		
Trihalogenemethane		
including Trichloromethane,		
Bromodichloromethane,		
Dibromochloromethane and		
Tribromomethane total		0.050
- 1,2-Dichloroethane		0.0030
- Tetrachloroethene and Trichloroethene		0.010
- Epichlorohydrine		0.00010
Organic chemical compounds used as		
pesticides and biocides including		
their toxic metabolites	maximum of	0.0001/substance
except for		
- Aldrin		0.000030
- Dieldrin		0.000030
- Heptachlor		0.000030
- Heptachloroepoxide		0.000030
maximum total of		0.00050
Tritium [Bq/L]		100
pH	between	6.5 and 9.5

Limitation for contaminants in the bedding material [mg/kg]

	max.
Aflatoxin (B ₁)	0.01
Chlordane	0.05
Endrin	0.02
Fluorine	150.00
Lindane	0.10
Heptachlor and epoxide	0.03
DDT, DDE, DDD	0.05
Dieldrin and aldrin	0.02
Arsenic	2.00
Lead	5.00
Mercury	0.10
Nitrite (Na-Nitrite)	15.00
HCB	0.03

A P P E N D I X 4

GLP Certificate of the Test Facility LPT



FREIE UND HANSESTADT HAMBURG
Behörde für Gesundheit und Verbraucherschutz

Gute Laborpraxis / Good Laboratory Practice

GLP – Bescheinigung / Statement of GLP Compliance
(gemäß/according to § 19b Abs.1 Chemikaliengesetz)

Eine GLP-Inspektion zur Überwachung der Einhaltung
der GLP-Grundsätze gemäß Chemikaliengesetz bzw.
Richtlinie 2004/9/EG wurde durchgeführt in:

Assessment of conformity with GLP according to
Chemikaliengesetz and Directive 2004/9/EEC at:



Prüfeinrichtung/Test facility



Prüfstandort/ Test site

LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG
Redderweg 8
21147 Hamburg

(Unverwechselbare Bezeichnung und Adresse/Unequivocal name and address)

Prüfungen nach Kategorien/ Areas of Expertise
(gemäß/according ChemVwV-GLP Nr. 5.3/OECD guidance)

Kategorie 2, 3, 4 und 9 (Sicherheitspharmakologie und Auftragsarchiv)

Datum der Inspektion/ Date of Inspection:
(Tag.Monat.Jahr/day.month.year)

16., 17., 18. und 19.04.2013

Die/Der genannte Prüfeinrichtung /Prüfstandort befindet
sich im nationalen GLP-Überwachungsverfahren und
wird regelmäßig auf Einhaltung der GLP-Grundsätze
überwacht.

Auf der Grundlage des Inspektionsberichtes wird hiermit
bestätigt, dass in dieser Prüfeinrichtung/diesem Prüf-
standort die oben genannten Prüfungen unter Einhaltung
der GLP-Grundsätze durchgeführt werden können.

The above mentioned test facility/test site is included
in the national GLP Compliance Programme and is
inspected on a regular basis.

Based on the inspection report it can be confirmed, that
this test facility/ test site is able to conduct the aforemen-
tioned studies in compliance with the Principles of GLP

Hamburg, den 14.05.2014



Behörde für Gesundheit und Verbraucherschutz
Marckmannstraße 129b, 20539 Hamburg


Dr. Volker Kregel
Direktor des Amtes für Arbeitsschutz

LPT Report No. 35015
Amendment No. 1 to Final Report

**2-WEEK TOXICITY STUDY OF
ALLOGENIC APOSEC™
BY REPEATED TWICE WEEKLY INTRAVENOUS INFUSION
TO CYNOMOLGUS MONKEYS
FOLLOWED BY A 2-WEEK TREATMENT-FREE PERIOD
- MULTI-SITE STUDY -**

(Final Report dated 11 November 2019)

Sponsor:

APOSCIENCE AG
Dresdner Str. 87/A 21
1200 Vienna
Austria

Study conducted by:

LPT Laboratory of Pharmacology
and Toxicology GmbH & Co. KG
Redderweg 8
21147 Hamburg
Germany

Contact person:

Dr. Silvio Wuschko

Contact person:

Dr. Jost Leuschner

24 August 2020

This Amendment No. 1 to Final Report consists of 3 + 779 pages.
- Page I -

REASON FOR AMENDMENT NO. 1 TO FINAL REPORT

As requested by the Sponsor, the Final Report is supplemented by additional information:

Final Report Section 2 GENERAL INFORMATION, 2.12 Study Plan deviations on page 25:

The first dose reduction for group 4 was carried out on 18 February 2019, 2 days before Study Plan Amendment No. 2 was issued:

Previous:

No statement

New:

A deviation was compiled.

Final Report Sections 1 SUMMARY, 1.2 Findings on page 14, 1.3 Conclusion on page 17, 4 RESULTS, 4.2.1 Mortality on page 50:

Number and mapping of group 4 males:

Previous:

Two of 3 male animals (nos. 26 and 27) treated with **350 U Allogenic APOSEC™/kg b.w.** had to be sacrificed prematurely after the first administration on test day 1.

New:

Two of 5 male animals (male nos. 26 and 27, assigned for recovery period at start of the study) treated with **350 U Allogenic APOSEC™/kg b.w.** had to be sacrificed prematurely after the first administration on test day 1.

In addition, two additional males (nos. 33 and 34) were added to group 4 to replace the prematurely sacrificed animals nos. 26 and 27.

Recovery period (restricted to groups 1 and 4)

None of the two animals (nos. 33 and 34) previously treated intravenously with reduced dosing **225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks died or had to be sacrificed prematurely during the recovery period.

Final Report Section 4 RESULTS, 4.2.2 Clinical signs (behaviour, external appearance, faeces) on pages 52:

More transparency concerning the actual received dosages in group 4:

Previous:

Fixed dosage statement

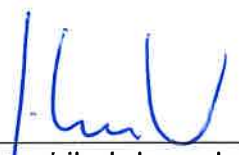
New:

Text table 4-3 'Individualized dosing schedule' was additionally inserted.

In addition, Table 2-2 'Clinical Signs - Systemic Tolerance - Individual Data' in Section 5 TABLES was modified accordingly.

The complete report is hereby amended.

This amendment does not affect the validity or interpretation of the data.



Dr. phil. J. Leuschner
Study Director

24 Aug 2020

Date

This Amendment No. 1 to Final Report has been audited by the Quality Assurance Unit (QAU) and is considered to be an accurate account of the project.



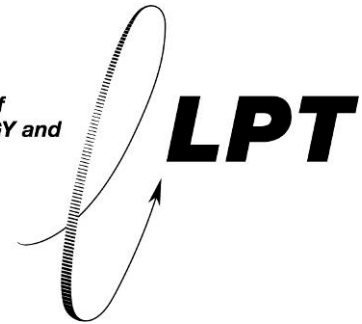
Dr. med. vet. habil. K. R. Sultan
Director of Quality Assurance Unit

24. Aug. 2020

Date

LPT Report No. 35015
Amendment No. 1 to Final Report

LABORATORY of
PHARMACOLOGY and
TOXICOLOGY



**2-WEEK TOXICITY STUDY OF
ALLOGENIC APOSEC™
BY REPEATED TWICE WEEKLY INTRAVENOUS INFUSION
TO CYNOMOLGUS MONKEYS
FOLLOWED BY A 2-WEEK TREATMENT-FREE PERIOD
- Multi-Site Study -**

Final Report

Sponsor:

APOSCIENCE AG
Dresdner Str. 87/A 21
1200 Vienna
Austria

Study conducted by:

LPT Laboratory of Pharmacology
and Toxicology GmbH & Co. KG
Redderweg 8
21147 Hamburg
Germany

Study Monitor:

Dr. Silvio Wuschko

Contact Person:

Dr. Jost Leuschner

24 August 2020

This report consists of 779 pages.
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STATEMENT OF COMPLIANCE

**2-WEEK TOXICITY STUDY OF
ALLOGENIC APOSEC™
BY REPEATED TWICE WEEKLY INTRAVENOUS INFUSION
TO CYNOMOLGUS MONKEYS
FOLLOWED BY A 2-WEEK TREATMENT-FREE PERIOD
- Multi-Site Study -**

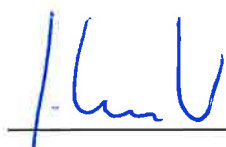
The study was performed in compliance with:

- 'Good Laboratory Practice' Regulations of the EC enacted in Germany in the 'Chemikaliengesetz' [Chemicals Act], current edition;
- 'OECD Principles of Good Laboratory Practice' Document No. 1, ENV/MC/CHEM (98) 17.

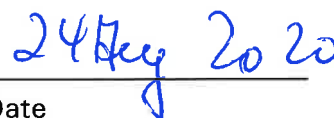
These principles are compatible with 'Good Laboratory Practice' (GLP) regulations specified by regulatory authorities throughout the European Community, the United States (EPA and FDA) and Japan (MHLW, MAFF, and METI).

There were no deviations from the 'Good Laboratory Practice' regulations. Raw data obtained during the performance of the study are accurately reflected.

The Principal Investigator (PI) was responsible for compliance with his national GLP regulations for any work performed at his Test Site (TS) and for data provided to LPT for inclusion in the study report (LPT).



Dr. phil. Jost Leuschner
Study Director



Date

QUALITY ASSURANCE STATEMENT

Based on a quality assurance review, it was concluded that this report accurately reflects the raw data for the study. Methods, procedures and observations are correctly and completely described in the report:

**2-WEEK TOXICITY STUDY OF
ALLOGENIC APOSEC™
BY REPEATED TWICE WEEKLY INTRAVENOUS INFUSION
TO CYNOMOLGUS MONKEYS
FOLLOWED BY A 2-WEEK TREATMENT-FREE PERIOD
- Multi-Site Study -**

Study Plan dated 05 February 2019 and 6 Study Plan amendments.

Text table 0-1: Inspections of LPT's QAU

Date of inspection	Criteria	Date of report to the Study Director and the Management
05 Feb 2019	Study Plan.	05 Feb 2019
11 Feb 2019	Preparation of the test item-formulations, pump setting, administration, ECG, blood pressure, animal housing, dissection, organ removal, organ weights, documentation.	11 Feb 2019
18 Feb 2019	Preparation of the test item-formulations, pump setting, administration, ECG, blood pressure, animal housing, documentation.	18 Feb 2019
21 Feb 2019	Preparation of the test item-formulations, pump setting, administration, ECG, blood pressure, animal housing, documentation.	21 Feb 2019
22 Feb 2019	Blood withdrawal and processing, sacrifice of the animals, dissection, organ removal, organ weights, bone marrow smears, documentation.	22 Feb 2019
28 Feb 2019	Preparation of the test item-formulations, pump setting, administration, ECG, blood pressure, documentation.	28 Feb 2019
01 Mar 2019	Sacrifice of the animals, dissection, organ removal, organ weights, bone marrow smears, documentation.	01 Mar 2019
08 Mar 2019	Sacrifice of the animals, dissection, organ removal, organ weights, bone marrow smears, documentation.	08 Mar 2019
11 Nov 2019	Final Report.	11 Nov 2019
21 + 24 Aug 2020	Amendment No. 1 to Final Report.	24 Aug 2020

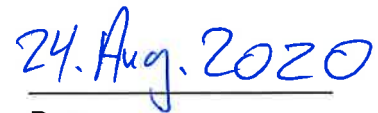
In addition to the detailed study-based inspections, series of routine facility inspections were also conducted and reported to the Management.

For further QAU audits at the Principal Investigator's Test Site please refer to the respective appendix.

Approved and
Submitted by:



Dr. med. vet. habil. K. R. Sultan
Director of Leading Quality
Assurance Unit (LQAU)



Date

EXPLANATIONS AND ABBREVIATIONS

Symbols

¹ _ n	reference to footnotes in the text section
#	reference to footnotes in the tables section
()	animal number in the tables section
*	statistically significant at $p \leq 0.05$
**	statistically significant at $p \leq 0.01$
%	per cent

Letters and acronyms

%Diff	% difference compared to the control group
a.m.	<i>ante meridiem</i>
abs.	absolute
approx.	approximately
b.w.	body weight
e.g.	<i>exempli gratia</i>
EC	European Commission
ECG	electrocardiography
EPA	Environmental Protection Agency
EU	European Union
f	female
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
GPS	Global Pathology Support
H & E	haematoxylin and eosin (staining method used in histology)
Hb	haemoglobin
HTS	Head of Test Site
i.e.	<i>id est</i>
incl.	Including
i.v.	Intravenous
LPT	Laboratory of Pharmacology and Toxicology GmbH & Co. KG
LQAU	Leading Quality Assurance Unit
LUFA-ITL	Landwirtschaftliche Untersuchungs- und Forschungsanstalt, Institut für Tiergesundheit und Lebensmittelqualität
m	male
MAFF	Ministry of Agriculture, Forestry and Fisheries (Japan)
Mean	mean value
METI	Ministry of Economy, Trade and Industry (Japan)
MHLW	Ministry of Health, Labour and Welfare (Japan)
MS	main study
n or N	number (group size)
N/A	not applicable
NOAEL	no-observed-adverse-effect level
ns	not statistically significant (at $p \leq 0.01$ or $p \leq 0.05$)
OECD	Organization for Economic Co-Operation and Development
p.m.	<i>post meridiem</i>
PBMC	peripheral blood mononuclear cell
PI	Principal Investigator

- Letters and acronyms continued on the next page -

Letters and acronyms (*continued*)

PreDs	predose
PS	premature sacrifice
QAU	Quality Assurance Unit
rel.	relative
RP	recovery period
SD	standard deviation
SOP	Standard Operating Procedure
TD	test day
TD -7 to -5	pre-drug examination
TS	terminal sacrifice (necropsy context) / Test Site (Multi Site context)
TSQAU	Test Site Quality Assurance Unit
TW	test week

Weights and measures

°C	degree Celsius
µL	microlitre
µmol	micromole
fL	femtolitre
fmol	femtomole
g	gram
h	hour
kg	kilogram
L	litre
mg	milligram
min	minute
mL	millilitre
mm	millimetre
mmHg	millimetres of mercury
mmol	millimole
ms	millisecond
mV	millivolt
sec	second
U	unit

Measuring units

Body weight in kg
Food intake in g/kg b.w./day
Relative organ weights in g/kg b.w.
Absolute organ weights in g

Electrocardiography

aVR	augmented unipolar limb lead I
aVL	augmented unipolar limb lead II
aVF	augmented unipolar limb lead III
ECG	electrocardiogram
HR	heart rate
P segment	first deflection resulting from atrial activity due to excitation of the atria
PQ interval	beginning of atrioventricular and ventricular excitation
QRS interval	deflections due to excitation of the ventricles
QT interval	total electrocardiographic ventricular activity
QTc value	QT interval corrected according to the formula of Bazett

Blood pressure

Press.	pressure
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Haematology / Coagulation

aPTT	activated partial thromboplastin time
Baso	basophilic granulocytes
Eos	eosinophilic granulocytes
ESR	erythrocyte sedimentation rate
HCT	haematocrit
HGB	haemoglobin
LUC	large unclassified cells
Lym	lymphocytes
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular volume
Mono	monocytes
Neut	neutrophilic granulocytes
PLT	platelets
PT	prothrombin time
RBC	erythrocytes (red blood cell count)
Reti	reticulocytes
WBC	leucocytes (white blood cell count)

Clinical chemistry

Alb.	albumin
ALAT	alanine aminotransferase
aP	alkaline phosphatase
ASAT	aspartate aminotransferase
Gamma-GT	gamma-glutamyl-transferase
Glob.	globulin
LDH	lactate dehydrogenase

Urinalysis

ery	erythrocyte
neg	negative/none found in any field examined
pos	positive
LC	lemon-coloured
SC	straw-coloured
+	'small amount' of analyte/few in some fields examined
+ +	'moderate amount' of analyte/few in all fields examined
+ + +	'large amount' of analyte/many in all fields examined

Organ weights

Adren.	adrenal
cerv.	cervical
Par.	parathyroid

Histopathology

For explanations see the 'Phase Report on Histopathology' in [Appendix 3](#).

1. SUMMARY

1.1 Conduct of study

Test item	Allogenic APOSEC™
Batch nos.	a) A000918399109 b) A000918399110 c) A000918399111 d) A000918399112 e) A000918399113 f) A000918399115 g) A000918399116 h) A000918399117 i) A000918399118
Negative control	Sterile 0.9% NaCl solution (provided by LPT)
Species / Strain	Monkey / Cynomolgus (<i>Macaca fascicularis</i>) - treatment naïve -
Breeder (country of origin)	Purpose-bred in the People's Republic of China; captive-bred
Imported through	Roberto C. Hartelust 5001 CD Tilburg The Netherlands
Number and sex of animals	34 (18 male and 16 female) animals <u>Main study animals</u> 26 animals (14 males and 12 females); 3 animals/sex and group for groups 1 to 3, 5 male and 3 female animals for group 4 <u>Recovery animals</u> 8 animals (4 males and 4 females); 2 animals/sex for groups 1 and 4.
Route of administration	Intravenous infusion into the <i>vena cephalica</i> of the left or right arm
Frequency of administration	Two times per week for 2 test weeks; in total 4 infusions/animal (on test days 1, 4, 8 and 11)
Infusion speed	<u>Male animals (except nos. 33 and 34)</u> 1 st Dose/30 minutes, 0.167 mL/min/kg b.w. 2 nd Dose/30 minutes, 0.5 mL/min/kg b.w. 3 rd Dose/30 minutes, 0.5 mL/min/kg b.w. 4 th Dose/40 minutes, 0.375 mL/min/kg b.w.

	<u>Female animals and male animals no. 33 and 34</u> 1 st Dose/30 minutes, 0.5 mL/min/kg b.w. 2 nd Dose/40 minutes, 0.375 mL/min/kg b.w. 3 rd Dose/40 minutes, 0.375 mL/min/kg b.w. 4 th Dose/40 minutes, 0.375 mL/min/kg b.w.
Dose levels	Group 1: Control (saline) twice weekly Group 2: 35 U/kg b.w. twice weekly Group 3: 110 U/kg b.w. twice weekly Group 4: 350/225/200 U/kg b.w. twice weekly Due to the poor health condition of the male animals of group 4, the initial dose of 350 U/kg b.w. was reduced to 225 U/kg b.w. as of test day 8 for the male animals (except nos. 33 and 34) and on test day 1 for all female animals and male animals no. 33 and 34 (<i>i.e.</i> 18 February 2019). The dose was further reduced to 200 U/kg b.w. on test day 11 for the male animals (except nos. 33 and 34) and on test day 4 for all female animals and male animals no. 33 and 34 (<i>i.e.</i> 21 February 2019), respectively. The reduction of the dose was made because the effect observed was thought to have been caused by exaggerated pharmacodynamics effects; the test item is a pronounced vasodilator.
Administration volumes	<u>Male animals (except nos. 33 and 34)</u> 1st Dose: 5 mL/kg b.w. 2nd to 4th Dose: 15 mL/kg b.w. <u>Female animals and male animals no. 33 and 34</u> 1st to 4th Dose: 15 mL/kg b.w. Due to the moribund condition after the first infusion, 2 male high dose animals were sacrificed prematurely. In order to reduce the risk of a vasodilatory effect, the administration volume was increased thereafter.
Duration of study	• 4 adaptation weeks for female animals and male animals no. 33 and 34 • 5 adaptation weeks for male animals (except nos. 33 and 34) • 2 treatment weeks • 2 recovery weeks for selected animals

1.2 Findings

Treatment period

Local tolerance

No test item-related signs of local intolerance reactions were noted during clinical observations and at macroscopic inspection at necropsy.

The histopathological examination of the infusion sites did not reveal any test item-related findings.

Systemic tolerance

Mortality

None of the animals treated intravenously with **35 or 110 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks died or had to be sacrificed prematurely.

Two of 5 male animals (male nos. 26 and 27, assigned for recovery period at start of the study) treated with **350 U Allogenic APOSEC™/kg b.w.** had to be sacrificed prematurely after the first administration on test day 1. For both animals, changes in form of increased body temperature (within 20 minutes p.a.), reduced motility (within 60 minutes p.a.), lateral position (within 2 hours p.a.), reduced reflexes (within 2 hours p.a.), convulsions (within 2 hours p.a.) and reduced body temperature (within 2 hours p.a.) were noted before sacrifice.

Enlarged axillary lymph nodes were observed for males no. 26 and 27 for which no microscopic correlate was noted. Emphysematous lungs were observed for male no. 26 that could not be associated with microscopy. This was also the case for enlarged cervical lymph node and adrenal glands in animal no. 27. However, haemorrhagic and oedematous subcutaneous tissue in the thighs and lower legs of animal no. 27 were associated with slight diffuse phlegmonous inflammation, consisting of acute inflammation with interstitial oedema and minimal haemorrhage as observed at microscopy. These macroscopic changes were related to the administration of the test item.

Presumably, the death of these animals was caused by an exaggerated vasodilation, the pharmacodynamic effect of the test item.

Clinical signs	Reduced motility was noted for 2 of 3 <u>males</u> treated intravenously with 110 U Allogenic APOSEC™/kg b.w. twice weekly for 2 weeks after the 3rd administration. In addition, 1 of 3 male animals revealed asthenia, mydriasis, a lateral position and clonic convulsions after the 3rd administration. At the high dose of 350/225/200 U Allogenic APOSEC™/kg b.w. changes in form of asthenia, somnolence, mydriasis, a lateral position, an increased respiratory rate, laboured breathing, a reduced motility, reduced reflexes, (clonic) convulsions, salivation and/or emesis on the administration days and up to 1 day thereafter. In addition, the 2 male animals (nos. 26 and 27) that had to be sacrificed prematurely revealed an increased body temperature (within 5 to 20 minutes p.a.) and a reduced body temperature (within 1 to 2 hours p.a.).
Body weight and body weight gain	No test item-related influence was noted.
Food and drinking water consumption	No test item-related influence was noted.
ECG	No test item-related influence was noted.
Blood pressure	No test item-related influence was noted.
Haematology and coagulation	No test item-related influence was noted.
Clinical chemistry	No test item-related influence was noted.
Urinalysis	No test item-related influence was noted.
Ophthalmological and auditory examination	No changes were noted.
Macroscopic post mortem findings	In the males treated intravenously with 350/225/200 U Allogenic APOSEC™/kg b.w. for 2 weeks, spleens were enlarged in males no. 23 and 25 (scheduled sacrifice), for which a microscopic correlate (follicular hyperplasia) was made for animal no. 23 only. Enlarged axillary lymph nodes were observed for male no. 13 treated with 35 U Allogenic APOSEC™/kg b.w. and for male no. 25 (high dose group 4) (scheduled sacrifice), for which

microscopic correlates were seen in animal nos. 13 and 25 (medullary hyperplasia).

Organ weights

No test item-related influence was noted.

Bone marrow

No test item-related influence was noted.

Histopathology

(performed by

Global Pathology Support B.V.)

Test item-related changes were observed in spleen of animal no. 23 (follicular cell hyperplasia) treated intravenously with **350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks. This finding was associated with splenic enlargement at autopsy. Lymphoid hyperplasia of the medulla in the axillary lymph node was observed for animal no. 25 treated with **350/225/200 U Allogenic APOSEC™/kg b.w.** with enlarged axillary lymph node at macroscopy. This was also observed for 1 of 3 males treated with **35 U Allogenic APOSEC™/kg b.w.** (no. 13) for which the draining axillary lymph node was also enlarged at macroscopy.

Recovery period

(restricted to groups 1 and 4)

None of the monkeys revealed any late test item-related local intolerance reactions. No premature deaths occurred and no clinical signs of systemic toxicity were noted. No test item-related changes were noted for body weight and body weight gain, food and drinking water consumption, electrocardiography, blood pressure, haematological, clinical chemistry and urinary parameters, at ophthalmological and auditory examinations, at necropsy, and for organ weights and bone marrow evaluation during or at the end of the 2-week treatment-free recovery period.

1.3 Conclusion

The aim of the study was to obtain information on the potential toxicity, including the local tolerance of Allogenic APOSEC™ given twice weekly by intravenous infusion to Cynomolgus monkeys for 2 weeks and to assess the reversibility of any effect after a 2-week recovery period.

The animals were initially treated intravenously with **35, 110 or 350 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks. However, two of 5 male animals (male nos. 26 and 27, assigned for recovery period at start of the study) treated with **350 U Allogenic APOSEC™/kg b.w.** had to be sacrificed prematurely after the first administration on test day 1 due to their poor condition. Enlarged axillary lymph nodes were observed for both males without any microscopic correlate. Emphysematous lungs were observed for male no. 26 that could not be associated with microscopy. This was also the case for enlarged cervical lymph node and adrenal glands in animal no. 27. However, haemorrhagic and oedematous subcutaneous tissue in the thighs and lower legs of animal no. 27 were associated with slight diffuse phlegmonous inflammation, consisting of acute inflammation with interstitial oedema and minimal haemorrhage as observed at microscopy. Presumably, the death of these animals was caused by an exaggerated vasodilation, the pharmacodynamic effect of the test item. Hence, the initial dose of **350 U/kg b.w.** was reduced to **225 U/kg b.w.** and further to **200 U/kg b.w.**

No test item-related signs of local intolerance reactions were observed.

Reduced motility was noted for 2 of 3 males treated intravenously with **110 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks after the 3rd administration. In addition, 1 of 3 male animals revealed asthenia, mydriasis, a lateral position and clonic convulsions after the 3rd administration. At the high dose of **350/225/200 U Allogenic APOSEC™/kg b.w.**, changes in form of asthenia, somnolence, mydriasis, a lateral position, an increased respiratory rate, laboured breathing, a reduced motility, reduced reflexes, (clonic) convulsions, salivation and/or emesis on the administration days and up to 1 day thereafter.

In the males treated with **350/225/200 U Allogenic APOSEC™/kg b.w.**, spleens were enlarged in males no. 23 and 25 (scheduled sacrifice), for which a microscopic correlate (follicular hyperplasia) was made for animal no. 23 only. Enlarged axillary lymph nodes were observed for male no. 13 treated with **35 U Allogenic APOSEC™/kg b.w.** and for male no. 25 (high dose group 4) (scheduled sacrifice), for which microscopic correlates were seen in animal nos. 13 and 25 (medullary hyperplasia). No further test item-related changes were noted at histopathological examination.

All effects observed are considered to be related to the pronounced vasodilating effects.

No test item-influence was observed on the body weight and body weight gain, the food and drinking water consumption, the heart rate and the electrical complexes, the blood pressure, the haematological, clinical chemistry and urinary parameters, the eyes, optic region and auditory acuity, the relative and absolute organ weights, and the myeloid:erythroid ratio at any dose level.

No test item-related changes were noted during or at the end of the 2-week treatment-free recovery period (groups 1 and 4).

In conclusion, intravenous treatment twice weekly for 2 weeks results in an experimental NOAEL of **200 U Allogenic APOSEC™/kg b.w.**



Dr. phil. Jost Leuschner
Study Director



Date

2. GENERAL INFORMATION

2.1 Aim of study

The aim of the study was to obtain information on the potential toxicity, including the local tolerance of Allogenic APOSEC™ given twice weekly by intravenous infusion to Cynomolgus monkeys for 2 weeks and to assess the reversibility of any effect after a 2-week recovery period.

2.2 Duration of study

- 4 adaptation weeks for female animals and male animals no. 33 and 34
- 5 adaptation weeks for male animals (except nos. 33 and 34)
- 2 treatment weeks
- 2 recovery weeks for selected animals

2.3 Test item

Designation	Allogenic APOSEC™
Batch nos.	a) A000918399109 b) A000918399110 c) A000918399111 d) A000918399112 e) A000918399113 f) A000918399115 g) A000918399116 h) A000918399117 i) A000918399118
Receipt nos.	a) 67582 b) 67583 c) 67584 d) 67585 e) 67586 f) 67587 g) 67588 h) 67589 i) 67590
Date of receipts	a-i) 08 February 2019
Characteristics	Lyophilisate
Storage conditions	At $\leq -80^{\circ}\text{C}$
Stability	Stability at -80°C at least 3 months after lyophilisation.

Content Each of the 100 mL glass bottles contains 20 mL lyophilised APOSEC™.
See the 'Certificates of Analysis' in [Appendix 1](#) for further details.

Retention sample (receipt no. 67582) Stored in **LPT**'s archives.

2.4 Identification of test item

After receipt at **LPT**, the test item was inspected (see the following text table). Batch number, amount, and characteristics (consistency and form) were determined and compared with information given by the Sponsor. An identification sheet was filed with the raw data.

Text table 2-1: Identification of test item

Test item	Parameter	LPT identification	Sponsor identification [#]
Allogenic APOSEC™	consistency form	solid pellet/powder	not specified lyophilisate

[#] According to the Study Plan.

No further identification was performed by **LPT**.

2.5 Sponsor / Test Facility / Responsible personnel

Sponsor APOSCIENCE AG
Dresdner Str. 87/A 21
1200 Vienna
Austria

Sponsor's contact Dr. Silvio Wuschko
Phone: +43 664 885 893 54
E-mail: acc_safety.research@gmx.at

Test Facility **LPT** Laboratory of Pharmacology
and Toxicology GmbH & Co. KG
Redderweg 8
21147 Hamburg
Germany
Phone: +49 40 70 20 20
Fax: +49 40 70 20 22 60
E-mail: LPT@LPT-Hamburg.de

Branch Facility **LPT**, Oldendorfer Straße 41
21629 Neu Wulmstorf-Mienenbüttel
Germany

Study Director	Dr. phil. Jost Leuschner LPT , Redderweg 8, 21147 Hamburg Germany
Deputy Study Director	Dr. rer. nat. Jörg Haferkorn
Test Facility Management	Dr. rer. nat. Andreas Winkler
Animal husbandry / Study conduct	Anett Burchardt
Haematology / Clinical chemistry / Blood sampling	Dr. rer. nat. Jan Stien
Veterinarian / Macropathology	Dr. med. vet. Matthias Wölm / Dipl. vet. med. Olga Batura
Statistics	Dipl. Biol. Jens Köpcke
Leading Quality Assurance Unit (LQAU)	Dr. med. vet. habil. Karim R. Sultan E-mail: QAU@LPT-Hamburg.de

2.6 Test Site for histopathological evaluation

Test Site (TS)	Global Pathology Support B.V. (GPS B.V.) Benoordenhoutseweg 23 2596 BA The Hague The Netherlands
Principal Investigator (PI)	Dr. R.J.M.M. Thoolen, PhD Board Certified Toxicologic Pathologist, CRP/TP Global Pathology Support B.V. (GPS B.V.) Benoordenhoutseweg 23 2596 BA The Hague The Netherlands Phone: +31 70 3142404 E-mail: bob.thoolen@gpstoxpath.com
Head of Test Site (HTS)	Dr. R.J.M.M. Thoolen, PhD
Test Site Quality Assurance Unit (TSQAU)	N. Tirtodikromo Phone: +31 70 3142404 E-mail: suzy.tirtodikromo@gpstoxpath.com
Test Site Reference No.	528

2.7 Rules and regulations

The study was performed in compliance with the 'Good Laboratory Practice' Regulations (see the 'Statement of Compliance' on [page 5](#) and the enclosed 'GLP Certificate of the Test Facility LPT' in [Appendix 4](#).

The study design was based on the following guidelines:

- ICH Guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals, (EMA/CPMP/ICH/286/1995) European Medicines Agency, June 2009,
- EMA guideline on Repeated Dose Toxicity (CPMP/SWP/1042/99, Rev. 1 Corr, 01 September 2010),
- Guideline on repeated dose toxicity, Committee for Human Medicinal Products (CPMP/ICH/300/95 Rev 1), European Medicines Agency, 18 March 2010,
- ICH guideline S3A on Toxicokinetics: A Guidance for Assessing Systemic Exposure in Toxicology Studies (CPMP/ICH/384/95, June 1995).

2.8 Multi-Site regulations

The Test Site followed its own SOPs and provided a Phase Report that was integrated in in the Study Report.

As details regarding the histopathological examination are standardized and already summarized in Study Plan amendment no. 3, a separate Phase Plan issued by GPS was not required.

The histopathology phase of the Study Plan, histopathology study procedures, and the histopathology phase of the Study Report were inspected by the Global Pathology Support Quality Assurance Unit. The Principal Investigator informed TSQAU when the histopathology was performed. In case LQAU requested to perform a study audit, GPS would have cooperated.

The Principal Investigator was responsible for compliance with his national GLP regulations for any work performed at his Test Site as well as for all data sent to LPT for inclusion in the Study Report. Any Phase Report provided by the PI includes a statement of GLP compliance signed by the PI and a Quality Assurance Statement signed by an authorized representative of the TSQAU. Archiving procedures for all work performed at the Test Site are described in the Phase Report. The Phase Report is given in [Appendix 3](#).

The PI informed his TSQAU and contacted the Study Director in case of unexpected findings or occurrences at his Test Site. The TSQAU reported these findings to the LQAU.

The TSQAU inspected the work at its Test Site as well as the Phase Report according to its SOPs. The TSQAU reported any inspections results in writing to the PI, Test Site Management, Study Director, Test Facility Management, and LQAU. Critical findings were reported immediately; other non-critical findings were communicated in due time.

2.9 Archiving and storage

2.9.1 Archiving and storage at the Test Facility

Archives of data and specimens

During the study:

All data generated at the Branch Facility:

In the depot

LPT, Oldendorfer Straße 41
21629 Neu Wulmstorf-Mienenbüttel
Germany

All remaining data:

In the depot

LPT, Redderweg 8
21147 Hamburg
Germany

After reporting:

The Final Report and Amendment no. 1 to Final Report will be archived by the Sponsor.

A copy of the final report and the Amendment no. 1 to final report as well as all specimens, written raw data and other study-related documents listed in the Study Plan section 'Study Materials to be Archived' are stored in the **LPT** archives.

Duration of storage

In compliance with the periods laid down in the German 'Chemikaliengesetz' [Chemicals Act], current edition, for 15 years.

All archived study materials will be destroyed after the 15-year GLP storage period in agreement with the Sponsor.

However, if the Sponsor cannot be reached, the archived materials will be destroyed without notice one (1) year after the required archiving period.

Storage of samples	Three months after issuance of the Final Study Report, any samples or aliquots not listed in the Study Plan section 'Study Materials to be Archived', and still remaining at LPT, will be destroyed unless the Sponsor requests otherwise.
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2.9.2 Archiving and storage at the Test Site

All slides and/or specimens will be transferred to the Test Facility after completion of the histopathology phase of the study. All raw data and relevant documentation and the original report appendix generated at the Test Site for histopathology evaluation will be archived by the Test Site under the Test Site reference number for 3 years. Thereafter, the data will be sent to the Test Facility for storage for the remainder of the legal archiving period required by the local authorities. The Principal Investigator will inform the Study Director of the time when the documentation was archived.

2.10 Standard Operating Procedures and staff safety

Standard Operating Procedures (SOPs)

All work was carried out according to Standard Operating Procedures which were followed for all stages of the study. The SOPs could be inspected in those divisions, which were engaged in the study and in the Quality Assurance Unit (QAU).

Staff safety

The standard safety precautions operating within the department were applied to this study.

2.11 Study dates

Code number of the study
in the raw data

35015

Start of study

Date of Study Plan

05 February 2019

Study Plan amendments

No. 1, dated 13 February 2019
No. 2, dated 20 February 2019
No. 3, dated 13 March 2019
No. 4, dated 04 April 2019
No. 5, dated 09 August 2019
No. 6, dated 11 November 2019

First Administration	Male animals (except nos. 33 and 34):	11 February 2019
	Males no. 33 and 34:	18 February 2019
	Female animals:	18 February 2019

Study termination

Termination of in-life phase	<u>Main study animals</u>	
	Male animals:	22 February 2019
	Female animals:	01 March 2019

Recovery animals

Male animals (except nos. 33 and 34):	08 March 2019
Males no. 33 and 34:	15 March 2019
Female animals:	15 March 2019

Date of Final Report	11 November 2019
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Date of Amendment No. 1 to Final Report	24 August 2020
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2.12 Study Plan deviations

The study was conducted in accordance with the Study Plan and 6 Study Plan amendments agreed upon. There was no major deviation from the Study Plan and the Study Plan amendments. However, the following minor deviations were noted:

- Partly, a paper speed of 25 mm/second instead of 50 mm/second as stated in the Study Plan was used inadvertently during ECG measurements for female no. 20, 5 min. after the end of the infusion on test day 11.
- The first dose reduction for group 4 was carried out on 18 February 2019. The Study Plan Amendment No. 2 was issued and signed 2 days later.

These minor deviations that were not reflected by a Study Plan amendment did not affect the validity and integrity of the scientific results obtained during the study.

3. MATERIAL AND METHODS

3.1 Materials

3.1.1 Animals

Captive-bred male and female *Cynomolgus* monkeys ordered from Roberto C. Hartelust, 5001 CD Tilburg, the Netherlands, were selected for entry into this study. Prior to delivery to **LPT**, the animals were kept in EC quarantine at the supplier's facilities in the Netherlands. Documentation (*i.e.* individual health certificates of the Chinese breeder with vaccination dates, tattoo number and tattoo number of the parents, certificate of health of the Dutch authorities at the release of the monkeys from EC quarantine, certificate of fitness by the Dutch authority for transport from the Netherlands to Germany) was provided by the supplier. Upon arrival at **LPT**, the animals were subjected to a veterinary examination, which included a detailed evaluation of each animal's condition. The animals were allowed to acclimatise to the **LPT** primate toxicology accommodation for a period of 4 or 5 weeks before the commencement of the study. All animals were dewormed by **LPT**.

A total of 34 animals were selected from a pool of 36 animals for entry into the study based on the results of a satisfactory preliminary health screening (including haematological examinations, clinical chemistry and urinalysis).

Species / Strain	Monkey / <i>Cynomolgus</i> (<i>Macaca fascicularis</i>) - treatment naïve -
Breeder (country of origin)	Purpose-bred in the People's Republic of China; captive-bred
Imported through	Roberto C. Hartelust 5001 CD Tilburg The Netherlands
Number and sex of animals	34 (18 male and 16 female) animals <u>Main study animals</u> 26 animals (14 males and 12 females); 3 animals/sex and group for groups 1 to 3 5 male and 3 female animals for group 4 <u>Recovery animals</u> 8 animals (4 males and 4 females); 2 animals/sex for groups 1 and 4. In addition, 2 female spare animals were available for possible replacement during the acclimatisation period.

Body weight

(at 1st administration)

Males: 2.3 kg - 2.6 kg

Females: 2.1 kg - 2.4 kg

Age

(at 1st administration)

Males: 28 - 34 months

Females: 29 - 34 months

Selection of species

Selected to comply with regulatory requirements for testing in a non-rodent animal species.

Identification of animals

By chest tattoo (see [Text table 3-1](#)) and cage label. The animal cages were labelled with study number, animal number, sex and treatment group.

Adaptation period

Male animals (except nos. 33 and 34)

5 adaptation weeks

Female animals and male animals no. 33 and 34

4 adaptation weeks

Text table 3-1: Animal allocation and tattoo numbers of male and female animals

Male animals			Female animals		
Group	Animal	Tattoo	Group	Animal	Tattoo
1	1	1610061	1	6	1606110
1	2	1608113	1	7	1609064
1	3	1608145	1	8	1605090
1	4 [#]	1606207	1	9 [#]	1609036
1	5 [#]	1607069	1	10 [#]	1609022
2	11	1604055	2	14	1605094
2	12	1607249	2	15	1610108
2	13	1607045	2	16	1609012
3	17	1610039	3	20	1606010
3	18	1610053	3	21	1609336
3	19	1608075	3	22	1609260
4	23	1607065	4	28	1609042
4	24	1610035	4	29	1610044
4	25	1607031	4	30	1609050
4	26	1606149	4	31 [#]	1606668
4	27	1610043	4	32 [#]	1608176
4	33 [#]	1609155			
4	34 [#]	1608159			

recovery animals

3.1.2 Housing and feeding

3.1.2.1 Diet

Commercial diet ssniff® Pri V3994 (ssniff Spezialdiäten GmbH, 59494 Soest, Germany, see [Appendix 2](#) 'Composition of the Diet') served as food. A total amount of 60 g/kg b.w. of this food was offered daily to each monkey.

Approximately 100 g were offered at 12.00 noon ('morning feeding'), the second part of the feeding started at approximately 3.00 p.m.

On Tuesdays and Thursdays approximately 70 g apples and bananas were offered to each animal.

The residue was removed the next morning at about 7.00 a.m. and weighed.

At regular intervals (at least twice a year) the food is analysed¹ for contaminants by LUFA-ITL² (see [Appendix 2](#) 'Limitation for Contaminants in the Diet'). Certificates of analysis of the composition and for contaminants were provided by the manufacturer and are included in the raw data.

3.1.2.2 Drinking water

Tap water of drinking water quality was offered *ad libitum*.

Samples of drinking water are taken twice a year by the Wasserbeschaffungsverband Harburg, 21220 Seevetal, Germany, and are analysed according to the 'Deutsche Trinkwasserverordnung'³ [German Regulations on drinking water 2001] (see [Appendix 2](#) 'Limitation for Contaminants in the Drinking Water').

In addition, drinking water samples taken at LPT are analysed by LUFA-ITL once a year for bacteriological investigations according to the 'Deutsche Trinkwasserverordnung 2001, Anlage 1' [German Regulations on drinking water 2001, Addendum 1].

¹ EPA/USA, Proposed Health Effects Test Standards for Toxic Substances Control Act Test Rules, Federal Register 44, 27334 - 27375, May 1979.

² Landwirtschaftliche Untersuchungs- und Forschungsanstalt, Institut für Tiergesundheit und Lebensmittelqualität GmbH, 24107 Kiel, Germany.

³ Deutsche Trinkwasserverordnung 2001 [German Regulations on Drinking Water 2001, Addendum 1], Version from 02 August 2013, revised on 18 November 2015.

3.1.2.3 Housing

The monkeys were housed in V₂A steel cages with a size of up to 1545 mm x 1500 mm x 2475 mm in collectives of up to three animals, and only one treatment group per collective. Males and females were housed separately.

The room temperature was maintained at 23°C ± 3°C (maximum range) and the relative humidity at 60% ± 20% (maximum range). Deviations from the maximum range caused for example during cleaning procedures are dealt with in SOPs.

Rooms were alternately lit and darkened in a 12-hour dark/12-hour light cycle.

3.1.3 Preparation of the administration formulations

The administration solutions were freshly prepared on each administration day.

The allogenic APOSEC™ was reconstituted and diluted with sterile 0.9% aqueous NaCl solution to the appropriate concentrations as described in [Text table 3-2](#).

The APOSEC™ drug substance was produced from the supernatant of standardized cultures of PBMCs with a cell density of 25x10⁶ PBMCs/mL.

Remainders of the administration solutions were stored at +2°C to +8°C for a maximum of 14 days after preparation. These remainders were stored and used for administration under sterile conditions within the stability period.

Text table 3-2: Dose levels and administration solutions

Dose level [Units/kg]	Content per test item vial [Units]	Volume of 0.9% NaCl to be added per Vial [mL/vial]	Resulting concentration of the administration solution [Units/mL]	Administration volume [mL/kg b.w.]	Infusion speed [mL/min/kg]
1st dose of male animals (except nos. 33 and 34) (i.e. on 11 February 2019)					
35	500	71.43	7	5	0.167
110	500	22.73	22	5	0.167
350	500	7.14	70	5	0.167
2nd and 3rd dose of male animals (except nos. 33 and 34) and 1st dose of all female animals and male animals no. 33 and 34 (i.e. on 14 and 18 February 2019)					
35	500	214.59	2.33	15	0.5
110	500	68.49	7.30	15	0.5
350	500	21.45	23.31	15	0.5
225 [#]	500	33.33	15.00	15	0.5
4th dose of male animals (except nos. 33 and 34) and 2nd to 4th infusion of all female animals and male animals no. 33 and 34 (i.e. as of 21 February 2019)					
35	500	214.59	2.33	15	0.375
110	500	68.49	7.30	15	0.375
200	500	37.50	13.33	15	0.375
# dose reduction as of 18 February 2019					

3.1.4 Administration

Route of administration	Intravenous infusion into the <i>vena cephalica</i> of the left or right arm
Frequency of administration	Two times per week for 2 test weeks; in total 4 infusions/animal (on test days 1, 4, 8 and 11)
Infusion speed	<u>Male animals (except nos. 33 and 34)</u> 1 st Dose/30 minutes, 0.167 mL/min/kg b.w. 2 nd Dose/30 minutes, 0.5 mL/min/kg b.w. 3 rd Dose/30 minutes, 0.5 mL/min/kg b.w. 4 th Dose/40 minutes, 0.375 mL/min/kg b.w. <u>Female animals and male animals no. 33 and 34</u> 1 st Dose/30 minutes, 0.5 mL/min/kg b.w. 2 nd Dose/40 minutes, 0.375 mL/min/kg b.w. 3 rd Dose/40 minutes, 0.375 mL/min/kg b.w. 4 th Dose/40 minutes, 0.375 mL/min/kg b.w.
Negative control and diluent for reconstitution	sterile 0.9% NaCl solution (provided by LPT , batch nos. 183668161 and 1815293001, B. Braun Melsungen AG, Melsungen, Germany)
Dose levels	Group 1: Control (saline), twice weekly Group 2: 35 U/kg b.w., twice weekly Group 3: 110 U/kg b.w., twice weekly Group 4: 350/225/200 U/kg b.w., twice weekly Due to the poor health condition of the male animals of group 4, the initial dose of 350 U/kg b.w. was reduced to 225 U/kg b.w. as of test day 8 for the male animals (except nos. 33 and 34) or on test day 1 for all female animals and male animals no. 33 and 34 (<i>i.e.</i> 18 February 2019), and further reduced to 200 U/kg b.w. on test day 11 for the male animals (except nos. 33 and 34) or on test day 4 for all female animals and male animals no. 33 and 34 (<i>i.e.</i> 21 February 2019), respectively, as the effect observed was thought to have been caused by exaggerated pharmacodynamics effects, the test item being a pronounced vasodilator.
Administration volumes	<u>Male animals (except nos. 33 and 34)</u> 1 st Dose: 5 mL/kg b.w. 2 nd to 4 th Dose: 15 mL/kg b.w.

Female animals and male animals no. 33 and 34

1st to 4th Dose: 15 mL/kg b.w.

Due to the moribund condition after the first infusion, 2 male high dose animals were sacrificed prematurely. In order to reduce the risk of a vasodilatory effect, the administration volume was increased thereafter.

Selection of route of administration

According to clinical use. The intravenous route is the anticipated route for human exposure to the test item.

The animals were conditioned to the restraining chair during the week before dosing was started.

The test item was administered intravenously at the appropriate administration volumes.

The control group animals (group 1) received the diluent in the same way.

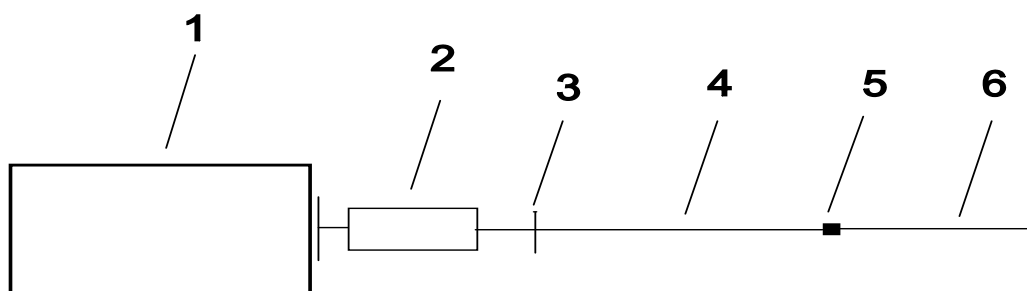
The amounts of test item administered were adjusted to each animal's current body weight on each administration day.

Technical specifications of the infusion pump used

The microprocessor-controlled syringe pump used had the following technical specifications:

- Flow range: 0.05 mL/h to 4200 mL/h
- Accuracy: $\pm < 3\%$
- Advance per microstep of 0.165 micrometres

The following set was employed:



- 1 Infusion pump 540220 (TSE Systems)
- 2 Disposable Perfusor syringe (50 mL, two 50 mL syringes in parallel, if necessary), Becton Dickinson, reference no. 300 865
- 3 Adapter
- 4 Perfusor tubing (1.5 metres); B. BRAUN MELSUNGEN AG, article no. 872296/0
- 5 Integrated luer
- 6 Vasofix 20G (B. BRAUN MELSUNGEN AG, article no. 4268113B)

3.1.5 Administration formulation analysis

No administration formulation analysis was carried out.

3.1.6 Dose selection

The dose levels for this study have been selected by the Sponsor.

3.1.7 Group size and dose levels

The animals were allocated to the test groups by body weight using a Provantis®-generated randomisation.

Text table 3-3: Group size, dose levels and administration volumes

Group	Allogenic APOSEC™ dose [Units/kg b.w.]	No. and sex of animals MS + RP	Animal number	
			MS	RP
1	0 (saline control)	3 + 2 m 3 + 2 f	1 - 3 6 - 8	4, 5 9, 10
2	35	3 + 0 m 3 + 0 f	11 - 13 14 - 16	None
3	110	3 + 0 m 3 + 0 f	17 - 19 20 - 22	None
4	350/225/200 [#]	5 + 2 m 3 + 2 f	23 - 27 28 - 30	33, 34 31, 32

Due to the poor health condition of the male animals of group 4, the initial dose of 350 U/kg b.w. was reduced to 225 U/kg b.w. as of test day 8 for the male animals (except nos. 33 and 34) or on test day 1 for all female animals and male animals no. 33 and 34 (*i.e.* 18 February 2019), and further reduced to 200 U/kg b.w. on test day 11 for the male animals (except nos. 33 and 34) or on test day 4 for all female animals and male animals no. 33 and 34 (*i.e.* 21 February 2019), respectively, as the effect observed was thought to have been caused by exaggerated pharmacodynamics effects, the test item being a pronounced vasodilator.

MS: Main study

RP: Recovery period

m: male

f: female

3.2 Observations

Dated and signed records of all activities relating to the day-to-day running and maintenance of the study within the animal unit as well as to the group observations and examinations outlined in the Study Plan were recorded in the appropriate documentation. In addition, observations related to individual animals were made throughout the study and recorded.

The observations made during the course of the study are described in the following.

3.2.1 Clinical signs

The animals were observed individually before and after dosing at each time of dosing for any signs of behavioural changes, reaction to treatment or illness.

In addition, animals were checked regularly throughout the working day from 7.00 a.m. to 4.00 p.m. by cage-side observations. On Saturdays and Sundays, animals were checked regularly from 8.00 a.m. to 12.00 noon with a final check performed at approximately 4.00 p.m.

Cage-side observations included skin/fur, eyes, mucous membranes, respiratory and circulatory systems, somatomotor activity and behaviour patterns. The onset, intensity, and duration of any signs observed were recorded.

Dated and signed records of appearance, change, and disappearance of clinical signs of individual animals were maintained on clinical history sheets.

Special attention was paid to the local tolerance of the test item at the infusion sites.

3.2.2 Mortality

Checks were made early in the morning and again in the afternoon of each working day to look for dead or moribund animals. This allowed post mortem examination to be carried out during the working period of that day. On Saturdays and Sundays a similar procedure was followed with a final check at approximately 4.00 p.m.

Premortal symptoms were recorded in detail; as soon as possible after exitus, a post mortem examination was performed as described in Section 3.3. No blood sampling was performed for the prematurely sacrificed animals (males nos. 26 and 27) for laboratory examinations (see Section 3.2.7).

3.2.3 Body weight

The body weight was recorded at group allocation, twice weekly (before each administration) during the in-life period, on the day of dissection and weekly during the recovery period.

3.2.4 Food and drinking water consumption

The quantity of food left by the animals in each cage was removed and recorded on a daily basis throughout the experimental period.

A mean amount consumed per animal was calculated by dividing the amount of food removed from the cage by the number of animals housed in the cage. The residue was discarded. The report includes weekly mean calculated values of the individual animals.

Drinking water consumption was monitored daily by visual appraisal throughout the study.

3.2.5 Electrocardiography

ECG recordings were carried out in the animals at the following times:

- On test days 1 and 11:
Predose (baseline) and 5 min after completion of infusion. All surviving main study and recovery animals.
- At the end of the recovery period:
At the same times as measured during the administration period. All 8 recovery animals

Recordings were made using the standard limb leads I, II, and III, augmented limb leads aVR, aVL, and aVF. A standardisation of 10 mm = 1 mV was used and a paper speed of 50 mm/second⁴. The recordings were carried out for 30 seconds which is a standard for monkeys.

The recordings were examined visually for any abnormalities of the electrical complexes. In addition, the heart rate was recorded.

⁴ Inadvertently, a paper speed of 25 mm/second instead of 50 mm/second as stated in the Study Plan was partly used during ECG measurements for female no. 20, 5 min. after the end of the infusion on test day 11.

The following parameters were evaluated⁵:

Heart rate	(beats/min)
P segment	(ms)
PQ interval	(ms)
QRS interval	(ms)
QT interval	(ms)

The QTc-values were calculated according to the following formula:

Bazett-formula

$$QTc = \frac{QT \text{ [sec]}}{\sqrt{(R - R \text{ distance [sec]})}}$$

3.2.6 Blood pressure

The peripheral arterial systolic and diastolic blood pressure was measured at the following times:

- On test days 1 and 11:
After completion of each ECG recording. All surviving main study and recovery animals.
- At the end of the recovery period:
After completion of each ECG recording. All 8 recovery animals

The peripheral arterial systolic and diastolic blood pressure was measured on the shaven tail of the conscious animal using a blood pressure monitor (HDO - Science Monitor)⁶.

The mean blood pressure was calculated.

3.2.7 Laboratory examinations

Blood samples were taken from the *vena cephalica* or *saphena magna* from animals fasted overnight.

The blood samples were collected into tubes as follows:

EDTA anticoagulant (whole blood)for haematological examinations and ESR
Citrate anticoagulant (plasma)..... for coagulation tests
Serum..... for clinical chemistry tests

⁵ CARDIOVIT AT-1, Schiller, Ottobrunn, Germany.

⁶ S + B medVet GmbH, 07407 Rudolstadt.

Blood samples for the determination of the haematological, coagulation and clinical chemistry parameters listed in the text tables below were taken for the assigned animals at the following occasions:

- Prior to the first dosing: All 36 pool animals
- At the end of the treatment period: All surviving 32 study animals
- At the end of the recovery period: All 8 recovery animals

3.2.7.1 Haematology

The following haematological parameters were determined for the assigned animals at the occasions listed above:

Text table 3-4: Haematological parameters

Parameter	Unit	Instrument
Haemoglobin content (HGB)	mmol/L blood	ADVIA™ 120 Siemens Diagnostics GmbH 35463 Fernwald Germany
Erythrocytes (RBC)	$10^6/\mu\text{L}$ blood	
Leucocytes (WBC)	$10^3/\mu\text{L}$ blood	
Reticulocytes (Reti)	% of the erythrocytes	
Platelets (PLT)	$10^3/\mu\text{L}$ blood	
Haematocrit value (HCT)	%	
Differential blood count (relative) [#]	%	
Differential blood count (absolute) [#]	$10^3/\mu\text{L}$ blood	
Mean corpuscular volume (MCV)	fL	
Mean corpuscular haemoglobin (MCH)	fmol	
Mean corpuscular haemoglobin concentration (MCHC)	mmol/L blood	

[#] Neutrophilic, eosinophilic and basophilic granulocytes, lymphocytes and monocytes. Large unstained cells were simultaneously quantified during measurement of the differential blood count.

Following the haematological examinations using the ADVIA system, blood smears were prepared from all samples, dried and stained for possible histopathological examinations in case of pathological findings (refer to [Section 3.3.3](#)).

3.2.7.2 Coagulation and ESR

The following coagulation parameters were determined for the assigned animals at the occasions listed before:

Text table 3-5: Coagulation parameters and ESR

Parameter	Unit	Instrument
Prothrombin time (PT)	sec	Amax Destiny Plus™ Tcoag Deutschland GmbH 32657 Lemgo, Germany
Activated partial thromboplastin time (aPTT)	sec	
Erythrocyte sedimentation rate (ESR)	mm/one hour	DISPETTE® (ICSH Reference Method) Guest Scientific AG 6330 Cham (Zug), Switzerland

3.2.7.3 Clinical chemistry

The following clinical chemistry parameters were determined for the assigned animals at the times listed before:

Text table 3-6: Clinical chemistry parameters

Parameter	Unit	Instrument / Method
Bile acids	μmol/L serum	KONELAB 30i Thermo Fisher Scientific, 63303 Dreieich, Germany
Bilirubin (total)	μmol/L serum	
Cholesterol (total)	mmol/L serum	
Creatinine	μmol/L serum	
Glucose	mmol/L serum	
Phosphate (inorganic)	mmol/L serum	
Protein (total)	g/L serum	
Albumin Globulin ⁷	g/L serum	agarose gel electrophoresis with Hydrasys LC, Sebia GmbH 36043 Fulda, Germany
Albumin/globulin ratio	(non-dimensional)	by calculation
Urea (in blood)	mmol/L serum	KONELAB 30i Thermo Fisher Scientific, 63303 Dreieich, Germany
Triglycerides	mmol/L serum	
Calcium	mmol/L serum	

⁷ Determination of alpha1-, alpha2-, beta- and gamma-globulin.

Text table 3-10: Clinical chemistry parameters (continued)

Parameter	Unit	Instrument / Method
Chloride	mmol/L serum	KONELAB 30i Thermo Fisher Scientific, 63303 Dreieich, Germany
Potassium	mmol/L serum	
Sodium	mmol/L serum	
Alanine aminotransferase (ALAT)	U/L serum	
Alkaline phosphatase (aP)	U/L serum	
Aspartate aminotransferase (ASAT)	U/L serum	
Lactate dehydrogenase (LDH)	U/L serum	
Gamma-glutamyl-transferase (Gamma-GT)	U/L serum	

3.2.7.4 Urinalysis

The urine samples were collected in the morning of the respective test day for 3 hours from animals fasted overnight. At start of the respective sampling period the animals received 50 mL tap water/kg body weight by gavage.

The following sampling times were employed and the parameters listed below were determined:

- Prior to the first administration: All animals including reserve animals
- At the end of the treatment period: All 32 surviving study animals
- At the end of the recovery period: All 8 recovery animals

The following parameters were measured using the methods given below:

Text table 3-7: Urinary parameters

Parameter	Unit	Instrument
pH	(non-dimensional)	Using a digital pH meter type WTW InoLab pH 720
Specific gravity	g/mL urine	Using Kern Refractometer, type ORA 2PA Sample compared with water (nominal value of 1.000)

The following tests were performed using semi-quantitative / qualitative indicators (Combur 9® Test, Roche Diagnostics GmbH, Mannheim, Germany) of analyte concentration:

Text table 3-8: Analytes of qualitative urinalysis

Parameter	Reporting convention					
	Unit	Semi-quantitative determination level				
Protein	g/L	neg	0.3	1	5	
Glucose	mmol/L	normal	2.8	5.5	17	55
Bilirubin	-	neg	+	++	+++	
Urobilinogen	μmol/L	normal	17	70	140	200
Ketones	-	neg	+	++	+++	
Haemoglobin (Hb, approx. values)	ery/μL	neg	10	25	50	250
Nitrite	-	neg	pos			

neg = negative

pos = positive

ery = erythrocyte count

+ 'Small amount' of analyte

++ 'Moderate amount' of analyte

+++ 'Large amount' of analyte

A microscopic examination of urine samples was carried out by centrifuging samples and spreading the resulting deposit on a microscope slide. The deposit was examined for the presence of the parameters listed below:

Text table 3-9: Urinary components

Parameter
Epithelial cells
Leucocytes
Erythrocytes
Organisms
Further constituents (<i>i.e.</i> sperm, casts)
Crystalluria

The frequency of the above parameters in the centrifugal deposit was recorded as follows:

0	None found in any field examined
+	Few in some fields examined
++	Few in all fields examined
+++	Many in all fields examined

The colour and the turbidity of the urine were examined visually.

3.2.8 Ophthalmological and auditory examinations

Examinations were performed on all animals before first dosing, at the end of the treatment period and at the end of the recovery period.

The eyes were examined with a HEINE ophthalmoscope.

After examination of the pupillary reflex, mydriasis was produced by instillation of STULLIN^{®8} eye drops onto the cornea.

The following ocular structures were then examined:

- Adnexa oculi (*i.e.* lids, lacrimal apparatus), conjunctiva
- Cornea, anterior chamber
- Lens, vitreous body, fundus (retina, optic disc)

The auditory acuity was checked with a simple noise test.

⁸ Ankerpharm GmbH, 07407 Rudolstadt, Germany.

3.3 Pathology and histopathology

3.3.1 Necropsy

On test day 12 (approx. 24 h after the last administration) the main study animals were dissected following a randomisation scheme. Necropsy of all animals allocated to the recovery period was performed on test day 26.

The animals were sacrificed (150 mg Pentobarbital/kg b.w., i.v.) and exsanguinated by carotid dissection, weighed, dissected and inspected macroscopically under the direction of a pathologist.

For the two animals which had to be sacrificed prematurely, the examinations were performed after sacrifice.

All superficial tissues were examined visually and by palpation and the cranial roof was removed to allow observation of the brain, pituitary gland and cranial nerves. After ventral midline incision and skin reflection all subcutaneous tissues were examined. The condition of the *thoracic viscera* was noted with due attention to the thymus, lymph nodes and heart.

The *abdominal viscera* were examined before and after removal, the urinary bladder was examined externally and by palpation. The gastro-intestinal tract was examined as a whole and the stomach and caecum were incised and examined. The lungs were removed and all pleural surfaces were examined under suitable illumination. The liver and the kidneys were examined. Any abnormalities in the appearance and size of the gonads, adrenal glands, uterus, intraabdominal lymph nodes and accessory reproductive organs was recorded.

The weights of the organs of all animals listed in the following text table were determined before fixation (the pituitary was shortly fixed before weighing):

Text table 3-10: Weighed organs

Weighed organs	
Adrenal gland (2)	Lymph node (one axillary)
Brain	Ovary (2)
Epididymides (2)	Pituitary
Heart	Spleen
Kidney (2)	Testicle (2)
Liver	Thymus
Lungs	Thyroid (two, incl. parathyroids)
Lymph node (one cervical)	Uterus

The paired organs (adrenal glands, gonads and kidneys) were identified as left or right and weighed individually.

Organ weights of the animals which had to be sacrificed prematurely were recorded but not included into the mean value comparison.

3.3.2 Organ preservation

The following tissue samples (or the whole organ) from all animals (including the two prematurely sacrificed animals) were preserved in neutral buffered 10% formalin. The eyes and lacrimal glands were preserved in Davidson's solution and the testicles including epididymides in modified Davidson's solution for optimum fixation:

Text table 3-11: Tissues collected for preservation / Histopathology

Tissues collected for preservation / Histopathology	
Adrenal gland (2)	Muscle (skeletal, leg)
Aorta abdominalis	Nerve (sciatic)
Bone (os femoris with joint)	Oesophagus
Bone marrow (os femoris)	Ovary (2)
Brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts)	Pancreas
Caecum	Pituitary
Epididymis (2)	Prostate
Eye with optic nerve (2)	Salivary glands (mandibular, parotid, sublingual)
Gall bladder	Seminal vesicle
Gross lesions, if present	Skin (left flank)
Heart (left and right ventricle, septum)	Spinal cord (3 sections)
Infusion site(s); last dosing	Spleen
Intestine, large (colon, rectum)	Sternum
Intestine, small incl. Peyer's patches (duodenum, jejunum, ileum)	Stomach
Kidney and ureter (2)	Testicle (2)
Lacrimal gland (2)	Thymus
Liver (3 sections: left (medial), right (medial) and caudal lobe)	Thyroid (2) (incl. parathyroids)
Lungs (with mainstem bronchi and bronchioles; 3 sections: one through each of three different lobes)	Tissue masses or tumours (including regional lymph nodes), if present
Lymph node (1, axillary)	Tongue (incl. base)
Lymph node (1, cervical)	Trachea (incl. larynx)
Mammary gland	Urinary bladder
	Uterus (incl. cervix and oviducts)
	Vagina

3.3.3 Histotechnique and histopathological examination

The organs listed in [Text table 3-11](#) of all surviving animals and the prematurely sacrificed animals were examined histopathologically after preparation of paraffin sections and haematoxylin-eosin staining.

In addition, frozen sections of the heart, liver, and one kidney were made, stained with Oil Red O and examined microscopically.

Parathyroids were only examined microscopically if identified macroscopically and if in the plane of section, or in case they were noted as grossly enlarged.

The blood smears prepared for the haematological examination (see Section [3.2.7.1](#)) are available for possible examination of pathological changes but will be examined and evaluated only depending on histopathological findings and upon agreement with the Sponsor. No examination was carried out so far.

The histotechnical processing was performed by **LPT**. The slides (labelled with study number, species, animal number, block number) were dispatched to GPS.

The transport of slides for the histopathology work performed by Global Pathology Support to the Test Site was arranged by **LPT**, whereas the return transport to the Test Facility was arranged by GPS.

Histopathology was performed by Dr. R.J.M.M. Thoolen, PhD, Global Pathology Support B.V., Benoordenhoutseweg 23, 2596 BA The Hague, The Netherlands, under Test Site Reference Number 528 according to all relevant GPS SOPs.

All observations upon final assessment were reported per animal and the findings considered relevant for the treatment in an incidence and occurrence table. All microscopic findings were recorded, reported, and archived with the Provantis system.

The report of this phase of the study comprises a description of objective, materials and methods, results (including results of macroscopic and microscopic changes), and conclusions. The unaudited Draft Phase Report was presented electronically to the Study Director for comments/review. Comments were addressed and the Final Draft Phase Report of the study was presented to the TSQAU for auditing. The audited Final Draft Phase Report of the histopathology phase of the study was sent electronically to the Study Director who provided documented approval on the contents of the Phase Report by e-mail to the Principle Investigator.

An original of the final, signed Phase Report was sent (on paper and electronically) to the Study Director. A copy will be archived by Global Pathology Support.

The 'Phase Report on Histopathology' issued by GPS is given in [Appendix 3](#).

3.3.4 Bone marrow

During dissection of all animals, fresh bone marrow was obtained from a suitable rib e.g. the 7th rib (3 air-dried smears per animal) from all animals, and stained according to PAPPENHEIM. The myeloid:erythroid ratio was determined by cell differentiation (counting of 200 nuclei-containing cells) for all animals.

3.4 Statistics

Toxicology and pathology data were captured, as far as possible, using the departmental computerized systems (Provantis® Integrated preclinical software, version 10.2.1, Instem LSS Ltd., Stone, Staffordshire ST15 0SD, United Kingdom). Raw data not fully compatible with the computerized systems were maintained on paper according to appropriate SOPs.

The following comparison was carried out:

The test item-treated groups 2 to 4 were compared to the control group 1.

The following statistical methods were used for the data captured with the Provantis system:

Text table 3-12: Statistical methods

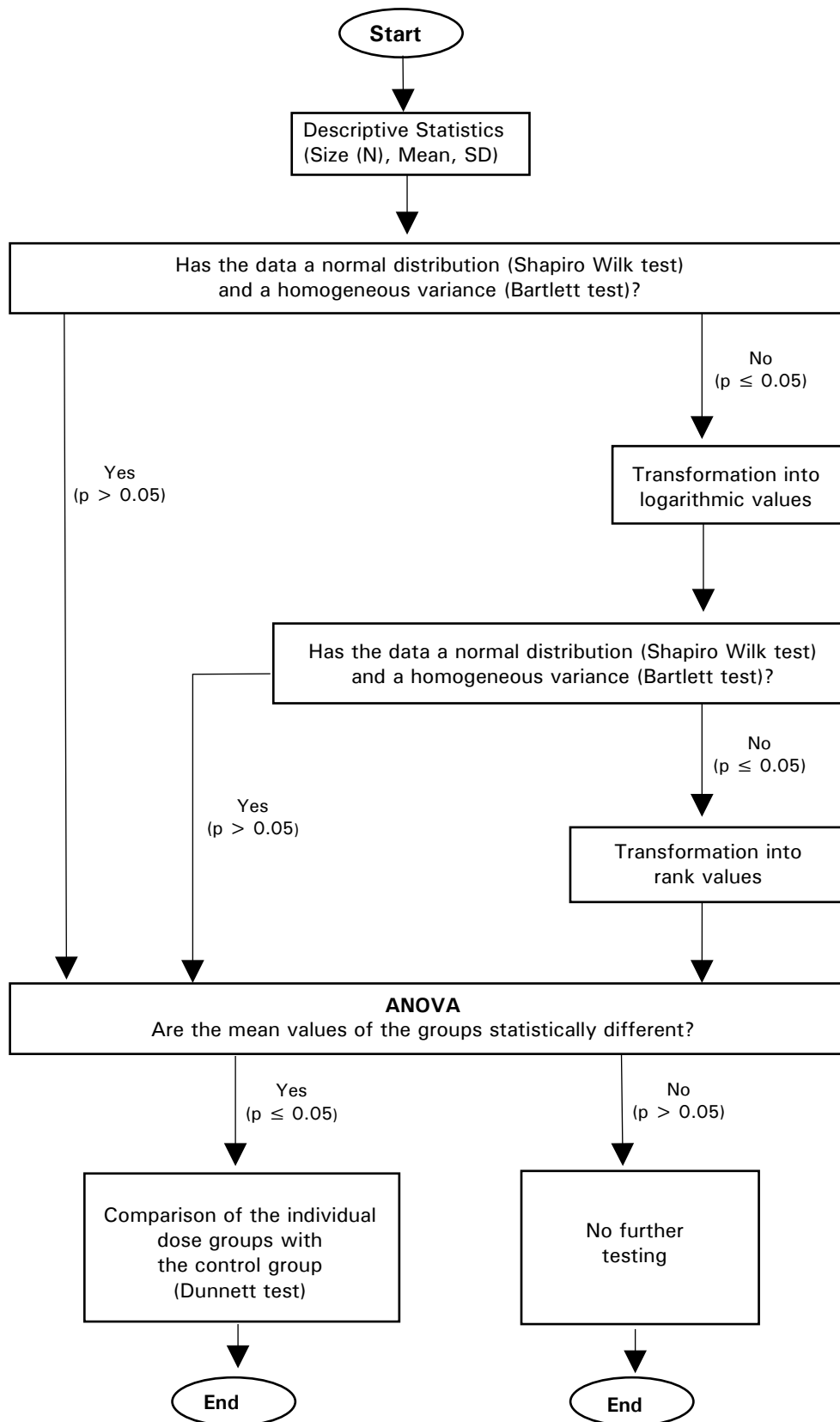
Statistical test	Parameter category
Multiple t-test based on DUNNETT, C. W. New tables for multiple Comparisons with a control <i>Biometrics</i> , 482-491 (Sept 1964)	- Body weight - ECG - Blood pressure - Haematology and coagulation - Clinical chemistry - Urinalysis - Relative and absolute organ weight ($p \leq 0.05$ and $p \leq 0.01$)
χ^2 test	Bone marrow ($p \leq 0.01$)
Exact test of R. A. FISHER	Histology ($p \leq 0.05$)

The statistical evaluation of the parametrical values captured by Provantis was performed as follows (see the decision tree flow chart on the next page):

Homogeneity of variances and normality of distribution were tested using BARTLETT's test and the SHAPIRO-WILKS's test. In case of heterogeneity and/or non-normality of distribution, stepwise transformation of the values into logarithmic or rank values was performed prior to ANOVA. If the ANOVA yielded a significant effect ($p \leq 0.05$), intergroup comparisons with the control group were made by DUNNETT's test (see above).

These statistical procedures were used for all data. Significantly different data are indicated in the text tables of the results section and in the result tables of the tables section of this report.

Flow Chart of Decision Tree of ANOVA and Dunnett's Test Calculation



4. RESULTS

4.1 Local tolerance

Main study / Recovery period (restricted to groups 1 and 4)

The daily visual inspection of the infusion sites did not reveal any test item-related signs of local intolerance reactions in the animals treated intravenously with **35, 110 or 350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks.

During the recovery period, no signs of a local intolerance reactions were noted for the male and female animals previously treated intravenously with **350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks.

Haematoma formation (noted at the daily inspections during the in-life phase) and/or subcutaneous haemorrhagic infusion sites (noted at macroscopic inspection) was observed for several monkeys including the control animals. These macroscopic observations did not show a dose-relationship and were not considered to be test item related, but regarded to be caused by the technical infusion procedure.

The number of animals with haematoma formation at the infusion sites during the in-life phase is given in the text table below:

Text table 4-1: Local intolerance reactions of male and female animals during the in-life period

Haematoma	Group 1: Control		Group 2: 35 U/kg		Group 3: 110 U/kg		Group 4: 350/225/200 U/kg	
	Male	female	male	female	male	female	male	female
Main study	0/5	3/5	0/3	2/3	0/3	1/3	1/7	1/5
Recovery period	0/2	0/2	N/A	N/A	N/A	N/A	0/2	0/2

../..: animals affected / animals examined

N/A: not applicable

The haematomas were noted on 2 to 4 test days starting on test day 9.

The number of animals with subcutaneous haemorrhagic infusion sites noted at the macroscopic inspection at main dissection on test day 12 and/or at recovery dissection on test day 26 is given in the following text table:

Text table 4-2: Local intolerance reactions of male and female animals at macroscopic inspection at necropsy

Infusion site (last): haemorrhagic (subcutaneous)	Group 1: Control		Group 2: 35 U/kg		Group 3: 110 U/kg		Group 4: 350/225/200 U/kg	
	male	female	male	female	male	female	male	female
Main dissection	2/3	2/3	2/3	2/3	3/3	3/3	3/5	1/3
Recovery dissection	0/2	0/2	N/A	N/A	N/A	N/A	0/2	0/2

../..: animals affected / animals examined

N/A: not applicable

The injection site of all groups (groups 1 to 4) showed microscopic changes (e.g. subcutis; acute inflammatory cell infiltrate, fibrosis, granulation tissue, haemorrhage, necrosis, (peri-) vasculitis, pigment deposition, vessel; intimal thickening) to different degree. In most cases the subcutaneous haemorrhage observed at the injection site at macroscopic inspection at autopsy, could be associated with microscopy (subcutaneous haemorrhage). These changes were not statistically different from the control groups.

For a complete listing of the results of the daily visual inspections see [Table 1-1](#) (Clinical Signs - Local Tolerance - Summary) and [Table 1-2](#) (Clinical Signs - Local Tolerance - Individual Data). The results of the macroscopic inspections of the infusion sites at necropsy are given in [Table 12](#) (Macroscopic Post Mortem Findings). For the results of the microscopic examination of the infusion sites refer to the 'Phase Report on Histopathology' in [Appendix 3](#).

4.2 Systemic tolerance

4.2.1 Mortality

Main study

None of the animals treated intravenously with **35** or **110 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks died or had to be sacrificed prematurely.

Two of 5 male animals (male nos. 26 and 27, assigned for recovery period at start of the study) treated with **350 U Allogenic APOSEC™/kg b.w.** had to be sacrificed prematurely after the first administration on test day 1. For both animals, changes in form of increased body temperature (within 20 minutes p.a.), reduced motility (within 60 minutes p.a.), lateral position (within 2 hours p.a.), reduced reflexes (within 2 hours p.a.), convulsions (within 2 hours p.a.) and reduced body temperature (within 2 hours p.a.) were noted before sacrifice.

As a prophylaxis to these severe effects, remaining animals, receiving the **350 U Allogenic APOSEC™/kg b.w.** on TD1, were treated with 0.5 mg Prednisolon-acetate (i.m) per animal. In addition, two additional males (nos. 33 and 34) were added to group 4 to replace the prematurely sacrificed animals nos. 26 and 27.

Enlarged axillary lymph nodes were observed for male nos. 26 and 27 for which no microscopic correlate was noted. Emphysematous lungs were observed for male no. 26 that could not be associated with microscopy. This was also the case for enlarged cervical lymph node and adrenal glands in animal no. 27. However, haemorrhagic and oedematous subcutaneous tissue in the thighs and lower legs of animal no. 27 were associated with slight diffuse phlegmonous inflammation, consisting of acute inflammation with interstitial oedema and minimal haemorrhage as observed at microscopy. These macroscopic changes were related to the administration of the test item.

Presumably, the death of these animals was caused by a vasodilation, a pharmacodynamic effect of the test item.

Recovery period (restricted to groups 1 and 4)

None of the two animals (nos. 33 and 34) previously treated intravenously with reduced dosing **225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks died or had to be sacrificed prematurely during the recovery period.

For detailed results see [Table 2-1](#) (Clinical Signs - Systemic Tolerance - Summary), [Table 2-2](#) (Clinical Signs - Systemic Tolerance - Individual Data), [Table 12](#) (Macroscopic Post Mortem Findings) the 'Phase Report on Histopathology' in [Appendix 3](#).

4.2.2 Clinical signs (behaviour, external appearance, faeces)

Text table 4-3: Individualized dosing schedule

Test day Dose [Units/kg b.w.]	Group 1 Nos. 1-10	Group 2 Nos. 11-16	Group 3 Nos. 17-22	Group 4 Nos. 23-34
Test day 1	0	35	110	350 (23-27) 225 (28-32) 225 (33 + 34)
Test day 4	0	35	110	350 (23-25)# 200 (28-32) 200 (33 + 34)
Test day 8	0	35	110	225 (23-25)# 200 (28-32) 200 (33 + 34)
Test day 11	0	35	110	200 (23-25)# 200 (28-32) 200 (33 + 34)

#: Male animals nos. 26 and 27 had to be sacrificed prematurely after the first administration on test day 1

Main study

No abnormalities in behaviour, external appearance, and consistency of faeces were observed for any animal treated intravenously with **35 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks and for the female animals treated intravenously with **110 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks.

Reduced motility was noted for 2 of 3 males treated with **110 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks starting 20 to 60 minutes p.a. lasting 5 minutes to 6 hours on test day 8. In addition, 1 of 3 male animals was infirm and revealed mydriasis, a lateral position and clonic convulsions starting within 20 to 60 minutes p.a. lasting 5 minutes to 6 hours on test day 8.

At the high dose of **350/225/200 U Allogenic APOSEC™/kg b.w.**, changes in form of asthenia, somnolence, mydriasis, a lateral position, an increased respiratory rate, laboured breathing, reduced motility, reduced reflexes, (clonic) convulsions, salivation and/or emesis on the administration days and up to 1 day thereafter. Most of the changes started within 20 to 60 minutes p.a. and lasted up to 6 hours.

In addition, the 2 male animals that had to be sacrificed prematurely revealed increased body temperature (within 5 to 20 minutes p.a.) and reduced body temperature (within 1 to 2 hours p.a.).

Details on the number of affected animals and the duration of the findings are given in [Text table 4-4](#):

Text table 4-4: Occurrence of systemic signs of toxicity

Dose level of Allogenic APOSEC™	Finding	Sex	Number of animals	Test day of first occurrence	Total no. of days
Group 1: Vehicle control	none	m:	0/5	N/A	N/A
		f:	0/5	N/A	N/A
Group 2: 35 U/kg	none	m:	0/3	N/A	N/A
		f:	0/3	N/A	N/A
Group 3: 110 U/kg	reduced motility	m:	2/3	8	1
		f:	0/3	N/A	N/A
	asthenia	m:	1/3	8	1
		f:	0/3	N/A	N/A
	mydriasis	m:	1/3	8	1
		f:	0/3	N/A	N/A
	lateral position	m:	1/3	8	1
		f:	0/3	N/A	N/A
	clonic convulsions	m:	1/3	8	1
		f:	0/3	N/A	N/A
Group 4: 350/225/200 U/kg	reduced motility	m:	7/7	1	1-4
		f:	5/5	1	1-4
	asthenia	m:	5/7	1	1-4
		f:	5/5	1	2-4
	mydriasis	m:	3/7	4	1-2
		f:	2/5	1	1-2
	lateral position	m:	6/7	1	1-2
		f:	5/5	1	1-3
	(clonic) convulsions	m:	5/7	1	1
		f:	4/5	1	1-3
	somnolent	m:	5/7	1	1-3
		f:	4/5	1	1-4
	increased respiratory rate	m:	3/7	4	1
		f:	0/5	N/A	N/A
	laboured breathing	m:	3/7	4	1
		f:	0/5	N/A	N/A
	reduced reflexes	m:	4/7	1	1
		f:	0/5	N/A	N/A
	salivation	m:	1/7	4	1
		f:	0/5	N/A	N/A
	increased body temperature	m:	2/7	1	1
		f:	0/5	N/A	N/A
	decreased body temperature	m:	2/7	1	1
		f:	0/5	N/A	N/A
	emesis	m:	1/7	4	1
		f:	0/5	N/A	N/A

.../... number of animals affected / number of animals examined

m males

f females

N/A not applicable

Recovery period (restricted to groups 1 and 4)

No abnormalities in behaviour, external appearance, and consistency of faeces were observed for any animal previously treated intravenously with **350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks during the 2-week recovery period.

For detailed results see [Table 2-1](#) (Clinical Signs - Systemic Tolerance - Summary) and [Table 2-2](#) (Clinical Signs - Systemic Tolerance - Individual Data).

4.2.3 Body weight and body weight gain

Main study / Recovery period (restricted to groups 1 and 4)

No test item-related influence was observed on the body weight and the body weight gain of the male and female animals treated intravenously with **35, 110 or 350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks compared to the control throughout the course of the treatment period. No test item-related differences were noted between the test item-treated animals and the control animals.

No test item-related influence was observed on the body weight, body weight gain and body weight at autopsy of the male and female animals previously treated intravenously with **350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks compared to the control throughout the course of the recovery period.

See [Table 3-1](#) (Body Weight - Summary) and [Table 3-2](#) (Body Weight - Individual Data) for the mean and individual body weights. The body weight gain is presented in [Table 3-3](#) (Body Weight Gain - Summary) and [Table 3-4](#) (Body Weight Gain - Individual Data), and body weight at autopsy in [Table 3-5](#) (Body Weight at Autopsy - Individual Data).

The weekly mean body weight is shown graphically in [Figure 1-1](#) (males) and [Figure 1-2](#) (females) on the following page.

Figure 1-1 Body weight of male monkeys after repeated intravenous infusion with Allogenic APOSEC, mean values per group

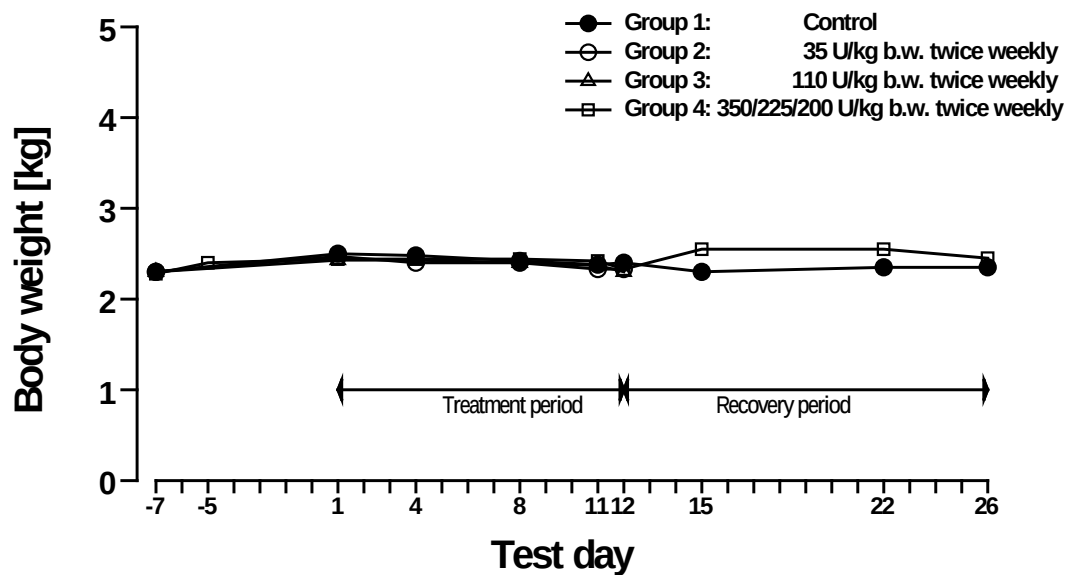
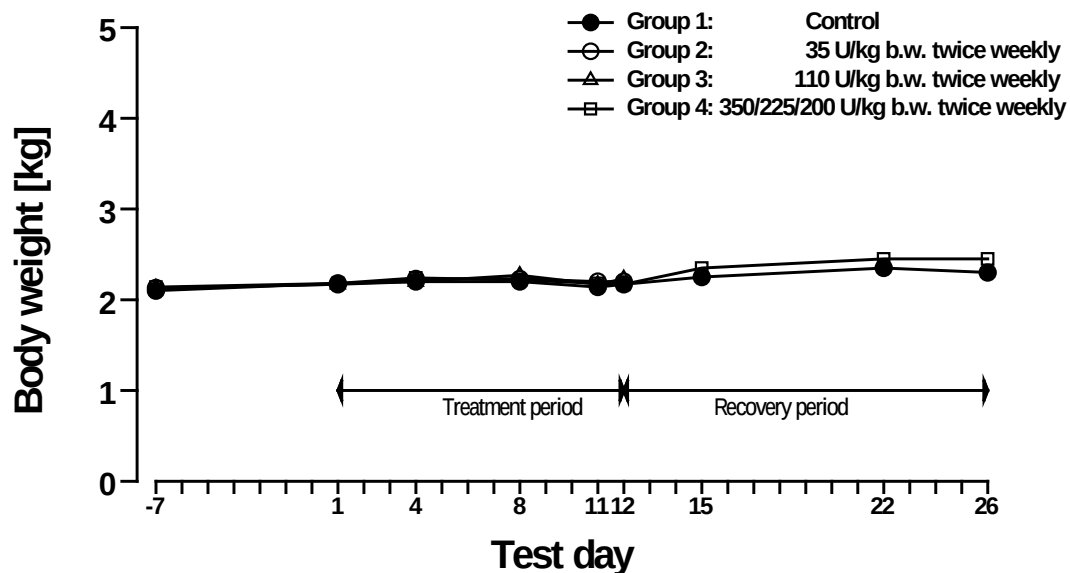


Figure 1-2 Body weight of female monkeys after repeated intravenous infusion with Allogenic APOSEC, mean values per group



4.2.4 Food and drinking water consumption

Main study / Recovery period (restricted to groups 1 and 4)

No test item-related influence was observed on the food consumption of the male and female animals treated intravenously with **35, 110 or 350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks compared to the control throughout the course of the treatment period.

No test item-related influence was observed on the food consumption of the male and female animals previously treated intravenously with **350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks compared to the control throughout the course of the recovery period.

The visual appraisal of the drinking water consumption did not reveal any test item-related differences between the test item-treated animals and the control animals throughout the treatment and recovery period.

See [Table 4-1](#) (Food Consumption - Summary) and [Table 4-2](#) (Food Consumption - Individual Data) for the mean and individual food intake.

The weekly mean food consumption (in g/kg b.w./day) is shown graphically in [Figure 2-1](#) (males) and [Figure 2-2](#) (females) on the following page.

Figure 2-1 Food consumption of male monkeys after repeated intravenous infusion with Allogenic APOSEC, mean values per group

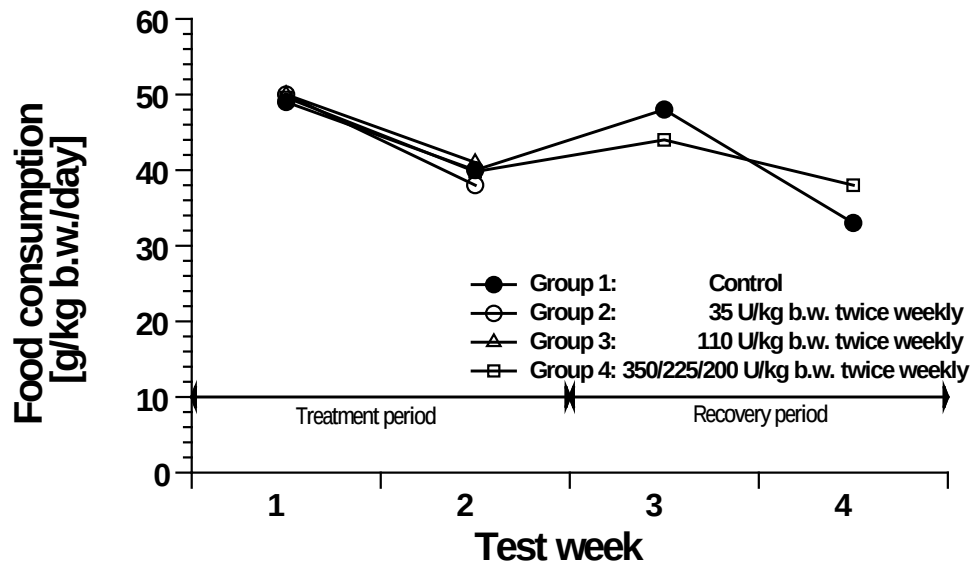
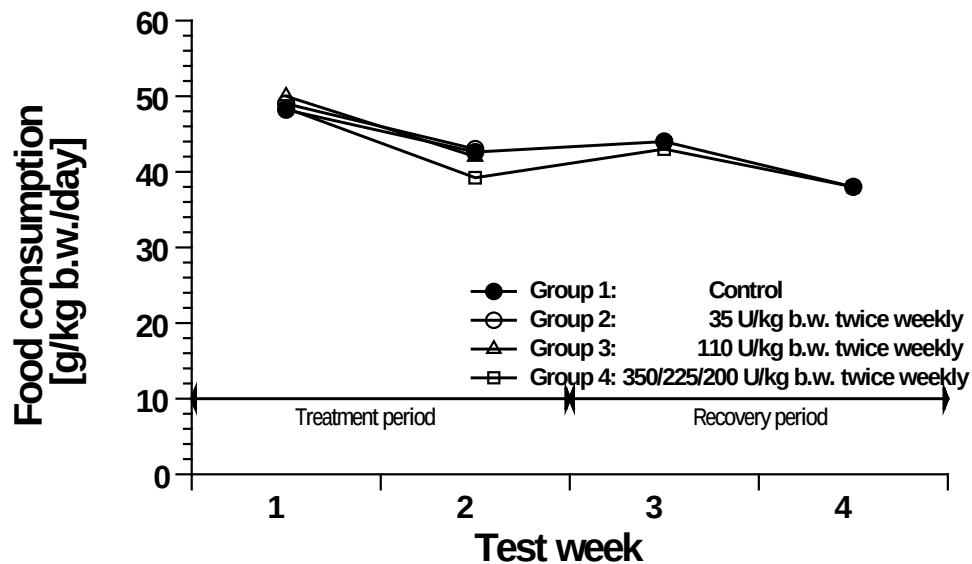


Figure 2-2 Food consumption of female monkeys after repeated intravenous infusion with Allogenic APOSEC, mean values per group



4.2.5 Electrocardiography

Main study / Recovery period (restricted to groups 1 and 4)

No test item-related influence was noted on the ECG parameters or the heart rate of the animals treated intravenously with **35, 110 or 350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks compared to the control on test day 1 and at the end of the treatment period (test day 11, all groups).

No test item-related influence was noted on the ECG parameters or the heart rate of the animals previously treated intravenously with **350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks compared to the control at the end of the recovery period (test day 25, groups 1 and 4).

No test item-related influence was noted on the heart rate, the P segment, PQ interval, the QRS interval, the QT interval, the QTc value (Bazett) compared to the control group.

However, the visual assessment of the ECG recordings revealed pathological arrhythmias in one male animal of the intermediate dose group (male no. 18) in form of a sinus tachycardia on test day 1 (before administration) and in one female animal of the intermediate dose group (female no. 20) in form of a single ventricular extrasystole on test day 1 (5 minutes after the end of infusion). These findings are regarded to be incidental.

A statistically significant difference in ECG parameters compared to the control, which is not considered to be test item-related is given in the text table below:

Text table 4-5: Statistically significant changes in ECG parameters considered not related to the administration of the test item

Parameter	Increase ↑ Decrease ↓	Group/ sex	Test day	Statistical significance	Reason
QT Interval	↑	4 f	11 (predose)	$p \leq 0.05$	A

f: female

A: the slight difference to the respective comparison group is within the normal range of biological variation and not considered to have toxicological relevance

Electrocardiographic parameters are listed in [Table 5-1](#) (Electrocardiographic Parameters - Summary) and [Table 5-2](#) (Electrocardiographic Parameters - Individual Data). Pathological Arrhythmias are listed in [Table 5-3](#) (Pathological Arrhythmias).

4.2.6 Blood pressure

Main study / Recovery period (restricted to groups 1 and 4)

No test item-related influence was noted on the peripheral arterial systolic and diastolic blood pressure as well as on the resulting mean blood pressure for the animals treated intravenously with **35, 110 or 350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks compared to the control on test day 1 and at the end of the treatment period (test day 11, all groups).

No test item-related influence was noted on the peripheral arterial systolic and diastolic blood pressure as well as on the resulting mean blood pressure of the animals previously treated intravenously with **350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks compared to the control at the end of the recovery period (test day 25, groups 1 and 4).

See [Table 6-1](#) (Blood Pressure Parameters - Summary) and [Table 6-2](#) (Blood Pressure Parameters - Individual Data) for details.

4.2.7 Laboratory examinations

4.2.7.1 Haematology and coagulation

Main study / Recovery period (restricted to groups 1 and 4)

No test item-related influence was noted on the haematological parameters of the animals treated intravenously with **35, 110 or 350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks compared to the control on test day 1 and at the end of the treatment period (test day 12, all groups).

No test item-related influence was noted on the haematological parameters of the animals previously treated intravenously with **350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks compared to the control at the end of the recovery period (test day 26, groups 1 and 4).

No test item-related effects were observed for the haemoglobin content (HGB), the numbers of erythrocytes (RBC), leucocytes (WBC) and platelets (PLT), the relative reticulocyte count (Reti), the haematocrit value (HCT), the relative and absolute count of neutrophilic granulocytes (Neut), lymphocytes (Lym), monocytes (Mono), eosinophilic granulocytes (Eos), large unstained cells (LUC) and basophilic granulocytes (Baso), the prothrombin time (PT), the activated partial thromboplastin time (aPTT), the erythrocyte sedimentation rate (ESR), the mean corpuscular volume (MCV), the mean corpuscular haemoglobin (MCH), and the mean corpuscular haemoglobin concentration (MCHC) throughout the treatment and recovery period.

Statistically significant difference in haematological parameters compared to the control, which are not considered to be test item-related is given in the text table below:

Text table 4-6: Statistically significant changes in haematological parameters considered not related to the administration of the test item

Parameter	Increase ↑ Decrease ↓	Group/ sex	Test day	Statistical significance	Reason
Neutrophilic granulocytes (Neut), abs.	↑	2 m	1 (predose)	$p \leq 0.05$	D
Monocytes (Mono), abs.	↓	3 f	1 (predose)	$p \leq 0.05$	D

m: male

f: female

D: effect observed before start of treatment

Group mean values and individual data of haematological parameters are listed in [Table 7-1](#) (Haematological Parameters - Summary) and [Table 7-2](#) (Haematological Parameters - Individual Data).

4.2.7.2 Clinical chemistry

Main study / Recovery period (restricted to groups 1 and 4)

No test item-related influence was noted on the clinical chemistry parameters for the animals treated intravenously with **35, 110 or 350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks compared to the control on test day 1 and at the end of the treatment period (test day 12, all groups).

No test item-related influence was noted on the clinical chemistry parameters of the animals previously treated intravenously with **350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks compared to the control at the end of the recovery period (test day 26, groups 1 and 4).

No test item-related effects were noted on the serum levels of bile acids, bilirubin (total), cholesterol (total), creatinine, glucose, phosphate, protein (total), albumin and globulin, the albumin/globulin ratio, the electrophoresis of serum proteins (alpha 1-, alpha 2-, beta- and gamma-globulin) and the serum levels of triglycerides, urea, calcium, chloride, potassium and sodium. No test item related changes were noted for the serum activities of alanine aminotransferase (ALAT), alkaline phosphatase (aP), aspartate aminotransferase (ASAT), lactate dehydrogenase (LDH) and gamma glutamyl transferase (Gamma-GT). All data are considered to be within the limits of normal biological variability.

Statistically significant differences in clinical chemistry parameters compared to the control, which are not considered to be test item-related is given in the text table below:

Text table 4-7: Statistically significant changes in clinical chemistry parameters considered not related to the administration of the test item

Parameter	Increase ↑ Decrease ↓	Group/ sex	Test day	Statistical significance	Reason
Chloride	↑	4 m	12	$p \leq 0.05$	A
	↑	2 f	12	$p \leq 0.05$	A, B
Bile acids	↑	2 f	1 (predose)	$p \leq 0.05$	D
Phosphate	↓	4 f	12	$p \leq 0.01$	A
Urea	↑	4 f	1 (predose)	$p \leq 0.05$	D

m: male

f: female

A: the slight difference to the respective comparison group is within the normal range of biological variation and not considered to have toxicological relevance

B: lacking dose dependence

D: effect observed before start of dosing

Mean values of clinical chemistry parameters are listed in [Table 8-1](#) (Biochemical Parameters - Summary), and individual data are presented in [Table 8-2](#) (Biochemical Parameters - Individual Data).

4.2.7.3 Urinalysis

Main study / Recovery period (restricted to groups 1 and 4)

No test item-related influence was noted on the urine parameters for the animals treated intravenously with **35, 110 or 350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks compared to the control on test day 1 and at the end of the treatment period (test day 12, all groups).

No test item-related influence was noted on the urine parameters of the animals previously treated intravenously with **350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks compared to the control at the end of the recovery period (test day 25, groups 1 and 4).

No test item-related changes were noted for the specific gravity and the pH value of the urine. The analyte concentrations of nitrite, protein, glucose, ketones, urobilinogen, bilirubin and haemoglobin were not influenced in male and female animals. No test item-related changes were observed in the urine colour and the microscopically analysed urine sediments.

Statistically significant differences in urine parameters compared to the control, which are not considered to be test item-related is given in the text table below:

Text table 4-8: Statistically significant changes in clinical chemistry parameters considered not related to the administration of the test item

Parameter	Increase ↑ Decrease ↓	Group/ sex	Test day	Statistical significance	Reason
Specific gravity	↑	2 f	10	$p \leq 0.05$	A, B
	↑	3 f	10	$p \leq 0.05$	A, B

f: female

A: the slight difference to the respective comparison group is within the normal range of biological variation and not considered to have toxicological relevance

B: lacking dose dependence

Mean and individual values of urinalysis are listed in [Table 9-1](#) (Urinalysis - Summary) and [Table 9-2](#) (Urinalysis - Individual Data).

4.2.8 Ophthalmological and auditory examination

Main study / Recovery period (restricted to groups 1 and 4)

The ophthalmological examination did not reveal any changes of the eyes and the optic region in any animal after intravenous treatment with **35, 110 or 350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks as assessed at the end of the treatment period (all groups).

No changes of the eyes and the optic region were noted for any animal previously treated intravenously with **350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks at the end of the recovery period (groups 1 and 4).

No test item-related pathological changes were noted on the adnexa oculi (*i.e.* lids, lacrimal apparatus), conjunctiva, cornea, anterior chamber, lens, vitreous body, and fundus (retina, optic disc).

There was no indication of any impairment to auditory acuity.

See [Table 10](#) (Ophthalmological Examination) and [Table 11](#) (Auditory Examination) for individual animal listings.

4.3 Final examinations and histopathology

4.3.1 Macroscopic post mortem findings

Main study

The macroscopic inspection at necropsy did not reveal any test item-related systemic changes in the organs and tissues of the male animals treated intravenously with **110 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks and for the female animals treated with **35, 110 or 350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks as assessed at the end of the treatment period (test day 12, all groups).

In the males treated with **350/225/200 U Allogenic APOSEC™/kg b.w.**, spleens were enlarged in males no. 23 and 25 (scheduled sacrifice), for which a microscopic correlate (follicular hyperplasia) was made for animal no. 23 only. Enlarged axillary lymph nodes were observed for males no. 13 treated with **35 U Allogenic APOSEC™/kg b.w.** and no. 25 (high dose group 4) (scheduled sacrifice), for which microscopic correlates were seen in animal nos. 13 and 25 (medullary hyperplasia). These macroscopic changes were related to the administration of the test item.

In addition, a few minor findings were noted in the thyroid (pale, reduced in size, soft consistency), ovary (cystic) and thymus (reduced in size associated with marked atrophy at histopathology) in individual animals in the various dose groups and the control group and are considered not test item-related and to be normal spontaneous background changes due to their isolated occurrence.

For systemic changes of the prematurely sacrificed animals please refer to Section 4.2.1.

For local macroscopic findings at the infusion sites please refer to Section 4.1.

Recovery period (restricted to groups 1 and 4)

The macroscopic inspection at necropsy did not reveal any changes for any animal previously treated intravenously with **350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks at the end of the recovery period (test day 26, groups 1 and 4).

Individual macroscopic findings are listed in [Table 12](#) (Macroscopic Post Mortem Findings).

4.3.2 Organ weights

Main study / Recovery period (restricted to groups 1 and 4)

No test item-related changes in organ weights were noted for the animals treated intravenously with **35, 110** or **350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks in comparison to the control group at the end of the treatment period (test day 12, all groups).

No changes in organ weights were noted for any animal previously treated intravenously with **350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks at the end of the recovery period (test day 26, groups 1 and 4).

However, the relative and/or absolute testes weights of the male animals of all dose groups were statistically significantly decreased in comparison to the control. These changes are not considered to be test item-related but to be coincidental and related to the juvenile age of the animals. These statistical significant (at $p \leq 0.05$ or $p \leq 0.01$) changes in comparison to the control are listed in the text table below.

Text table 4-9: Statistically significant changes in organ weights considered not related to the administration of the test item

Organ	Increase ↑ Decrease ↓	Group/ sex	Test day	Statistical significance	Reason
Relative organ weights					
Testis (left)	↓	4 m	12	$p \leq 0.01$	A
Testis (right)	↓	4 m	12	$p \leq 0.05$	A
Absolute organ weights					
Testis (left)	↓	3 m	12	$p \leq 0.05$	A
	↓	4 m	12	$p \leq 0.01$	A
Testis (right)	↓	2 m	12	$p \leq 0.05$	A
	↓	4 m	12	$p \leq 0.01$	A

m: male

A: the slight difference to the respective comparison group is within the normal range of biological variation and not considered to have toxicological relevance

Relative organ weights are listed in [Table 13-1](#) (Relative Organ Weights - Summary) and [Table 13-2](#) (Relative Organ Weights - Individual Data). Absolute organ weights are listed in [Table 14-1](#) (Absolute Organ Weights - Summary) and [Table 14-2](#) (Absolute Organ Weights - Individual Data).

4.3.3 Bone marrow

Main study / Recovery period (restricted to groups 1 and 4)

No test item-related influence was noted on the myeloid:erythroid ratio for the animals treated intravenously with **35, 110 or 350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks in comparison to the control group at the end of the treatment period (test day 12, all groups).

No test item-related influence was noted on the myeloid:erythroid ratio for any animal previously treated intravenously with **350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks at the end of the recovery period (test day 26, groups 1 and 4).

See [Table 15-1](#) (Bone Marrow - Summary) and [Table 15-2](#) (Bone Marrow - Individual Data) for details.

4.3.4 Histopathology

Main study

The histopathological examination was performed by the Test Site Global Pathology Support B.V., The Netherlands.

Test item-related changes were observed in spleen of animal no. 23 (follicular cell hyperplasia) treated intravenously with **350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks. This finding was associated with splenic enlargement at autopsy. Lymphoid hyperplasia of the medulla in the axillary lymph node was observed for animal no. 25 treated with **350/225/200 U Allogenic APOSEC™/kg b.w.** with enlarged axillary lymph node at macroscopy. This was also observed for 1 of 3 males treated with **35 U Allogenic APOSEC™/kg b.w.** (no. 13) for which the draining axillary lymph node was also enlarged at macroscopy.

Recovery period (restricted to groups 1 and 4)

The macroscopic inspection at necropsy did not reveal any toxicologically relevant changes for any animal previously treated intravenously with **350/225/200 U Allogenic APOSEC™/kg b.w.** twice weekly for 2 weeks at the end of the recovery period (test day 26, groups 1 and 4).

All microscopic changes in all animals were either coincidental, related to macroscopic incidental findings, mode of administration (intravenous infusion) and/or of spontaneous background origin.

For detailed results of the microscopic examination see the 'Phase Report on Histopathology' in [Appendix 3](#).

5. TABLES

Allogenic APOSEC™								
TABLE 1-1	Clinical Signs - Local Tolerance - Summary							Monkey
Symptoms / Criteria	Group	Test week 1 - Treatment period						
		Test day						
		1	2	3	4	5	6	7
Administration		x			x			
Males								
Haematoma	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	0/7	0/5	0/5	0/5	0/5	0/5	0/5
Females								
Haematoma	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	0/5	0/5	0/5	0/5	0/5	0/5	0/5

.../... : number of affected animals / number of animals examined

Allogenic APOSEC™								
TABLE 1-1	Clinical Signs - Local Tolerance - Summary							Monkey
Symptoms / Criteria	Group	Test week 2 - Treatment/Recovery period						
		Test day						
		8	9	10	11	12	13	14
Administration		x			x	↑ Main dissection		
Males								
Haematoma	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	0/3	0/3	0/3	0/3	0/3	-	-
	4	0/5	1/5	1/5	1/5	0/5	0/2	0/2
Females								
Haematoma	1	0/5	3/5	3/5	3/5	0/5	0/2	0/2
	2	0/3	2/3	2/3	2/3	0/3	-	-
	3	0/3	1/3	1/3	0/3	0/3	-	-
	4	0/5	1/5	1/5	1/5	1/5	0/2	0/2

.../... : number of affected animals / number of animals examined

Allogenic APOSEC™								
TABLE 1-1	Clinical Signs - Local Tolerance - Summary							Monkey
Symptoms / Criteria	Group	Test week 3 - Recovery period						
		Test day						
		15	16	17	18	19	20	21
Administration								
Males								
Haematoma	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2
Females								
Haematoma	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2

Allogenic APOSEC™						
TABLE 1-1	Clinical Signs - Local Tolerance - Summary					Monkey
Symptoms / Criteria	Group	Test week 4 - Recovery period				
		Test day				
		22	23	24	25	26
Administration					↑	Recovery dissection
						Males
Haematoma	1	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-
	3	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2
						Females
Haematoma	1	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-
	3	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local Tolerance - Individual Data Monkey

Males

Group 1: Control - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(1)	N/A	N/A	no signs of local intolerance
(2)	N/A	N/A	no signs of local intolerance
(3)	N/A	N/A	no signs of local intolerance
(4)	N/A	N/A	no signs of local intolerance
(5)	N/A	N/A	no signs of local intolerance

Group 1: Control - Recovery period

Animal no.	Observed on test day	Total no. of days	Observation
(4)	N/A	N/A	no signs of local intolerance
(5)	N/A	N/A	no signs of local intolerance

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local Tolerance - Individual Data Monkey

Males

Group 2: 35 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(11)	N/A	N/A	no signs of local intolerance
(12)	N/A	N/A	no signs of local intolerance
(13)	N/A	N/A	no signs of local intolerance

Group 3: 110 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(17)	N/A	N/A	no signs of local intolerance
(18)	N/A	N/A	no signs of local intolerance
(19)	N/A	N/A	no signs of local intolerance

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local Tolerance - Individual Data Monkey

Males

Group 4: 350/225/200 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(23)	N/A	N/A	no signs of local intolerance
(24)	N/A	N/A	no signs of local intolerance
(25)	N/A	N/A	no signs of local intolerance
(26)	N/A	N/A	no signs of local intolerance
(27)	N/A	N/A	no signs of local intolerance
(33)	N/A	N/A	no signs of local intolerance
(34)	9 - 11	3	haematoma (size: up to 8x3 cm)

Group 4: 350/225/200 U/kg - Recovery period

Animal no.	Observed on test day	Total no. of days	Observation
(33)	N/A	N/A	no signs of local intolerance
(34)	N/A	N/A	no signs of local intolerance

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local Tolerance - Individual Data Monkey

Females

Group 1: Control - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(6)	9 - 11	3	haematoma (size: up to 4x2 cm)
(7)	9 - 11	3	haematoma (size: up to 2x2 cm)
(8)	N/A	N/A	no signs of local intolerance
(9)	N/A	N/A	no signs of local intolerance
(10)	9 - 11	3	haematoma (size: up to 2x2 cm)

Group 1: Control - Recovery period

Animal no.	Observed on test day	Total no. of days	Observation
(9)	N/A	N/A	no signs of local intolerance
(10)	N/A	N/A	no signs of local intolerance

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local Tolerance - Individual Data Monkey

Females

Group 2: 35 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(14)	N/A	N/A	no signs of local intolerance
(15)	9 - 11	3	haematoma (size: up to 4x2 cm)
(16)	9 - 11	3	haematoma (size: up to 4x2 cm)

Group 3: 110 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(20)	N/A	N/A	no signs of local intolerance
(21)	9 - 10	2	haematoma (size: up to 1x1 cm)
(22)	N/A	N/A	no signs of local intolerance

Allogenic APOSEC™

TABLE 1-2 Clinical Signs - Local Tolerance - Individual Data Monkey

Females

Group 4: 350/225/200 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(28)	N/A	N/A	no signs of local intolerance
(29)	9 - 12	4	haematoma (size: up to 6x3 cm)
(30)	N/A	N/A	no signs of local intolerance
(31)	N/A	N/A	no signs of local intolerance
(32)	N/A	N/A	no signs of local intolerance

Group 4: 350/225/200 U/kg - Recovery period

Animal no.	Observed on test day	Total no. of days	Observation
(31)	N/A	N/A	no signs of local intolerance
(32)	N/A	N/A	no signs of local intolerance

Allogenic APOSEC™								
TABLE 2-1	Clinical Signs - Systemic Tolerance - Summary							Monkey
Symptoms / Criteria	Group	Test week 1 - Treatment period						
		Test day						
		1	2	3	4	5	6	7
Administration		x			x			
Male animals								
Death	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	2 ^{#1} /7	0/5	0/5	0/5	0/5	0/5	0/5
Reduced motility	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	3/7	0/5	0/5	1/5	0/5	0/5	0/5
Asthenia	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	1/7	0/5	0/5	4/5	1/5	0/5	0/5
Somnolent	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	1/7	0/5	0/5	4/5	0/5	0/5	0/5
Mydriasis	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	0/7	0/5	0/5	3/5	0/5	0/5	0/5

#1 : Males no. 26 and 27 had to be sacrificed prematurely on test day 1.
.../... : number of affected animals / number of animals examined

TABLE 2-1 Allogenic APOSEC™
Clinical Signs - Systemic Tolerance - Summary Monkey

Symptoms / Criteria	Group	Test week 1 - Treatment period Test day						
		1	2	3	4	5	6	7
Administration		x			x			
Male animals								
Lateral position	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	2/7	0/5	0/5	4/5	0/5	0/5	0/5
Increased respiratory rate	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	0/7	0/5	0/5	3/5	0/5	0/5	0/5
Laboured breathing	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	0/7	0/5	0/5	3/5	0/5	0/5	0/5
Reduced reflexes	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	2/7	0/5	0/5	2/5	0/5	0/5	0/5
Clonic convulsions/ convulsions	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	2/7	0/5	0/5	2/5	0/5	0/5	0/5
Further changes of behaviour or external appearance	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	2 ^{#2} /7	0/5	0/5	2 ^{#1} /5	0/5	0/5	0/5

#1 : salivation and emesis

#2 : increased and afterwards reduced temperature

.../... : number of affected animals / number of animals examined

Allogenic APOSEC™
TABLE 2-1 Clinical Signs - Systemic Tolerance - Summary Monkey

Symptoms / Criteria	Group	Test week 2 - Treatment/Recovery period						
		Test day						
		8	9	10	11	12	13	14
Administration		x			x	↑ Main dissection		
Male animals								
Death	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	0/3	0/3	0/3	0/3	0/3	-	-
	4	0/5	0/5	0/5	0/5	0/5	0/2	0/2
Reduced motility	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	2/3	0/3	0/3	0/3	0/3	-	-
	4	5/5	0/5	0/5	2/5	0/5	0/2	0/2
Asthenia	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	1/3	0/3	0/3	0/3	0/3	-	-
	4	3/5	0/5	0/5	1/5	0/5	0/2	0/2
Somnolent	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	0/3	0/3	0/3	0/3	0/3	-	-
	4	4/5	0/5	0/5	1/5	0/5	0/2	0/2
Mydriasis	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	1/3	0/3	0/3	0/3	0/3	-	-
	4	1/5	0/5	0/5	0/5	0/5	0/2	0/2

.../... : number of affected animals / number of animals examined

Allogenic APOSEC™								
Clinical Signs - Systemic Tolerance - Summary								Monkey
Symptoms / Criteria	Group	Test week 2 - Treatment/Recovery period						
		Test day						
		8	9	10	11	12	13	14
Administration		x			x	↑ Main dissection		
Male animals								
Lateral position	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	1/3	0/3	0/3	0/3	0/3	-	-
	4	1/5	0/5	0/5	1/5	0/5	0/2	0/2
Increased respiratory rate	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	0/3	0/3	0/3	0/3	0/3	-	-
	4	0/5	0/5	0/5	0/5	0/5	0/2	0/2
Laboured breathing	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	0/3	0/3	0/3	0/3	0/3	-	-
	4	0/5	0/5	0/5	0/5	0/5	0/2	0/2
Reduced reflexes	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	0/3	0/3	0/3	0/3	0/3	-	-
	4	0/5	0/5	0/5	0/5	0/5	0/2	0/2
Clonic convulsions/ convulsions	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	1/3	0/3	0/3	0/3	0/3	-	-
	4	0/5	0/5	0/5	1/5	0/5	0/2	0/2
Further changes of behaviour or external appearance	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	0/3	0/3	0/3	0/3	0/3	-	-
	4	0/5	0/5	0/5	0/5	0/5	0/2	0/2

.../... : number of affected animals / number of animals examined

Allogenic APOSEC™
TABLE 2-1 Clinical Signs - Systemic Tolerance - Summary Monkey

Symptoms / Criteria	Group	Test week 3 - Recovery period						
		Test day						
		15	16	17	18	19	20	21
Administration								
		Male animals						
Death	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2
Reduced motility	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2
Asthenia	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2
Somnolent	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2
Mydriasis	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2

.../... : number of affected animals / number of animals examined

Allogenic APOSEC™								
Clinical Signs - Systemic Tolerance - Summary								Monkey
Symptoms / Criteria	Group	Test week 3 - Recovery period						
		Test day						
		15	16	17	18	19	20	21
Administration								
Male animals								
Lateral position	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2
Increased respiratory rate	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2
Laboured breathing	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2
Reduced reflexes	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2
Clonic convulsions/ convulsions	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2
Further changes of behaviour or external appearance	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2

.../... : number of affected animals / number of animals examined

Allogenic APOSEC™						
TABLE 2-1	Clinical Signs - Systemic Tolerance - Summary					Monkey
Symptoms / Criteria	Group	Test week 4 - Recovery period				
		Test day				
		22	23	24	25	26
Administration						↑ Recovery dissection
				Male animals		
Death	1	0/2	0/2	0/2	0/2	
	2	-	-	-	-	
	3	-	-	-	-	
	4	0/2	0/2	0/2	0/2	
Reduced motility	1	0/2	0/2	0/2	0/2	
	2	-	-	-	-	
	3	-	-	-	-	
	4	0/2	0/2	0/2	0/2	
Asthenia	1	0/2	0/2	0/2	0/2	
	2	-	-	-	-	
	3	-	-	-	-	
	4	0/2	0/2	0/2	0/2	
Somnolent	1	0/2	0/2	0/2	0/2	
	2	-	-	-	-	
	3	-	-	-	-	
	4	0/2	0/2	0/2	0/2	
Mydriasis	1	0/2	0/2	0/2	0/2	
	2	-	-	-	-	
	3	-	-	-	-	
	4	0/2	0/2	0/2	0/2	

.../... : number of affected animals / number of animals examined

Allogenic APOSEC™					
TABLE 2-1	Clinical Signs - Systemic Tolerance - Summary				Monkey
Symptoms / Criteria	Group	Test week 4 - Recovery period			
		Test day			
		22	23	24	25 26
Administration					
↑ Recovery dissection					
Male animals					
Lateral position	1	0/2	0/2	0/2	0/2
	2	-	-	-	-
	3	-	-	-	-
	4	0/2	0/2	0/2	0/2
Increased respiratory rate	1	0/2	0/2	0/2	0/2
	2	-	-	-	-
	3	-	-	-	-
	4	0/2	0/2	0/2	0/2
Laboured breathing	1	0/2	0/2	0/2	0/2
	2	-	-	-	-
	3	-	-	-	-
	4	0/2	0/2	0/2	0/2
Reduced reflexes	1	0/2	0/2	0/2	0/2
	2	-	-	-	-
	3	-	-	-	-
	4	0/2	0/2	0/2	0/2
Clonic convulsions/ convulsions	1	0/2	0/2	0/2	0/2
	2	-	-	-	-
	3	-	-	-	-
	4	0/2	0/2	0/2	0/2
Further changes of behaviour or external appearance	1	0/2	0/2	0/2	0/2
	2	-	-	-	-
	3	-	-	-	-
	4	0/2	0/2	0/2	0/2

.../... : number of affected animals / number of animals examined

Allogenic APOSEC™
TABLE 2-1 Clinical Signs - Systemic Tolerance - Summary Monkey

Symptoms / Criteria	Group	Test week 1 - Treatment period Test day						
		1	2	3	4	5	6	7
Administration		x			x			
Female animals								
Death	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	0/5	0/5	0/5	0/5	0/5	0/5	0/5
Reduced motility	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	3/5	0/5	0/5	4/5	0/5	0/5	0/5
Asthenia	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	3/5	0/5	0/5	5/5	0/5	0/5	0/5
Somnolent	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	3/5	0/5	0/5	5/5	0/5	0/5	0/5
Mydriasis	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	2/5	0/5	0/5	0/5	0/5	0/5	0/5

.../... : number of affected animals / number of animals examined

Allogenic APOSEC™								
TABLE 2-1	Clinical Signs - Systemic Tolerance - Summary							Monkey
Symptoms / Criteria	Group	Test week 1 - Treatment period						
		Test day						
		1	2	3	4	5	6	7
Administration		x			x			
Female animals								
Lateral position	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	1/5	0/5	0/5	5/5	0/5	0/5	0/5
Clonic convulsions	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	1/5	0/5	0/5	4/5	0/5	0/5	0/5
Further changes of behaviour or external appearance	1	0/5	0/5	0/5	0/5	0/5	0/5	0/5
	2	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	3	0/3	0/3	0/3	0/3	0/3	0/3	0/3
	4	0/5	0/5	0/5	0/5	0/5	0/5	0/5

.../... : number of affected animals / number of animals examined

Allogenic APOSEC™
TABLE 2-1 Clinical Signs - Systemic Tolerance - Summary Monkey

Symptoms / Criteria	Group	Test week 2 - Treatment/Recovery period Test day						
		8	9	10	11	12	13	14
Administration		x			x	↑ Main dissection		
		Female animals						
Death	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	0/3	0/3	0/3	0/3	0/3	-	-
	4	0/5	0/5	0/5	0/5	0/5	0/2	0/2
Reduced motility	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	0/3	0/3	0/3	0/3	0/3	-	-
	4	3/5	0/5	0/5	5/5	0/5	0/2	0/2
Asthenia	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	0/3	0/3	0/3	0/3	0/3	-	-
	4	5/5	0/5	0/5	3/5	0/5	0/2	0/2
Somnolent	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	0/3	0/3	0/3	0/3	0/3	-	-
	4	4/5	0/5	0/5	4/5	0/5	0/2	0/2
Mydriasis	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	0/3	0/3	0/3	0/3	0/3	-	-
	4	1/5	0/5	0/5	0/5	0/5	0/2	0/2

.../... : number of affected animals / number of animals examined

Allogenic APOSEC™								
TABLE 2-1	Clinical Signs - Systemic Tolerance - Summary							Monkey
Symptoms / Criteria	Group	Test week 2 - Treatment/Recovery period						
		Test day						
		8	9	10	11	12	13	14
Administration		x			x	↑ Main dissection		
		Female animals						
Lateral position	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	0/3	0/3	0/3	0/3	0/3	-	-
	4	1/5	0/5	0/5	2/5	0/5	0/2	0/2
Clonic convulsions	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	0/3	0/3	0/3	0/3	0/3	-	-
	4	1/5	0/5	0/5	1/5	0/5	0/2	0/2
Further changes of behaviour or external appearance	1	0/5	0/5	0/5	0/5	0/5	0/2	0/2
	2	0/3	0/3	0/3	0/3	0/3	-	-
	3	0/3	0/3	0/3	0/3	0/3	-	-
	4	0/5	0/5	0/5	0/5	0/5	0/2	0/2

.../... : number of affected animals / number of animals examined

Allogenic APOSEC™
TABLE 2-1 Clinical Signs - Systemic Tolerance - Summary Monkey

Symptoms / Criteria	Group	Test week 3 - Recovery period						
		Test day						
		15	16	17	18	19	20	21
Administration								
		Female animals						
Death	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2
Reduced motility	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2
Asthenia	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2
Somnolent	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2
Mydriasis	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2

.../... : number of affected animals / number of animals examined

Allogenic APOSEC™								
TABLE 2-1	Clinical Signs - Systemic Tolerance - Summary							Monkey
Symptoms / Criteria	Group	Test week 3 - Recovery period						
		Test day						
		15	16	17	18	19	20	21
Administration								
Female animals								
Lateral position	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2
Clonic convulsions	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2
Further changes of behaviour or external appearance	1	0/2	0/2	0/2	0/2	0/2	0/2	0/2
	2	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-
	4	0/2	0/2	0/2	0/2	0/2	0/2	0/2

.../... : number of affected animals / number of animals examined

Allogenic APOSEC™						
TABLE 2-1	Clinical Signs - Systemic Tolerance - Summary					Monkey
Symptoms / Criteria	Group	Test week 4 - Recovery period				
		Test day				
		22	23	24	25	26
Administration						↑ Recovery dissection
				Female animals		
Death	1	0/2	0/2	0/2	0/2	
	2	-	-	-	-	
	3	-	-	-	-	
	4	0/2	0/2	0/2	0/2	
Reduced motility	1	0/2	0/2	0/2	0/2	
	2	-	-	-	-	
	3	-	-	-	-	
	4	0/2	0/2	0/2	0/2	
Asthenia	1	0/2	0/2	0/2	0/2	
	2	-	-	-	-	
	3	-	-	-	-	
	4	0/2	0/2	0/2	0/2	
Somnolent	1	0/2	0/2	0/2	0/2	
	2	-	-	-	-	
	3	-	-	-	-	
	4	0/2	0/2	0/2	0/2	
Mydriasis	1	0/2	0/2	0/2	0/2	
	2	-	-	-	-	
	3	-	-	-	-	
	4	0/2	0/2	0/2	0/2	

.../... : number of affected animals / number of animals examined

TABLE 2-1		Allogenic APOSEC™ Clinical Signs - Systemic Tolerance - Summary					Monkey
Symptoms / Criteria	Group	Test week 4 - Recovery period					
		Test day					
		22	23	24	25	26	
Administration						↑ Recovery dissection	
Female animals							
Lateral position	1	0/2	0/2	0/2	0/2		
	2	-	-	-	-		
	3	-	-	-	-		
	4	0/2	0/2	0/2	0/2		
Clonic convulsions	1	0/2	0/2	0/2	0/2		
	2	-	-	-	-		
	3	-	-	-	-		
	4	0/2	0/2	0/2	0/2		
Further changes of behaviour or external appearance	1	0/2	0/2	0/2	0/2		
	2	-	-	-	-		
	3	-	-	-	-		
	4	0/2	0/2	0/2	0/2		

.../... : number of affected animals / number of animals examined

Allogenic APOSEC™

TABLE 2-2 Clinical Signs - Systemic Tolerance - Individual Data Monkey

Males

Group 1: Control - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(1)	N/A	N/A	no signs of systemic intolerance
(2)	N/A	N/A	no signs of systemic intolerance
(3)	N/A	N/A	no signs of systemic intolerance
(4)	N/A	N/A	no signs of systemic intolerance
(5)	N/A	N/A	no signs of systemic intolerance

Group 1: Control - Recovery period

Animal no.	Observed on test day	Total no. of days	Observation
(4)	N/A	N/A	no signs of systemic intolerance
(5)	N/A	N/A	no signs of systemic intolerance

Allogenic APOSEC™

TABLE 2-2 Clinical Signs - Systemic Tolerance - Individual Data Monkey

Males

Group 2: 35 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(11)	N/A	N/A	no signs of systemic intolerance
(12)	N/A	N/A	no signs of systemic intolerance
(13)	N/A	N/A	no signs of systemic intolerance

Group 3: 110 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(17)	N/A	N/A	no signs of systemic intolerance
(18)	8	1	reduced motility starting 20 - 60 min p.a. lasting 2 - 6 h
	8	1	asthenia starting 20 - 60 min p.a. lasting 2 - 6 h
	8	1	mydriasis starting 20 - 60 min p.a. lasting 5 - 20 min
	8	1	lateral position starting 20 - 60 min p.a. lasting 2 - 6 h
	8	1	clonic convulsions (once) starting 20 - 60 min p.a. lasting 5 - 20 min

Allogenic APOSEC™

TABLE 2-2 Clinical Signs - Systemic Tolerance - Individual Data Monkey

Males

Group 3: 110 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(19)	8	1	reduced motility starting 20 - 60 min p.a. lasting 5 - 20 min

Group 4: 350/225/200 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(23)	4 (350 U/kg)	1	asthenia starting 20 - 60 min p.a. lasting 5 - 20 min
	4 (350 U/kg)	1	somnolent starting 20 - 60 min p.a. lasting 2 - 6 h
	4 (350 U/kg)	1	mydriasis (slight) starting 20 - 60 min p.a. lasting 20 - 60 min
	4 (350 U/kg)	1	lateral position starting 20 - 60 min p.a. lasting 2 - 6 h
	4 (350 U/kg)	1	increased respiratory rate (slight) starting 20 - 60 min p.a. lasting 2 - 6 h
	4 (350 U/kg)	1	laboured breathing starting 20 - 60 min p.a. lasting 2 - 6 h
	8 (225 U/kg)	1	reduced motility starting 20 - 60 min p.a. lasting 20 - 60 min

Allogenic APOSEC™

TABLE 2-2 Clinical Signs - Systemic Tolerance - Individual Data Monkey

Males

Group 4: 350/225/200 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(24)	4 (350 U/kg)	1	asthenia starting 20 - 60 min p.a. lasting 20 - 60 min
	4, 8 (350/225 U/kg)	2	somnolent starting 20 - 60 min p.a. lasting 20 min - 2 h
	4, 8 (350/225 U/kg)	2	mydriasis (slight) starting 20 - 60 min p.a. lasting 5 - 60 min
	4 (350 U/kg)	1	lateral position starting 20 - 60 min p.a. lasting 1 - 2 h
	4 (350 U/kg)	1	increased respiratory rate (slight) starting 20 - 60 min p.a. lasting 1 - 2 h
	4 (350 U/kg)	1	laboured breathing starting 20 - 60 min p.a. lasting 1 - 2 h
	4 (350 U/kg)	1	reduced reflexes starting 1 - 2 h p.a. lasting 20 - 60 min
	4 (350 U/kg)	1	clonic convulsions (twice) starting 20 min - 2 h p.a. lasting 5 - 20 min
	8 (225 U/kg)	1	reduced motility starting 20 - 60 min p.a. lasting 20 - 60 min

Allogenic APOSEC™

TABLE 2-2 Clinical Signs - Systemic Tolerance - Individual Data Monkey

Males

Group 4: 350/225/200 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(25)	4 - 5, 8 (350/225 U/kg)	3	asthenia noted at start of workshift or starting 20 - 60 min p.a. lasting 5 min - 24 h
	4, 8 (350/225 U/kg)	2	somnolent starting 20 - 60 min p.a. lasting 2 - 6 h
	4 (350 U/kg)	1	mydriasis (slight) starting 20 - 60 min p.a. lasting 20 - 60 min
	4, 8 (350/225 U/kg)	2	lateral position starting 20 - 60 min p.a. lasting 2 - 6 h
	4 (350 U/kg)	1	increased respiratory rate (slight) starting 20 - 60 min p.a. lasting 2 - 6 h
	4 (350 U/kg)	1	laboured breathing starting 20 - 60 min p.a. lasting 2 - 6 h
	4 (350 U/kg)	1	reduced reflexes starting 1 - 2 h p.a. lasting 2 - 6 h
	4 (350 U/kg)	1	clonic convulsions (4 times) starting 20 min - 6 h p.a. lasting 5 - 60 min
	4 (350 U/kg)	1	salivation (slight) starting 2 - 6 h p.a. lasting 20 - 60 min
	8 (225 U/kg)	1	reduced motility starting 20 - 60 min p.a. lasting 2 - 6 h

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TABLE 2-2 Clinical Signs - Systemic Tolerance - Individual Data Monkey

Males

Group 4: 350/225/200 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(26)	1 (350 U/kg)	1	increased body temperature starting 5 - 20 min p.a. lasting 5 - 20 min
	1 (350 U/kg)	1	reduced motility starting 20 - 60 min p.a. lasting 1 - 2 h
	1 (350 U/kg)	1	lateral position starting 1 - 2 h p.a. lasting 20 - 60 min
	1 (350 U/kg)	1	reduced reflexes starting 1 - 2 h p.a. lasting 20 - 60 min
	1 (350 U/kg)	1	convulsions starting 1 - 2 h p.a. lasting 20 - 60 min
	1 (350 U/kg)	1	reduced body temperature starting 1 - 2 h p.a. lasting 5 - 20 min
	1 (350 U/kg)	N/A	premature sacrifice (at 01:10 p.m.)

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TABLE 2-2 Clinical Signs - Systemic Tolerance - Individual Data Monkey

Males

Group 4: 350/225/200 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(27)	1 (350 U/kg)	1	increased body temperature starting 5 - 20 min p.a. lasting 5 - 20 min
	1 (350 U/kg)	1	reduced motility starting 20 - 60 min p.a. lasting 20 - 60 min
	1 (350 U/kg)	1	lateral position starting 20 - 60 min p.a. lasting 20 - 60 min
	1 (350 U/kg)	1	reduced reflexes starting 1 - 2 h p.a. lasting 20 - 60 min
	1 (350 U/kg)	1	convulsions starting 20 - 60 min p.a. lasting 20 - 60 min
	1 (350 U/kg)	1	reduced body temperature starting 1 - 2 h p.a. lasting 5 - 20 min
	1 (350 U/kg)	N/A	premature sacrifice (at 01:10 p.m.)

Allogenic APOSEC™

TABLE 2-2 Clinical Signs - Systemic Tolerance - Individual Data Monkey

Males

Group 4: 350/225/200 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(33)	1, 4, 8, 11 (225/200/200/200 U/kg)	4	reduced motility starting 20 min - 2 h p.a. lasting 20 min - 2 h
	1, 4, 8, 11 (225/200/200/200 U/kg)	4	asthenia starting 20 - 60 min p.a. lasting 20 min - 6 h
	1, 4, 8 (225/200/200 U/kg)	3	somnolent starting 20 min - 2 h p.a. lasting 20 min - 6 h
	4, 11 (200/200 U/kg)	2	lateral position starting 20 min - 2 h p.a. lasting 5 min - 6 h
	4 (200 U/kg)	1	emesis (twice, approx. 5 mL, (white foam or yellow liquid) starting 20- 60 min p.a.
	11 (200 U/kg)	1	clonic convulsions (once) starting 20 - 60 min p.a. lasting 0 - 5 min

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TABLE 2-2 Clinical Signs - Systemic Tolerance - Individual Data Monkey

Males

Group 4: 350/225/200 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(34)	8, 11 (200/200 U/kg)	2	reduced motility starting 20 - 60 min p.a. lasting 20 min - 2 h
	8 (200 U/kg)	1	asthenia starting 20 - 60 min p.a. lasting 1 - 2 h
	8, 11 (200/200 U/kg)	2	somnolent starting 20 - 60 min p.a. lasting 20 min - 2 h

Group 4: 350/225/200 U/kg - Recovery period

Animal no.	Observed on test day	Total no.	Observation
(33)	N/A	N/A	no signs of systemic intolerance
(34)	N/A	N/A	no signs of systemic intolerance

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TABLE 2-2 Clinical Signs - Systemic Tolerance - Individual Data Monkey

Females

Group 1: Control - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(6)	N/A	N/A	no signs of systemic intolerance
(7)	N/A	N/A	no signs of systemic intolerance
(8)	N/A	N/A	no signs of systemic intolerance
(9)	N/A	N/A	no signs of systemic intolerance
(10)	N/A	N/A	no signs of systemic intolerance

Group 1: Control - Recovery period

Animal no.	Observed on test day	Total no. of days	Observation
(9)	N/A	N/A	no signs of systemic intolerance
(10)	N/A	N/A	no signs of systemic intolerance

Allogenic APOSEC™

TABLE 2-2 Clinical Signs - Systemic Tolerance - Individual Data Monkey

Females

Group 2: 35 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(14)	N/A	N/A	no signs of systemic intolerance
(15)	N/A	N/A	no signs of systemic intolerance
(16)	N/A	N/A	no signs of systemic intolerance

Group 3: 110 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(20)	N/A	N/A	no signs of systemic intolerance
(21)	N/A	N/A	no signs of systemic intolerance
(22)	N/A	N/A	no signs of systemic intolerance

Allogenic APOSEC™

TABLE 2-2 Clinical Signs - Systemic Tolerance - Individual Data Monkey

Females

Group 4: 350/225/200 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(28)	1, 4, 8, 11 (225/200/200/200 U/kg)	4	reduced motility starting 20 - 60 min p.a. lasting 1 - 6 h
	1, 4, 8, 11 (225/200/200/200 U/kg)	4	asthenia starting 20 min - 2 h p.a. lasting 20 min - 6 h
	1, 4, 8, 11 (225/200/200/200 U/kg)	4	somnolent starting 20 min - 2 h p.a. lasting 20 min - 6 h
	4 (200 U/kg)	1	lateral position starting 20 - 60 min p.a. lasting 2 - 6 h
(29)	4, 8, 11 (200/200/200 U/kg)	3	reduced motility starting 20 - 60 min p.a. lasting 20 min - 2 h
	4, 8 (200/200 U/kg)	2	asthenia starting 20 - 60 min p.a. lasting 20 min - 2 h
	4 (200 U/kg)	1	lateral position starting 20 - 60 min p.a. lasting 1 - 2 h
	4 (200 U/kg)	1	clonic convulsions (once) starting 20 - 60 min p.a. lasting 0 - 5 min
	4 (200 U/kg)	1	somnolent starting 20 - 60 min p.a. lasting 1 - 2 h

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TABLE 2-2 Clinical Signs - Systemic Tolerance - Individual Data Monkey

Females

Group 4: 350/225/200 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(30)	1, 4, 11 (225/200/200 U/kg)	3	reduced motility starting 20 min - 2 h p.a. lasting 5 min - 6 h
	1, 4, 8, 11 (225/200/200/200 U/kg)	4	asthenia starting 20 min - 2 h p.a. lasting 5 min - 6 h
	4, 8, 11 (200/200/200 U/kg)	3	lateral position starting 20 min - 2 h p.a. lasting 20 min - 6 h
	4, 8, 11 (200/200/200 U/kg)	3	clonic convulsions (once) starting 20 - 60 min p.a. lasting 0 - 5 min

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TABLE 2-2 Clinical Signs - Systemic Tolerance - Individual Data Monkey

Females

Group 4: 350/225/200 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(31)	1, 4, 8 (225/200/200 U/kg)	3	asthenia starting 20 - 60 min p.a. lasting 20 min - 6 h
	1 (225 U/kg)	1	mydriasis starting 20 - 60 min p.a. lasting 5 - 20 min
	1, 4 (225/200 U/kg)	2	lateral position starting 20 min - 2 h p.a. lasting 20 min - 2 h
	1, 4 (225/200 U/kg)	2	clonic convulsions (once) starting 20 - 60 min p.a. lasting 0 - 20 min
	4, 8, 11 (200/200/200 U/kg)	3	reduced motility starting 20 - 60 min p.a. lasting 20 min - 2 h
	4, 8, 11 (200/200/200 U/kg)	3	somnolent starting 20 - 60 min p.a. lasting 20 min - 2 h

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TABLE 2-2 Clinical Signs - Systemic Tolerance - Individual Data Monkey

Females

Group 4: 350/225/200 U/kg - Treatment period

Animal no.	Observed on test day	Total no. of days	Observation
(32)	1, 11 (225/200 U/kg)	2	reduced motility starting 20 - 60 min p.a. lasting 20 - 60 min
	1, 4, 8, 11 (225/200/200/200 U/kg)	4	somnolent starting 20 - 60 min p.a. lasting 5 - 60 min
	1, 8 (225/200 U/kg)	2	mydriasis starting 20 - 60 min p.a. lasting 5 - 60 min
	4, 8, 11 (200/200/200 U/kg)	3	asthenia starting 20 - 60 min p.a. lasting 20 - 60 min
	4, 11 (200/200 U/kg)	2	lateral position starting 20 - 60 min p.a. lasting 5 - 60 min
	4 (200 U/kg)	1	clonic convulsions (once) starting 20 - 60 min p.a. lasting 0 - 5 min

Group 4: 350/225/200 U/kg - Recovery period

Animal no.	Observed on test day	Total no. of days	Observation
(31)	N/A	N/A	no signs of systemic intolerance
(32)	N/A	N/A	no signs of systemic intolerance

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TABLE 3-1

Body Weight - Summary

Monkey

Bodyweight (kg)		Day(s) Relative to Start Date									
Sex: Male		-7	-5	1	4	8	11	12			
Group 1: Control	Mean	2.30	-	2.50	2.48	2.42	2.38	2.40			
	SD	0.07	-	0.10	0.08	0.13	0.08	0.10			
	N	5	-	5	5	5	5	3			
		-	-	-	-	-	-	-			
Group 2: 35 Units/kg	Mean	2.30	-	2.47	2.40	2.40	2.33	2.33			
	SD	0.10	-	0.15	0.10	0.10	0.12	0.15			
	N	3	-	3	3	3	3	3			
	%Diff	0.0	-	-1.3	-3.2	-0.8	-2.0	-2.8			
Group 3: 110 Units/kg	Mean	2.30	-	2.43	2.43	2.40	2.37	2.30			
	SD	0.00	-	0.06	0.06	0.00	0.06	0.00			
	N	3	-	3	3	3	3	3			
	%Diff	0.0	-	-2.7	-1.9	-0.8	-0.6	-4.2			
Group 4: 350/225/ 200 Units/kg	Mean	2.28	2.40n	2.44	2.44	2.44	2.42	2.33			
	SD	0.13	-	0.13	0.13	0.09	0.08	0.12			
	N	5	2	7	5	5	5	3			
	%Diff	-0.9	-	-2.3	-1.6	0.8	1.7	-2.8			

Anova & Dunnett: n - Inappropriate for statistics

Allogenic APOSEC™

TABLE 3-1 Body Weight - Summary Monkey

Bodyweight (kg)		Day(s) Relative to Start Date			
Sex: Male		15		26	
		22		2	
Group 1: Control	Mean	2.30n	2.35n	2.35n	
	SD	-	-	-	
	N	2	2	2	
		-	-	-	
Group 2: 35 Units/kg	Mean	-	-	-	
	SD	-	-	-	
	N	-	-	-	
	%Diff	-	-	-	
Group 3: 110 Units/kg	Mean	-	-	-	
	SD	-	-	-	
	N	-	-	-	
	%Diff	-	-	-	
Group 4: 350/225/ 200 Units/kg	Mean	2.55n	2.55n	2.45n	
	SD	-	-	-	
	N	2	2	2	
	%Diff	10.9	8.5	4.3	

Anova & Dunnett: n - Inappropriate for statistics

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TABLE 3-1

Body Weight - Summary

Monkey

Bodyweight (kg)		Day(s) Relative to Start Date									
Sex: Female		-7 [a]	1 [a1]	4 [a]	8 [a]	11 [a1]	12 [a]	15 [a]			
Group 1: Control	Mean	2.10	2.18	2.20	2.20	2.14	2.17	2.25n			
	SD	0.07	0.04	0.07	0.07	0.05	0.06	-			
	N	5	5	5	5	5	3	2			
		-	-	-	-	-	-	-			
Group 2: 35 Units/kg	Mean	2.13	2.17	2.23	2.23	2.20	2.20	-			
	SD	0.06	0.06	0.06	0.06	0.00	0.10	-			
	N	3	3	3	3	3	3	-			
	%Diff	1.6	-0.6	1.5	1.5	2.8	1.5	-			
Group 3: 110 Units/kg	Mean	2.13	2.17	2.20	2.27	2.17	2.23	-			
	SD	0.15	0.12	0.17	0.12	0.12	0.15	-			
	N	3	3	3	3	3	3	-			
	%Diff	1.6	-0.6	0.0	3.0	1.2	3.1	-			
Group 4: 350/225/ 200 Units/kg	Mean	2.14	2.18	2.24	2.22	2.18	2.17	2.35n			
	SD	0.15	0.13	0.17	0.18	0.13	0.06	-			
	N	5	5	5	5	5	3	2			
	%Diff	1.9	0.0	1.8	0.9	1.9	0.0	4.4			

[a] - Anova & Dunnett: n - Inappropriate for statistics

[a1] - Anova & Dunnett(Rank)

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Body Weight - Summary

Monkey

TABLE 3-1

Bodyweight (kg)		Day(s) Relative to Start Date	
Sex: Female		22	26
Group 1: Control	Mean	2.35 n	2.30 n
	SD	-	-
	N	2	2
		-	-
Group 2: 35 Units/kg	Mean	-	-
	SD	-	-
	N	-	-
	%Diff	-	-
Group 3: 110 Units/kg	Mean	-	-
	SD	-	-
	N	-	-
	%Diff	-	-
Group 4: 350/225/200 Units/kg	Mean	2.45 n	2.45 n
	SD	-	-
	N	2	2
	%Diff	4.3	6.5

Anova & Dunnett: n - Inappropriate for statistics

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TABLE 3-1

Body Weight - Summary

Monkey

Comments and Markers

Page	Measurement	Group	Sex	Day	Marker	Comment
	Bodyweight	4	Male	-5	n	Anova & Dunnett: n - Inappropriate for statistics
	Bodyweight	1	Male	15	n	Anova & Dunnett: n - Inappropriate for statistics
	Bodyweight	1	Male	22	n	Anova & Dunnett: n - Inappropriate for statistics
	Bodyweight	1	Male	26	n	Anova & Dunnett: n - Inappropriate for statistics
	Bodyweight	4	Male	15	n	Anova & Dunnett: n - Inappropriate for statistics
	Bodyweight	4	Male	22	n	Anova & Dunnett: n - Inappropriate for statistics
	Bodyweight	4	Male	26	n	Anova & Dunnett: n - Inappropriate for statistics

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TABLE 3-1

Body Weight - Summary

Monkey

Comments and Markers

Page	Measurement	Group	Sex	Day	Marker	Comment
	Bodyweight	1	Female	15	n	Anova & Dunnett: n - Inappropriate for statistics
	Bodyweight	4	Female	15	n	Anova & Dunnett: n - Inappropriate for statistics
	Bodyweight	1	Female	22	n	Anova & Dunnett: n - Inappropriate for statistics
	Bodyweight	1	Female	26	n	Anova & Dunnett: n - Inappropriate for statistics
	Bodyweight	4	Female	22	n	Anova & Dunnett: n - Inappropriate for statistics
	Bodyweight	4	Female	26	n	Anova & Dunnett: n - Inappropriate for statistics

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TABLE 3-2

Monkey

Body Weight - Individual Data

Sex: Male Bodyweight (kg)

Group 1: Control	Day(s) Relative to Start Date									
	-7	-5	1	4	8	11	12			
1	2.4	-	2.6	2.6	2.6	2.5	2.5	2.5	2.4	2.5
2	2.3	-	2.5	2.5	2.5	2.4	2.4	2.4	2.4	2.4
3	2.3	-	2.6	2.5	2.4	2.3	2.3	2.3	-	2.3
4	2.2	-	2.4	2.4	2.3	2.3	-	-	-	-
5	2.3	-	2.4	2.4	2.3	2.3	-	-	-	-
Mean	2.30	-	2.50	2.48	2.42	2.38	2.40	2.38	2.40	2.40
SD	0.07	-	0.10	0.08	0.13	0.08	0.10	0.08	0.10	0.10
N	5	-	5	5	5	5	3	5	3	3

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TABLE 3-2 Body Weight - Individual Data Monkey

Sex: Male Bodyweight (kg)					
Group 1: Control	Day(s) Relative to Start Date				
	15	22	26		
1	-	-	-	-	
2	-	-	-	-	
3	-	-	-	-	
4	2.3	2.4	2.4	2.4	
5	2.3	2.3	2.3	2.3	
Mean	2.30	2.35	2.35	2.35	
SD	-	-	-	-	
N	2	2	2	2	

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TABLE 3-2

Sex: Male Bodyweight (kg)									
Group 2: 35 Units/kg	Day(s) Relative to Start Date								
	-7	-5	1	4	8	11	12		
11	2.3	-	2.5	2.4	2.4	2.4	2.3		
12	2.4	-	2.6	2.5	2.5	2.4	2.5		
13	2.2	-	2.3	2.3	2.3	2.2	2.2		
Mean	2.30	-	2.47	2.40	2.40	2.33	2.33		
SD	0.10	-	0.15	0.10	0.10	0.12	0.15		
N	3	-	3	3	3	3	3		

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TABLE 3-2

Sex: Male		Bodyweight (kg)		TABLE 3-2				Body Weight - Individual Data		Monkey	
Group 3: 110 Units/kg		Day(s) Relative to Start Date									
		-7	-5	1	4	8	11	12			
17	2.3		-	2.4	2.4	2.4	2.4	2.3			
18	2.3		-	2.5	2.5	2.4	2.4	2.3			
19	2.3		-	2.4	2.4	2.4	2.3	2.3			
Mean	2.30		-	2.43	2.43	2.40	2.37	2.30			
SD	0.00		-	0.06	0.06	0.00	0.06	0.00			
N	3		-	3	3	3	3	3			

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TABLE 3-2

Sex: Male Bodyweight (kg)									
Group 4: 350/225/ 200 Units/kg	Day(s) Relative to Start Date								
	-7	-5	1	4	8	11	12		
23	2.3	-	2.6	2.5	2.5	2.5	2.4		
24	2.2	-	2.3	2.3	2.3	2.3	2.2		
25	2.4	-	2.6	2.6	2.5	2.4	2.4		
26	2.4	-	2.4	-	-	-	-		
27	2.1	-	2.3	-	-	-	-		
33	-	2.4	2.5	2.5	2.5	2.5	-		
34	-	2.4	2.4	2.3	2.4	2.4	-		
Mean	2.28	2.40	2.44	2.44	2.44	2.42	2.33		
SD	0.13	-	0.13	0.13	0.09	0.08	0.12		
N	5	2	7	5	5	5	3		

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TABLE 3-2 Body Weight - Individual Data Monkey

Sex: Male	Bodyweight (kg)		
		Day(s) Relative to Start Date	
Group 4: 350/225/ 200 Units/kg	15	22	26
	23	-	-
	24	-	-
	25	-	-
	26	-	-
	27	-	-
	33	2.6	2.5
	34	2.5	2.4
	Mean	2.55	2.45
	SD	-	-
	N	2	2

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TABLE 3-2

Sex: Female Bodyweight (kg)										
Group 1: Control	Day(s) Relative to Start Date									
	-7	1	4	8	11	12	15			
6	2.2	2.2	2.2	2.2	2.2	2.2	-			
7	2.1	2.2	2.2	2.2	2.1	2.2	-			
8	2.0	2.1	2.1	2.1	2.1	2.1	-			
9	2.1	2.2	2.2	2.2	2.1	-	2.2			
10	2.1	2.2	2.3	2.3	2.2	-	2.3			
Mean	2.10	2.18	2.20	2.20	2.14	2.17	2.25			
SD	0.07	0.04	0.07	0.07	0.05	0.06	-			
N	5	5	5	5	5	3	2			

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TABLE 3-2 Body Weight - Individual Data Monkey

Sex: Female			Bodyweight (kg)		
Group 1: Control	Day(s) Relative to Start Date		22	26	
6	-	-	-	-	
7	-	-	-	-	
8	-	-	-	-	
9	2.3	2.3	2.3	2.3	
10	2.4	2.3	2.3	2.3	
Mean	2.35	2.30			
SD	-	-			
N	2	2			

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TABLE 3-2

Sex: Female Bodyweight (kg)									
Group 2: 35 Units/kg		Day(s) Relative to Start Date							
		-7	1	4	8	11	12	15	
14	2.2		2.2	2.3	2.3	2.2	2.3	-	
15	2.1		2.2	2.2	2.2	2.2	2.2	-	
16	2.1		2.1	2.2	2.2	2.2	2.1	-	
Mean	2.13		2.17	2.23	2.23	2.20	2.20	-	
SD	0.06		0.06	0.06	0.06	0.00	0.10	-	
N	3		3	3	3	3	3	-	

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TABLE 3-2

Sex: Female Bodyweight (kg)									
Group 3: 110 Units/kg		Day(s) Relative to Start Date							
		-7	1	4	8	11	12	15	
20	2.3		2.3	2.4	2.4	2.3	2.4	-	
21	2.0		2.1	2.1	2.2	2.1	2.2	-	
22	2.1		2.1	2.1	2.2	2.1	2.1	-	
Mean	2.13		2.17	2.20	2.27	2.17	2.23	-	
SD	0.15		0.12	0.17	0.12	0.12	0.15	-	
N	3		3	3	3	3	3	-	

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TABLE 3-2

Sex: Female		Bodyweight (kg)	TABLE 3-2		Body Weight - Individual Data	Monkey		
Group 4: 350/225/ 200 Units/kg		Day(s) Relative to Start Date						
		-7	1	4	8	11	12	15
28	2.0		2.1	2.2	2.1	2.1	2.2	-
29	2.1		2.1	2.1	2.1	2.1	2.1	-
30	2.1		2.2	2.3	2.3	2.2	2.2	-
31	2.1		2.1	2.1	2.1	2.1	-	2.2
32	2.4		2.4	2.5	2.5	2.4	-	2.5
Mean	2.14		2.18	2.24	2.22	2.18	2.17	2.35
SD	0.15		0.13	0.17	0.18	0.13	0.06	-
N	5		5	5	5	5	3	2

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TABLE 3-2

Sex: Female		Bodyweight (kg)		Body Weight - Individual Data		Monkey
Group 4: 350/225/ 200 Units/kg	Day(s) Relative to Start Date					
	22	26				
28	-	-				
29	-	-				
30	-	-				
31	2.3	2.3				
32	2.6	2.6				
Mean	2.45	2.45				
SD	-	-				
N	2	2				

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TABLE 3-3

Body Weight Gain - Summary

Monkey

Body Weight Gain (%)		Day(s) Relative to Start Date							
Sex: Male		1 → 4	1 → 8	1 → 11	1 → 12	11 → 15	11 → 22	11 → 26	
Group 1: Control	Mean	-0.77	-3.21	-4.77	-6.46	0.00	2.17	2.17	
	SD	1.72	3.26	1.64	4.40	0.00	3.07	3.07	
	N	5	5	5	3	2	2	2	
Group 2: 35 Units/kg	Mean	-2.62	-2.62	-5.35	-5.40	-	-	-	
	SD	2.27	2.27	2.04	2.27	-	-	-	
	N	3	3	3	3	-	-	-	
Group 3: 110 Units/kg	Mean	0.00	-1.33	-2.72	-5.44	-	-	-	
	SD	0.00	2.31	2.36	2.21	-	-	-	
	N	3	3	3	3	-	-	-	
Group 4: 350/225/ 200 Units/kg	Mean	-1.60	-1.54	-2.31	-6.58	4.08	4.08	0.00	
	SD	2.20	2.11	3.44	1.93	0.12	0.12	0.00	
	N	5	5	5	3	2	2	2	
		-	-	-	-	-	-	-	

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TABLE 3-3

Body Weight Gain - Summary

Monkey

Body Weight Gain (%)		Day(s) Relative to Start Date							
Sex: Female		1 → 4	1 → 8	1 → 11	1 → 12	11 → 15	11 → 22	11 → 26	
Group 1: Control	Mean	0.91	0.91	-1.82	0.00	4.65	9.31	7.03	
	SD	2.03	2.03	2.49	0.00	0.15	0.31	3.52	
	N	5	5	5	3	2	2	2	
Group 2: 35 Units/kg	Mean	-	-	-	-	-	-	-	
	SD	3.10	3.10	1.59	1.52	-	-	-	
	N	3	3	3	3	-	-	-	
Group 3: 110 Units/kg	Mean	-	-	-	-	-	-	-	
	SD	1.45	4.62	0.00	3.04	-	-	-	
	N	3	3	3	3	-	-	-	
Group 4: 350/225/ 200 Units/kg	Mean	-	-	-	-	-	-	-	
	SD	2.69	1.74	0.00	1.59	4.46	8.93	8.93	
	N	5	5	5	3	2	2	2	

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TABLE 3-4

Body Weight Gain - Individual Data

Monkey

Sex: Male Body Weight Gain (%)

Group 1: Control	Day(s) Relative to Start Date						
	1 → 4	1 → 8	1 → 11	1 → 12	11 → 15	11 → 22	11 → 26
1	0.0	0.0	-3.8	-3.8	-	-	-
2	0.0	0.0	-4.0	-4.0	-	-	-
3	-3.8	-7.7	-7.7	-11.5	-	-	-
4	0.0	-4.2	-4.2	-	0.0	4.3	4.3
5	0.0	-4.2	-4.2	-	0.0	0.0	0.0
Mean	-0.77	-3.21	-4.77	-6.46	0.00	2.17	2.17
SD	1.72	3.26	1.64	4.40	0.00	3.07	3.07
N	5	5	5	3	2	2	2

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TABLE 3-4

Body Weight Gain - Individual Data

Monkey

Sex: Female	Body Weight Gain (%)	Day(s) Relative to Start Date							
		1 → 4	1 → 8	1 → 11	1 → 12	11 → 15	11 → 22	11 → 26	
Group 1: Control	6	0.0	0.0	0.0	0.0	-	-	-	
	7	0.0	0.0	-4.5	0.0	-	-	-	
	8	0.0	0.0	0.0	0.0	-	-	-	
	9	0.0	0.0	-4.5	-	4.8	9.5	9.5	
	10	4.5	4.5	0.0	-	4.5	9.1	4.5	
Mean SD N	Mean	0.91	0.91	-1.82	0.00	4.65	9.31	7.03	
	SD	2.03	2.03	2.49	0.00	0.15	0.31	3.52	
	N	5	5	5	3	2	2	2	

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TABLE 3-4

Sex: Male		Body Weight Gain (%)													
		TABLE 3-4					Body Weight Gain - Individual Data					Monkey			
		Day(s) Relative to Start Date													
Group 2: 35 Units/kg		1 → 4		1 → 8		1 → 11		1 → 12		11 → 15		11 → 22		11 → 26	
		11	-4.0	-4.0	-4.0	-4.0	-8.0	-	-	-	-	-	-	-	
		12	-3.8	-3.8	-7.7	-3.8	-3.8	-	-	-	-	-	-	-	
		13	0.0	0.0	-4.3	-4.3	-4.3	-	-	-	-	-	-	-	
		Mean	-2.62	-2.62	-5.35	-5.40	-5.40	-	-	-	-	-	-	-	
	SD	2.27	2.27	2.04	2.27	2.27	-	-	-	-	-	-	-		
	N	3	3	3	3	3	-	-	-	-	-	-	-		

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TABLE 3-4

Sex: Male		Body Weight Gain (%)						
		TABLE 3-4					Body Weight Gain - Individual Data	Monkey
		Day(s) Relative to Start Date						
Group 3: 110 Units/kg		1 → 4	1 → 8	1 → 11	1 → 12	11 → 15	11 → 22	11 → 26
	17	0.0	0.0	0.0	-4.2	-	-	-
	18	0.0	-4.0	-4.0	-8.0	-	-	-
	19	0.0	0.0	-4.2	-4.2	-	-	-
Mean	0.00	-1.33	-2.72	-5.44	-	-	-	-
SD	0.00	2.31	2.36	2.21	-	-	-	-
N	3	3	3	3	3	-	-	-

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TABLE 3-4

Monkey

Body Weight Gain - Individual Data

Sex: Male Body Weight Gain (%)

Group 4: 350/225/ 200 Units/kg	Day(s) Relative to Start Date					
	1 → 4	1 → 8	1 → 11	1 → 12	11 → 15	11 → 22
23	-3.8	-3.8	-3.8	-7.7	-	-
24	0.0	0.0	0.0	-4.3	-	-
25	0.0	-3.8	-7.7	-7.7	-	-
33	0.0	0.0	0.0	-	4.0	4.0
34	-4.2	0.0	0.0	-	4.2	4.2
Mean	-1.60	-1.54	-2.31	-6.58	4.08	4.08
SD	2.20	2.11	3.44	1.93	0.12	0.12
N	5	5	5	3	2	2

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TABLE 3-4

Sex: Female		Body Weight Gain (%)		TABLE 3-4		Body Weight Gain - Individual Data		Monkey	
Group 2: 35 Units/kg		Day(s) Relative to Start Date							
		1 → 4	1 → 8	1 → 11	1 → 12	11 → 15	11 → 22	11 → 26	
14	4.5		4.5	0.0	4.5	-	-	-	
15	0.0		0.0	0.0	0.0	-	-	-	
16	4.8		4.8	4.8	0.0	-	-	-	
Mean	3.10		3.10	1.59	1.52	-	-	-	
SD	2.69		2.69	2.75	2.62	-	-	-	
N	3		3	3	3	-	-	-	

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TABLE 3-4

Sex: Female		Body Weight Gain (%)		TABLE 3-4		Body Weight Gain - Individual Data		Monkey	
Group 3: 110 Units/kg		Day(s) Relative to Start Date							
		1 → 4	1 → 8	1 → 11	1 → 12	11 → 15	11 → 22	11 → 26	
20	4.3		4.3	0.0	4.3	-	-	-	
21	0.0		4.8	0.0	4.8	-	-	-	
22	0.0		4.8	0.0	0.0	-	-	-	
Mean	1.45		4.62	0.00	3.04	-	-	-	
SD	2.51		0.24	0.00	2.64	-	-	-	
N	3		3	3	3	-	-	-	

Allogenic APOSEC™

TABLE 3-4

Sex: Female Body Weight Gain (%) Individual Data Monkey

Group 4: 350/225/ 200 Units/kg	Day(s) Relative to Start Date					
	1 → 4	1 → 8	1 → 11	1 → 12	11 → 15	11 → 26
28	4.8	0.0	0.0	4.8	-	-
29	0.0	0.0	0.0	0.0	-	-
30	4.5	4.5	0.0	0.0	-	-
31	0.0	0.0	0.0	-	4.8	9.5
32	4.2	4.2	0.0	-	4.2	8.3
Mean	2.69	1.74	0.00	1.59	4.46	8.93
SD	2.47	2.39	0.00	2.75	0.42	0.84
N	5	5	5	3	2	2

Allogenic APOSEC™

TABLE 3-5 Body Weight at Autopsy - Individual Data Monkey

Sex: Male	Body Weight at Autopsy (kg)	
Group 4: 350/225/ 200 Units/kg	Day(s) Relative to Start Date	
	1	
	26	2.5
	27	2.3
	Mean	2.40
	SD	-
	N	2

Allogenic APOSEC™

TABLE 3-5 Body Weight at Autopsy - Individual Data Monkey

Sex: Male	Group 1: Control	Body Weight at Autopsy (kg)		Day(s) Relative to Start Date
		12	26	
	1	2.5	-	
	2	2.3	-	
	3	2.3	-	
	4	-	2.3	
	5	-	2.2	
	Mean	2.37	2.25	
	SD	0.12	-	
	N	3	2	

Allogenic APOSEC™

TABLE 3-5 Body Weight at Autopsy - Individual Data Monkey

Sex: Male	Body Weight at Autopsy (kg)	
Group 2: 35 Units/kg	Day(s) Relative to Start Date	
	12	26
	11	
	12	
	13	
Mean SD N	2.30	-
	0.10	-
	3	-

Allogenic APOSEC™

TABLE 3-5 Body Weight at Autopsy - Individual Data Monkey

Sex: Male	Body Weight at Autopsy (kg)	
	Day(s) Relative to Start Date	
Group 3: 110 Units/kg	12	26
	17	
	18	-
	19	-
Mean SD N	2.30 0.00 3	- - -

Allogenic APOSEC™

TABLE 3-5 Body Weight at Autopsy - Individual Data Monkey

Sex: Male	Body Weight at Autopsy (kg)		
Group 4: 350/225/ 200 Units/kg	Day(s) Relative to Start Date		
	12		26
	23	2.3	-
	24	2.2	-
	25	2.4	-
	33	-	2.4
	34	-	2.3
Mean	2.30		2.35
SD	0.10		-
N	3		2

Allogenic APOSEC™

TABLE 3-5 Body Weight at Autopsy - Individual Data Monkey

Sex: Female			Body Weight at Autopsy (kg)		
Group 1: Control	Day(s) Relative to Start Date		12	26	
6	2.1	-			
7	2.2	-			
8	2.0	-			
9	-	2.2			
10	-	2.2			
Mean	2.10	2.20			
SD	0.10	-			
N	3	2			

Allogenic APOSEC™

TABLE 3-5 Body Weight at Autopsy - Individual Data Monkey

Sex: Female	Body Weight at Autopsy (kg)	
Group 2: 35 Units/kg	Day(s) Relative to Start Date	
	12	26
	14	-
	15	-
	16	-
Mean	2.13	-
SD	0.06	-
N	3	-

Allogenic APOSEC™

TABLE 3-5 Body Weight at Autopsy - Individual Data Monkey

Sex: Female	Body Weight at Autopsy (kg)	
Group 3: 110 Units/kg	Day(s) Relative to Start Date	
	12	26
	20	2.3
	21	2.1
	22	2.1
Mean SD N	2.17	-
	0.12	-
	3	-

Allogenic APOSEC™

TABLE 3-5 Body Weight at Autopsy - Individual Data Monkey

Sex: Female			Body Weight at Autopsy (kg)			
Group 4: 350/225/ 200 Units/kg	Day(s) Relative to Start Date					
	12					
	26					
	28	2.1				-
	29	2.0				-
	30	2.1				-
	31	-				2.1
32	-	2.4				
Mean	2.07	2.25				
SD	0.06	-				
N	3	2				

TABLE 4-1 Allogenic APOSEC™
Food Consumption - Summary Monkey

Group 1 Control		Group 2 35 Units/kg		Group 3 110 Units/kg		Group 4 350/225/200 Units/kg	
m	f	m	f	m	f	m	f

Food Consumption (g/kg b.w./day)
(weekly mean value)

TW 1

Mean:	49.0	48.2	50.0	49.0	50.0	50.0	49.6	48.4
SD:	2.7	1.1	0.0	0.0	0.0	0.0	3.3	0.5

TW 2

Mean:	40.0	42.6	38.0	43.0	41.0	42.0	39.8	39.2
SD:	2.7	0.5	0.0	0.0	0.0	0.0	3.8	4.4

TW 3

Mean:	48.0	44.0					44.0	43.0
-------	------	------	--	--	--	--	------	------

TW 4

Mean:	33.0	38.0					38.0	38.0
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Allogenic APOSEC™
TABLE 4-2 Food Consumption - Individual Data Monkey

Group 1 Control	Group 2 35 Units/kg	Group 3 110 Units/kg	Group 4 350/225/200 Units/kg
males	males	males	males

Food Consumption (g/kg b.w./day)
(weekly mean value)

TW 1

(1)	51	(11)	50	(17)	50	(23)	52
(2)	51	(12)	50	(18)	50	(24)	52
(3)	51	(13)	50	(19)	50	(25)	52
(4)	46					(33)	46
(5)	46					(34)	46
Mean:	49.0		50.0		50.0		49.6
SD:	2.7		0.0		0.0		3.3

TW 2

(1)	38	(11)	38	(17)	41	(23)	37
(2)	38	(12)	38	(18)	41	(24)	37
(3)	38	(13)	38	(19)	41	(25)	37
(4)	43					(33)	44
(5)	43					(34)	44
Mean:	40.0		38.0		41.0		39.8
SD:	2.7		0.0		0.0		3.8

TW 3

(4)	48					(33)	44
(5)	48					(34)	44
Mean:	48.0						44.0

TW 4

(4)	33					(33)	38
(5)	33					(34)	38
Mean:	33.0						38.0

Allogenic APOSEC™
 TABLE 4-2 Food Consumption - Individual Data Monkey

Group 1 Control	Group 2 35 Units/kg	Group 3 110 Units/kg	Group 4 350/225/200 Units/kg
females	females	females	females

Food Consumption (g/kg b.w./day)
 (weekly mean value)

TW 1

(6)	49	(14)	49	(20)	50	(28)	48
(7)	49	(15)	49	(21)	50	(29)	48
(8)	49	(16)	49	(22)	50	(30)	48
(9)	47					(31)	49
(10)	47					(32)	49
Mean:	48.2		49.0		50.0		48.4
SD:	1.1		0.0		0.0		0.5

TW 2

(6)	43	(14)	43	(20)	42	(28)	36
(7)	43	(15)	43	(21)	42	(29)	36
(8)	43	(16)	43	(22)	42	(30)	36
(9)	42					(31)	44
(10)	42					(32)	44
Mean:	42.6		43.0		42.0		39.2
SD:	0.5		0.0		0.0		4.4

TW 3

(9)	44					(31)	43
(10)	44					(32)	43
Mean:	44.0						43.0

TW 4

(9)	38					(31)	38
(10)	38					(32)	38
Mean:	38.0						38.0

Allogenic APOSEC™

TABLE 5-1 Electrocardiographic Parameters - Summary Monkey

Day: 1 Relative to Start Date (PreDs)

Sex: Male		Electrocardiography					
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
		[a]	[a]	[a]	[a]	[a]	[a]
Group 1: Control	Mean	226.2	35.2	65.6	31.2	156.0	302.8
	SD	18.8	3.3	5.9	2.7	5.5	17.5
	N	5	5	5	5	5	5
		-	-	-	-	-	-
Group 2: 35 Units/kg	Mean	251.3	28.7	61.3	29.3	153.3	312.7
	SD	23.2	8.1	8.1	1.2	11.5	10.2
	N	3	3	3	3	3	3
	%Diff	11.1	-18.6	-6.5	-6.0	-1.7	3.3
Group 3: 110 Units/kg	Mean	258.0	33.3	58.7	34.0	150.0	310.0
	SD	37.0	5.8	8.1	5.3	17.3	34.6
	N	3	3	3	3	3	3
	%Diff	14.1	-5.3	-10.6	9.0	-3.8	2.4
Group 4: 350/225/ 200 Units/kg	Mean	253.0	30.3	59.1	32.6	148.9	304.7
	SD	26.7	5.5	4.3	6.1	10.8	20.0
	N	7	7	7	7	7	7
	%Diff	11.8	-14.0	-9.8	4.4	-4.6	0.6

[a] - Anova & Dunnett

Allogenic APOSEC™

TABLE 5-1Electrocardiographic Parameters - SummaryMonkey

Day: 1 Relative to Start Date (5minpa)

Sex: Male		Electrocardiography					
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 1: Control	[a]		[a]	[a]	[a]	[a]	[a]
	Mean	234.2	33.2	64.8	28.8	158.0	311.8
	SD	20.8	5.0	5.6	7.6	8.4	17.8
	N	5	5	5	5	5	5
Group 2: 35 Units/kg	-		-	-	-	-	-
	Mean	217.0	32.7	68.7	34.0	173.3	323.0
	SD	51.8	4.6	10.3	5.3	41.6	49.7
	N	3	3	3	3	3	3
Group 3: 110 Units/kg	%Diff	-7.3	-1.6	6.0	18.1	9.7	3.6
	Mean	241.3	33.3	61.3	36.0	152.7	304.0
	SD	35.2	4.2	2.3	6.9	21.9	29.1
	N	3	3	3	3	3	3
Group 4: 350/225/ 200 Units/kg	%Diff	3.0	0.4	-5.3	25.0	-3.4	-2.5
	Mean	224.7	29.4	64.3	31.7	163.7	315.0
	SD	33.4	6.0	9.5	3.1	13.8	21.7
	N	7	7	7	7	7	7
	%Diff	-4.1	-11.4	-0.8	10.1	3.6	1.0

[a] - Anova & Dunnett

Allogenic APOSEC™

TABLE 5-1 Electrocardiographic Parameters - Summary Monkey

Day: 11 Relative to Start Date (PreDs)		Electrocardiography					
Sex: Male		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
		[a]	[a]	[a]	[a]	[a1]	[a]
Group 1: Control	Mean	234.6	30.4	65.2	32.0	162.0	319.8
	SD	20.8	3.3	5.0	2.8	8.4	13.6
	N	5	5	5	5	5	5
		-	-	-	-	-	-
Group 2: 35 Units/kg	Mean	245.7	30.0	63.3	30.0	160.0	322.0
	SD	25.7	0.0	5.8	10.0	20.0	23.5
	N	3	3	3	3	3	3
	%Diff	4.7	-1.3	-2.9	-6.3	-1.2	0.7
Group 3: 110 Units/kg	Mean	239.0	32.7	58.0	38.0	159.3	316.7
	SD	45.0	4.6	7.2	2.0	1.2	29.4
	N	3	3	3	3	3	3
	%Diff	1.9	7.5	-11.0	18.8	-1.6	-1.0
Group 4: 350/225/ 200 Units/kg	Mean	240.4	25.6	58.4	34.8	164.0	326.4
	SD	30.5	5.2	3.6	5.0	11.4	11.1
	N	5	5	5	5	5	5
	%Diff	2.5	-15.8	-10.4	8.8	1.2	2.1

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Rank)

Allogenic APOSEC™

TABLE 5-1 Electrocardiographic Parameters - Summary Monkey

Day: 11 Relative to Start Date (5minpa)		Electrocardiography					
Sex: Male		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
		[a]	[a]	[a]	[a]	[a]	[a]
Group 1: Control	Mean	212.4	32.4	67.2	32.8	167.6	314.6
	SD	21.2	3.3	8.7	1.8	10.4	14.4
	N	5	5	5	5	5	5
		-	-	-	-	-	-
Group 2: 35 Units/kg	Mean	215.0	34.7	64.7	37.3	168.7	314.3
	SD	46.4	1.2	8.1	4.6	30.1	29.2
	N	3	3	3	3	3	3
	%Diff	1.2	7.0	-3.8	13.8	0.6	-0.1
Group 3: 110 Units/kg	Mean	223.7	31.3	59.3	34.0	163.3	312.7
	SD	43.9	6.1	9.0	6.0	20.8	30.6
	N	3	3	3	3	3	3
	%Diff	5.3	-3.3	-11.7	3.7	-2.5	-0.6
Group 4: 350/225/ 200 Units/kg	Mean	226.6	28.0	60.0	37.6	168.8	326.6
	SD	31.1	5.3	0.0	4.3	9.7	9.9
	N	5	5	5	5	5	5
	%Diff	6.7	-13.6	-10.7	14.6	0.7	3.8

[a] - Anova & Dunnett

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TABLE 5-1 Electrocardiographic Parameters - Summary Monkey

Day: 25 Relative to Start Date							
Sex: Male		Electrocardiography					
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 1: Control	Mean	[a]	[a]	[a]	[a]	[a]	[a]
	SD	238.5n	30.0n	60.0n	39.0n	160.0n	319.0n
	N	- 2	- 2	- 2	- 2	- 2	- 2
Group 4: 350/225/ 200 Units/kg	Mean	239.0n	27.0n	59.0n	38.0n	170.0n	338.5n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
	%Diff	0.2	-10.0	-1.7	-2.6	6.3	6.1

[a] - Anova & Dunnett: n - Inappropriate for statistics

Allogenic APOSEC™

TABLE 5-1 Electrocardiographic Parameters - Summary Monkey

Day: 1 Relative to Start Date (PreDs)

Sex: Female		Electrocardiography					
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 1: Control	[a]	[a]	[a]	[a]	[a]	[a]	
	Mean	243.4	32.8	64.4	34.0	151.6	305.2
	SD	17.4	4.4	4.6	4.2	11.7	23.6
	N	5	5	5	5	5	5
Group 2: 35 Units/kg	-	-	-	-	-	-	
	Mean	247.0	35.3	66.0	34.0	152.7	309.0
	SD	20.4	3.1	3.5	5.3	12.7	14.2
	N	3	3	3	3	3	3
Group 3: 110 Units/kg	%Diff	1.5	7.7	2.5	0.0	0.7	1.2
	Mean	250.0	25.3	65.3	31.3	150.0	305.3
	SD	36.2	5.0	5.0	2.3	10.0	19.6
	N	3	3	3	3	3	3
Group 4: 350/225/ 200 Units/kg	%Diff	2.7	-22.8	1.4	-7.8	-1.1	0.0
	Mean	237.4	27.6	63.2	35.2	154.0	305.6
	SD	22.4	4.3	6.9	5.8	8.9	17.8
	N	5	5	5	5	5	5
Units/kg	%Diff	-2.5	-15.9	-1.9	3.5	1.6	0.1

[a] - Anova & Dunnett

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TABLE 5-1 Electrocardiographic Parameters - Summary Monkey

Day: 1 Relative to Start Date (5minpa)		Electrocardiography					
Sex: Female		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 1: Control	[a]	[a]	[a]	[a1]	[a1]	[a1]	[a]
	Mean	214.0	32.8	64.4	38.0	164.8	310.0
	SD	24.2	4.1	9.0	4.5	7.8	5.9
	N	5	5	5	5	5	5
Group 2: 35 Units/kg	-	-	-	-	-	-	-
	Mean	217.3	32.7	64.0	32.0	166.7	317.0
	SD	17.2	4.6	6.9	6.9	5.8	8.2
	N	3	3	3	3	3	3
Group 3: 110 Units/kg	%Diff	1.6	-0.4	-0.6	-15.8	1.1	2.3
	Mean	214.7	34.0	70.0	31.3	166.7	314.3
	SD	32.5	4.0	4.0	3.1	11.5	23.7
	N	3	3	3	3	3	3
Group 4: 350/225/ 200 Units/kg	%Diff	0.3	3.7	8.7	-17.5	1.1	1.4
	Mean	211.2	31.2	72.4	37.2	164.8	307.8
	SD	27.5	3.9	7.1	6.3	10.3	10.2
	N	5	5	5	5	5	5
Units/kg	%Diff	-1.3	-4.9	12.4	-2.1	0.0	-0.7

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Rank)

Allogenic APOSEC™

TABLE 5-1 Electrocardiographic Parameters - Summary Monkey

Day: 11 Relative to Start Date (PreDs)		Electrocardiography					
Sex: Female		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
		[a]	[a1]	[a]	[a]	[a]	[a]
Group 1: Control	Mean	251.8	31.2	63.2	32.8	144.0	294.6
	SD	12.1	1.8	6.1	2.7	8.9	11.8
	N	5	5	5	5	5	5
Group 2: 35 Units/kg		-	-	-	-	-	-
	Mean	244.0	31.3	60.7	32.7	156.7	315.3
	SD	27.5	2.3	1.2	6.4	5.8	12.6
	N	3	3	3	3	3	3
Group 3: 110 Units/kg	%Diff	-3.1	0.4	-4.0	-0.4	8.8	7.0
	Mean	223.0	29.3	71.3	33.3	156.7	299.7
	SD	45.1	1.2	10.3	4.2	10.1	12.6
	N	3	3	3	3	3	3
Group 4: 350/225/ 200 Units/kg	%Diff	-11.4	-6.0	12.9	1.6	8.8	1.7
	Mean	230.2	32.0	63.6	36.0	158.0*	309.0
	SD	26.6	4.7	4.1	2.8	4.5	19.0
	N	5	5	5	5	5	5
Units/kg	%Diff	-8.6	2.6	0.6	9.8	9.7	4.9

[a] - Anova & Dunnett: * = $p \leq 0.05$

[a1] - Anova & Dunnett(Rank)

Allogenic APOSEC™

TABLE 5-1 Electrocardiographic Parameters - Summary Monkey

Day: 11 Relative to Start Date (5minpa)		Electrocardiography					
Sex: Female		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
		[a]	[a]	[a]	[a1]	[a1]	[a]
Group 1: Control	Mean	223.2	32.0	64.8	37.6	156.0	300.2
	SD	18.2	4.2	5.6	4.8	8.9	14.1
	N	5	5	5	5	5	5
		-	-	-	-	-	-
Group 2: 35 Units/kg	Mean	238.3	33.3	62.0	29.3	160.7	320.0
	SD	8.4	5.8	3.5	3.1	1.2	5.0
	N	3	3	3	3	3	3
	%Diff	6.8	4.2	-4.3	-22.0	3.0	6.6
Group 3: 110 Units/kg	Mean	224.7	29.3	68.7	30.0	158.0	302.7
	SD	42.9	3.1	8.1	0.0	17.1	6.4
	N	3	3	3	3	3	3
	%Diff	0.7	-8.3	6.0	-20.2	1.3	0.8
Group 4: 350/225/ 200 Units/kg	Mean	222.2	31.2	67.2	36.4	160.0	307.8
	SD	15.4	3.0	5.9	5.4	0.0	10.8
	N	5	5	5	5	5	5
	%Diff	-0.4	-2.5	3.7	-3.2	2.6	2.5

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Rank)

Allogenic APOSEC™

TABLE 5-1 Electrocardiographic Parameters - Summary Monkey

Day: 25 Relative to Start Date		Electrocardiography						
Sex: Female		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)	
		[a]	[a]	[a]	[a]	[a]	[a]	
Group 1: Control	Mean	258.0n	30.0n	65.0n	37.0n	157.0n	325.0n	
	SD	-	-	-	-	-	-	
	N	2	2	2	2	2	2	
Group 4: 350/225/ 200 Units/kg	Mean	226.5n	28.0n	63.0n	34.0n	158.0n	303.5n	
	SD	-	-	-	-	-	-	
	N	2	2	2	2	2	2	
	%Diff	-12.2	-6.7	-3.1	-8.1	0.6	-6.6	

[a] - Anova & Dunnett: n - Inappropriate for statistics

Allogenic APOSEC™

TABLE 5-1 Electrocardiographic Parameters - Summary Monkey

Comments and Markers

Page	Day	Group	Sex	Measurement	Marker	Comment
25	25	1	Male	Heart Rate	n	Anova & Dunnett: n - Inappropriate for statistics
25	25	1	Male	P Segment	n	Anova & Dunnett: n - Inappropriate for statistics
25	25	1	Male	PQ Interval	n	Anova & Dunnett: n - Inappropriate for statistics
25	25	1	Male	QRS Interval	n	Anova & Dunnett: n - Inappropriate for statistics
25	25	1	Male	QT Interval	n	Anova & Dunnett: n - Inappropriate for statistics
25	25	1	Male	QTc Value Bazett	n	Anova & Dunnett: n - Inappropriate for statistics
25	25	4	Male	Heart Rate	n	Anova & Dunnett: n - Inappropriate for statistics
25	25	4	Male	P Segment	n	Anova & Dunnett: n - Inappropriate for statistics
25	25	4	Male	PQ Interval	n	Anova & Dunnett: n - Inappropriate for statistics
25	25	4	Male	QRS Interval	n	Anova & Dunnett: n - Inappropriate for statistics
25	25	4	Male	QT Interval	n	Anova & Dunnett: n - Inappropriate for statistics
25	25	4	Male	QTc Value Bazett	n	Anova & Dunnett: n - Inappropriate for statistics

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TABLE 5-1 Electrocardiographic Parameters - Summary Monkey

Comments and Markers

<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker</u>	<u>Comment</u>
	11 (PreDs)	4	Female	QT Interval	*	Anova & Dunnett: * = $p \leq 0.05$
	25	1	Female	Heart Rate	n	Anova & Dunnett: n - Inappropriate for statistics
	25	1	Female	P Segment	n	Anova & Dunnett: n - Inappropriate for statistics
	25	1	Female	PQ Interval	n	Anova & Dunnett: n - Inappropriate for statistics
	25	1	Female	QRS Interval	n	Anova & Dunnett: n - Inappropriate for statistics
	25	1	Female	QT Interval	n	Anova & Dunnett: n - Inappropriate for statistics
	25	1	Female	QTc Value Bazett	n	Anova & Dunnett: n - Inappropriate for statistics
	25	4	Female	Heart Rate	n	Anova & Dunnett: n - Inappropriate for statistics
	25	4	Female	P Segment	n	Anova & Dunnett: n - Inappropriate for statistics
	25	4	Female	PQ Interval	n	Anova & Dunnett: n - Inappropriate for statistics
	25	4	Female	QRS Interval	n	Anova & Dunnett: n - Inappropriate for statistics
	25	4	Female	QT Interval	n	Anova & Dunnett: n - Inappropriate for statistics
	25	4	Female	QTc Value Bazett	n	Anova & Dunnett: n - Inappropriate for statistics

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Sex: Male	Day: 1 Relative to Start Date (PreDs)	Electrocardiography					Monkey
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 1: Control	1	217	38	72	34	160	304
	2	246	36	72	34	150	304
	3	226	38	62	30	160	311
	4	200	30	60	30	150	274
	5	242	34	62	28	160	321
Mean		226.2	35.2	65.6	31.2	156.0	302.8
SD		18.8	3.3	5.9	2.7	5.5	17.5
N		5	5	5	5	5	5

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Sex: Male		Day: 1 Relative to Start Date (PreDs)	Electrocardiography				Monkey
Group 2: 35 Units/kg	Heart Rate (beats/min)		P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
	11	278	36	54	30	140	301
	12	236	20	60	28	160	317
	13	240	30	70	30	160	320
	Mean	251.3	28.7	61.3	29.3	153.3	312.7
	SD	23.2	8.1	8.1	1.2	11.5	10.2
	N	3	3	3	3	3	3

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Sex: Male	Day: 1 Relative to Start Date (PreDs)	Electrocardiography					Monkey
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 3: 110 Units/kg	17	244	40	66	40	170	343
	18	300	30	50	32	140	313
	19	230	30	60	30	140	274
	Mean	258.0	33.3	58.7	34.0	150.0	310.0
	SD	37.0	5.8	8.1	5.3	17.3	34.6
	N	3	3	3	3	3	3

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TABLE 5-2 Electrocardiographic Parameters - Individual Data Monkey

Sex: Male	Day: 1 Relative to Start Date (PreDs)	Electrocardiography					
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 4: 350/225/ 200 Units/kg	23	288	20	50	30	140	307
	24	217	30	60	40	152	289
	25	261	30	60	42	160	334
	26	236	38	60	26	160	317
	27	226	34	64	28	150	291
	33	273	30	60	30	130	277
	34	270	30	60	32	150	318
	Mean	253.0	30.3	59.1	32.6	148.9	304.7
	SD	26.7	5.5	4.3	6.1	10.8	20.0
	N	7	7	7	7	7	7

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TABLE 5-2 Electrocardiographic Parameters - Individual Data Monkey

Sex: Male	Day: 1 Relative to Start Date (5minpa)	Electrocardiography				
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)
Group 1: Control	1	238	36	66	24	160
	2	248	26	70	30	150
	3	210	38	70	40	170
	4	216	30	60	20	150
	5	259	36	58	30	160
Mean		234.2	33.2	64.8	28.8	158.0
SD		20.8	5.0	5.6	7.6	8.4
N		5	5	5	5	5
						QTc Value Bazett (ms)
						319
						305
						318
						285
						332
						311.8
						17.8
						5

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Monkey

Sex: Male	Day: 1 Relative to Start Date (5minpa)	Electrocardiography					
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 2: 35 Units/kg							
	11	276	38	60	32	140	300
	12	179	30	66	40	220	380
	13	196	30	80	30	160	289
Mean SD N		217.0	32.7	68.7	34.0	173.3	323.0
		51.8	4.6	10.3	5.3	41.6	49.7
		3	3	3	3	3	3

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Sex: Male	Day: 1 Relative to Start Date (5minpa)	Electrocardiography					Monkey
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	
Group 3: 110 Units/kg							QTc Value Bazett (ms)
	17	211	32	64	40	178	334
	18	280	30	60	40	140	302
	19	233	38	60	28	140	276
Mean SD N		241.3	33.3	61.3	36.0	152.7	304.0
		35.2	4.2	2.3	6.9	21.9	29.1
		3	3	3	3	3	3

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TABLE 5-2 Electrocardiographic Parameters - Individual Data Monkey

Sex: Male	Day: 1 Relative to Start Date (5minpa)	Electrocardiography				
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)
Group 4: 350/225/ 200 Units/kg						QTc Value Bazett (ms)
	23	261	20	50	38	160
	24	183	26	60	30	180
	25	265	30	60	34	160
	26	203	30	72	30	180
	27	236	30	60	30	160
	33	236	40	70	30	140
	34	189	30	78	30	166
	Mean	224.7	29.4	64.3	31.7	163.7
	SD	33.4	6.0	9.5	3.1	13.8
	N	7	7	7	7	7
						334
						314
						336
						331
						317
						278
						295
						315.0
						21.7
						7

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TABLE 5-2 Electrocardiographic Parameters - Individual Data Monkey

Sex: Male	Day: 11 Relative to Start Date (PreDs)	Electrocardiography				
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)
Group 1: Control	1	266	28	60	34	150
	2	229	30	70	34	170
	3	240	30	70	34	160
	4	209	36	66	28	160
	5	229	28	60	30	170
Mean SD N	Mean	234.6	30.4	65.2	32.0	162.0
	SD	20.8	3.3	5.0	2.8	8.4
	N	5	5	5	5	5
		QTc Value Bazett (ms)				
		316				
		332				
		320				
		299				
		332				
		319.8				
		13.6				
		5				

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TABLE 5-2 Electrocardiographic Parameters - Individual Data Monkey

Sex: Male	Day: 11 Relative to Start Date (PreDs)	Electrocardiography					
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 2: 35 Units/kg							
	11	273	30	60	30	140	299
	12	222	30	60	40	180	346
	13	242	30	70	20	160	321
Mean SD N		245.7	30.0	63.3	30.0	160.0	322.0
		25.7	0.0	5.8	10.0	20.0	23.5
		3	3	3	3	3	3

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TABLE 5-2 Electrocardiographic Parameters - Individual Data Monkey

Sex: Male	Day: 11 Relative to Start Date (PreDs)	Electrocardiography					
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 3: 110 Units/kg	17	256	30	50	40	160	330
	18	273	30	60	38	158	337
	19	188	38	64	36	160	283
	Mean	239.0	32.7	58.0	38.0	159.3	316.7
	SD	45.0	4.6	7.2	2.0	1.2	29.4
	N	3	3	3	3	3	3

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Monkey

Sex: Male Day: 11 Relative to Start Date (PreDs)

Group 4: 350/225/ 200 Units/kg	Electrocardiography					
	Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
23	252	30	60	34	160	328
24	196	28	60	40	180	325
25	273	20	60	30	160	341
33	257	20	60	30	150	310
34	224	30	52	40	170	328
Mean	240.4	25.6	58.4	34.8	164.0	326.4
SD	30.5	5.2	3.6	5.0	11.4	11.1
N	5	5	5	5	5	5

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TABLE 5-2 Electrocardiographic Parameters - Individual Data Monkey

Sex: Male	Day: 11 Relative to Start Date (5minpa)	Electrocardiography				
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)
Group 1: Control						QTc Value Bazett (ms)
	1	248	30	60	34	160
	2	214	36	72	32	160
	3	194	30	80	34	180
	4	205	36	64	34	160
	5	201	30	60	30	178
Mean SD N		212.4	32.4	67.2	32.8	167.6
		21.2	3.3	8.7	1.8	10.4
		5	5	5	5	5
						314.6
						14.4
						5

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Sex: Male		Day: 11 Relative to Start Date (5minpa)		Electrocardiography				Monkey
Group 2: 35 Units/kg	Day: 11 Relative to Start Date (5minpa)		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
	11		268	36	60	40	140	296
	12		182	34	60	40	200	348
	13		195	34	74	32	166	299
	Mean		215.0	34.7	64.7	37.3	168.7	314.3
	SD		46.4	1.2	8.1	4.6	30.1	29.2
	N		3	3	3	3	3	3

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Monkey

Sex: Male Day: 11 Relative to Start Date (5minpa)

Group 3: 110 Units/kg	Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
17	248	30	50	40	170	346
18	250	26	60	34	140	286
19	173	38	68	28	180	306
Mean	223.7	31.3	59.3	34.0	163.3	312.7
SD	43.9	6.1	9.0	6.0	20.8	30.6
N	3	3	3	3	3	3

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Sex: Male	Day: 11 Relative to Start Date (5minpa)	Electrocardiography					Monkey
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 4: 350/225/ 200 Units/kg	23	242	34	60	40	166	333
	24	181	30	60	40	180	313
	25	261	20	60	38	160	334
	33	238	30	60	30	160	319
	34	211	26	60	40	178	334
Mean		226.6	28.0	60.0	37.6	168.8	326.6
SD		31.1	5.3	0.0	4.3	9.7	9.9
N		5	5	5	5	5	5

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Sex: Male		Day: 25 Relative to Start Date	Electrocardiography				Monkey
Group 1: Control	Heart Rate (beats/min)		P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
	4	229	30	60	38	160	313
	5	248	30	60	40	160	325
	Mean	238.5	30.0	60.0	39.0	160.0	319.0
	SD	-	-	-	-	-	-
N		2	2	2	2	2	2

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Sex: Male		Day: 25 Relative to Start Date		Electrocardiography				Monkey	
				Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 4: 350/225/ 200 Units/kg	33	254		20	50	40	160	329	
	34	224		34	68	36	180	348	
	Mean	239.0		27.0	59.0	38.0	170.0	338.5	
	SD	-		-	-	-	-	-	-
	N	2		2	2	2	2	2	2

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Sex: Female		Day: 1 Relative to Start Date (PreDs)		Electrocardiography				Monkey
Group 1: Control		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)	
	6	221	34	70	34	166		
	7	252	30	64	34	160		
	8	248	30	60	40	140		
	9	265	30	60	28	152		
	10	231	40	68	34	140		
Mean		243.4	32.8	64.4	34.0	151.6	305.2	
SD		17.4	4.4	4.6	4.2	11.7	23.6	
N		5	5	5	5	5	5	

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TABLE 5-2 Electrocardiographic Parameters - Individual Data Monkey

Sex: Female	Day: 1 Relative to Start Date (PreDs)	Electrocardiography					
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 2: 35 Units/kg							
	14	231	36	64	32	160	314
	15	270	38	70	30	138	293
	16	240	32	64	40	160	320
Mean SD N		247.0	35.3	66.0	34.0	152.7	309.0
		20.4	3.1	3.5	5.3	12.7	14.2
		3	3	3	3	3	3

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Sex: Female	Day: 1 Relative to Start Date (PreDs)	Electrocardiography					Monkey
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 3: 110 Units/kg	20	246	20	66	34	160	324
	21	288	26	60	30	140	307
	22	216	30	70	30	150	285
	Mean	250.0	25.3	65.3	31.3	150.0	305.3
	SD	36.2	5.0	5.0	2.3	10.0	19.6
	N	3	3	3	3	3	3

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Sex: Female	Day: 1 Relative to Start Date (PreDs)	Electrocardiography					Monkey
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 4: 350/225/ 200 Units/kg	28	252	28	54	36	160	328
	29	236	20	70	40	160	317
	30	252	30	70	26	150	307
	31	199	30	62	34	160	291
	32	248	30	60	40	140	285
Mean SD N	Mean	237.4	27.6	63.2	35.2	154.0	305.6
	SD	22.4	4.3	6.9	5.8	8.9	17.8
	N	5	5	5	5	5	5

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Sex: Female		Day: 1 Relative to Start Date (5minpa)		Electrocardiography				Monkey
Group 1: Control		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)	
		205	32	64	40	170	314	
		222	32	60	40	160	308	
		233	30	60	40	158	311	
		234	30	58	30	160	316	
		176	40	80	40	176	301	
Mean		214.0	32.8	64.4	38.0	164.8	310.0	
SD		24.2	4.1	9.0	4.5	7.8	5.9	
N		5	5	5	5	5	5	

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Sex: Female		Day: 1 Relative to Start Date (5minpa)	Electrocardiography				Monkey
Group 2: 35 Units/kg	Heart Rate (beats/min)		P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
	14	220	30	60	28	170	326
	15	199	38	72	28	170	310
	16	233	30	60	40	160	315
	Mean	217.3	32.7	64.0	32.0	166.7	317.0
	SD	17.2	4.6	6.9	6.9	5.8	8.2
	N	3	3	3	3	3	3

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Sex: Female		Day: 1 Relative to Start Date (5minpa)		Electrocardiography				Monkey
Group 3: 110 Units/kg	Heart Rate (beats/min)		P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)	
	20	199	38	70	34	180	328	
	21	252	30	66	28	160	328	
	22	193	34	74	32	160	287	
	Mean	214.7	34.0	70.0	31.3	166.7	314.3	
	SD	32.5	4.0	4.0	3.1	11.5	23.7	
	N	3	3	3	3	3	3	

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TABLE 5-2 Electrocardiographic Parameters - Individual Data Monkey

Sex: Female	Day: 1 Relative to Start Date (5minpa)	Electrocardiography					
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 4: 350/225/ 200 Units/kg	28	217	36	66	40	170	323
	29	205	30	80	40	160	296
	30	244	34	70	26	154	311
	31	169	26	80	40	180	302
	32	221	30	66	40	160	307
	Mean	211.2	31.2	72.4	37.2	164.8	307.8
	SD	27.5	3.9	7.1	6.3	10.3	10.2
	N	5	5	5	5	5	5

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TABLE 5-2 Electrocardiographic Parameters - Individual Data Monkey

Sex: Female		Day: 11 Relative to Start Date (PreDs)		Electrocardiography				
Group 1: Control		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value	
							Bazett (ms)	
	6	233	32	62	34	160	315	
	7	263	30	60	34	140	293	
	8	261	30	60	30	140	292	
	9	254	34	60	30	140	288	
	10	248	30	74	36	140	285	
Mean		251.8	31.2	63.2	32.8	144.0	294.6	
SD		12.1	1.8	6.1	2.7	8.9	11.8	
N		5	5	5	5	5	5	

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TABLE 5-2 Electrocardiographic Parameters - Individual Data Monkey

Sex: Female	Day: 11 Relative to Start Date (PreDs)	Electrocardiography					
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 2: 35 Units/kg							
	14	250	30	62	28	160	327
	15	268	34	60	30	150	317
	16	214	30	60	40	160	302
Mean		244.0	31.3	60.7	32.7	156.7	315.3
SD		27.5	2.3	1.2	6.4	5.8	12.6
N		3	3	3	3	3	3

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Sex: Female	Day: 11 Relative to Start Date (PreDs)	Electrocardiography					Monkey
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 3: 110 Units/kg	20	200	28	80	38	158	288
	21	275	30	60	30	146	313
	22	194	30	74	32	166	298
	Mean	223.0	29.3	71.3	33.3	156.7	299.7
	SD	45.1	1.2	10.3	4.2	10.1	12.6
	N	3	3	3	3	3	3

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TABLE 5-2 Electrocardiographic Parameters - Individual Data

Monkey

Sex: Female	Day: 11 Relative to Start Date (PreDs)	Electrocardiography				
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)
Group 4: 350/225/ 200 Units/kg						QTc Value Bazett (ms)
	28	246	40	64	38	160
	29	210	30	70	40	160
	30	261	30	60	34	160
	31	196	32	64	34	160
	32	238	28	60	34	150
Mean SD N		230.2	32.0	63.6	36.0	158.0
		26.6	4.7	4.1	2.8	4.5
		5	5	5	5	5
						309.0
						19.0
						5

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TABLE 5-2 Electrocardiographic Parameters - Individual Data Monkey

Sex: Female		Day: 11 Relative to Start Date (5minpa)		Electrocardiography				
Group 1: Control		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value	
							Bazett (ms)	
	6	203	26	58	36	160	294	
	7	231	36	66	40	160	314	
	8	233	36	60	42	160	315	
	9	244	32	70	30	140	282	
	10	205	30	70	40	160	296	
Mean		223.2	32.0	64.8	37.6	156.0	300.2	
SD		18.2	4.2	5.6	4.8	8.9	14.1	
N		5	5	5	5	5	5	

Allogenic APOSEC™

TABLE 5-2 Electrocardiographic Parameters - Individual Data Monkey

Sex: Female	Day: 11 Relative to Start Date (5minpa)	Electrocardiography					
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 2: 35 Units/kg							
	14	234	30	60	30	162	320
	15	233	30	60	32	160	315
	16	248	40	66	26	160	325
Mean		238.3	33.3	62.0	29.3	160.7	320.0
SD		8.4	5.8	3.5	3.1	1.2	5.0
N		3	3	3	3	3	3

Allogenic APOSEC™

TABLE 5-2 Electrocardiographic Parameters - Individual Data

Sex: Female		Day: 11 Relative to Start Date (5minpa)	Electrocardiography				Monkey
Group 3: 110 Units/kg	Heart Rate (beats/min)		P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
	20	191	30	70	30	174	310
	21	273	26	60	30	140	299
	22	210	32	76	30	160	299
	Mean	224.7	29.3	68.7	30.0	158.0	302.7
	SD	42.9	3.1	8.1	0.0	17.1	6.4
	N	3	3	3	3	3	3

Allogenic APOSEC™

TABLE 5-2 Electrocardiographic Parameters - Individual Data Monkey

Sex: Female	Day: 11 Relative to Start Date (5minpa)	Electrocardiography					
		Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
Group 4: 350/225/ 200 Units/kg	28	221	36	70	40	160	307
	29	234	30	70	40	160	316
	30	235	30	60	28	160	317
	31	224	28	62	34	160	309
	32	197	32	74	40	160	290
	Mean	222.2	31.2	67.2	36.4	160.0	307.8
	SD	15.4	3.0	5.9	5.4	0.0	10.8
	N	5	5	5	5	5	5

Allogenic APOSEC™

TABLE 5-2 Electrocardiographic Parameters - Individual Data

Sex: Female		Day: 25 Relative to Start Date	Electrocardiography				Monkey
Group 1: Control	Heart Rate (beats/min)		P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
	9	268	30	60	36	154	325
	10	248	30	70	38	160	325
	Mean	258.0	30.0	65.0	37.0	157.0	325.0
SD		-	-	-	-	-	-
N		2	2	2	2	2	2

Allogenic APOSEC™

TABLE 5-2 Electrocardiographic Parameters - Individual Data

Monkey

Sex: Female Day: 25 Relative to Start Date

Group 4: 350/225/ 200 Units/kg	Electrocardiography					
	Heart Rate (beats/min)	P Segment (ms)	PQ Interval (ms)	QRS Interval (ms)	QT Interval (ms)	QTc Value Bazett (ms)
31	197	26	66	28	180	326
32	256	30	60	40	136	281
Mean	226.5	28.0	63.0	34.0	158.0	303.5
SD	-	-	-	-	-	-
N	2	2	2	2	2	2

Allogenic APOSEC™					
TABLE 5-3	Pathological Arrhythmia - Individual Data				Monkey
	Group 1	Group 2	Group 3	Group 4	
	Control	35 U/kg	110 U/kg	350/225/200 U/kg	
	males	males	males	males	

Pathological arrhythmia

before administration

TD 1

(1)	0	(11)	0	(17)	0	(23)	0
(2)	0	(12)	0	(18)	1 ^{#1}	(24)	0
(3)	0	(13)	0	(19)	0	(25)	0
(4)	0					(26)	0
(5)	0					(27)	0
						(33)	0
						(34)	0

5 min after administration

TD 1

(1)	0	(11)	0	(17)	0	(23)	0
(2)	0	(12)	0	(18)	0	(24)	0
(3)	0	(13)	0	(19)	0	(25)	0
(4)	0					(26)	0
(5)	0					(27)	0
						(33)	0
						(34)	0

0: no pathological findings

1: pathological finding

#: sinus tachycardia

Allogenic APOSEC™					
TABLE 5-3	Pathological Arrhythmia - Individual Data				Monkey
	Group 1	Group 2	Group 3	Group 4	
	Control	35 U/kg	110 U/kg	350/225/200 U/kg	
	males	males	males	males	

Pathological arrhythmia

before administration

TD 11

(1)	0	(11)	0	(17)	0	(23)	0
(2)	0	(12)	0	(18)	0	(24)	0
(3)	0	(13)	0	(19)	0	(25)	0
(4)	0					(26)	-
(5)	0					(27)	-
						(33)	0
						(34)	0

5 min after administration

TD 11

(1)	0	(11)	0	(17)	0	(23)	0
(2)	0	(12)	0	(18)	0	(24)	0
(3)	0	(13)	0	(19)	0	(25)	0
(4)	0					(26) ^{#1}	-
(5)	0					(27) ^{#2}	-
						(33)	0
						(34)	0

0: no pathological findings

#1: Male no. 26 had to be sacrificed prematurely on test day 1.

#2: Male no. 27 had to be sacrificed prematurely on test day 1.

Allogenic APOSEC™					
TABLE 5-3	Pathological Arrhythmia - Individual Data				Monkey
	Group 1	Group 2	Group 3	Group 4	
	Control	35 U/kg	110 U/kg	350/225/200 U/kg	
	males	males	males	males	

Pathological arrhythmia

TD 25

(4)	0	(33)	0
(5)	0	(34)	0

0: no pathological findings

TABLE 5-3		Allogenic APOSEC™ Pathological Arrhythmia - Individual Data				Monkey	
		Group 1	Group 2	Group 3	Group 4		
		Control	35 U/kg	110 U/kg	350/225/200 U/kg		
		females	females	females	females		

Pathological arrhythmia

before administration

TD 1

(6)	0	(14)	0	(20)	0	(28)	0
(7)	0	(15)	0	(21)	0	(29)	0
(8)	0	(16)	0	(22)	0	(30)	0
(9)	0					(31)	0
(10)	0					(32)	0

5 min after administration

TD 1

(6)	0	(14)	0	(20)	1 ^{#1}	(28)	0
(7)	0	(15)	0	(21)	0	(29)	0
(8)	0	(16)	0	(22)	0	(30)	0
(9)	0					(31)	0
(10)	0					(32)	0

0: no pathological findings
 1: pathological finding
 #1: 1x ventricular extrasystole

TABLE 5-3	Allogenic APOSEC™ Pathological Arrhythmia - Individual Data				Monkey
	Group 1 Control	Group 2 35 U/kg	Group 3 110 U/kg	Group 4 350/225/200 U/kg	
	females	females	females	females	

Pathological arrhythmia

before administration

TD 11

(6)	0	(14)	0	(20)	0	(28)	0
(7)	0	(15)	0	(21)	0	(29)	0
(8)	0	(16)	0	(22)	0	(30)	0
(9)	0					(31)	0
(10)	0					(32)	0

5 min after administration

TD 11

(6)	0	(14)	0	(20)	0	(28)	0
(7)	0	(15)	0	(21)	0	(29)	0
(8)	0	(16)	0	(22)	0	(30)	0
(9)	0					(31)	0
(10)	0					(32)	0

0: no pathological findings

Allogenic APOSEC™					
TABLE 5-3	Pathological Arrhythmia - Individual Data				Monkey
	Group 1	Group 2	Group 3	Group 4	
	Control	35 U/kg	110 U/kg	350/225/200 U/kg	
	females	females	females	females	

Pathological arrhythmia

TD 25

(9)	0	(31)	0
(10)	0	(32)	0

0: no pathological findings

Allogenic APOSEC™

TABLE 6-1 Blood Pressure Parameters - Summary Monkey

Day: 1 Relative to Start Date (PreDs)		Blood Pressure		
Sex: Male		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
		[a]	[a]	[a]
Group 1: Control	Mean	148.2	97.6	116.0
	SD	20.0	18.8	18.9
	N	5	5	5
		-	-	-
Group 2: 35 Units/kg	Mean	158.0	111.7	128.3
	SD	37.5	29.7	32.1
	N	3	3	3
	%Diff	6.6	14.4	10.6
Group 3: 110 Units/kg	Mean	145.3	108.3	122.0
	SD	36.7	24.6	28.4
	N	3	3	3
	%Diff	-1.9	11.0	5.2
Group 4: 350/225/ 200 Units/kg	Mean	144.1	99.4	115.6
	SD	37.4	27.6	30.5
	N	7	7	7
	%Diff	-2.7	1.9	-0.4

[a] - Anova & Dunnett

Allogenic APOSEC™

TABLE 6-1 Blood Pressure Parameters - Summary Monkey

Day: 1 Relative to Start Date (5minpa)					
Sex: Male		Blood Pressure			
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)	
		[a]	[a]	[a]	
Group 1: Control	Mean	143.6	95.2	112.6	
	SD	17.0	17.2	16.3	
	N	5	5	5	
		-	-	-	
Group 2: 35 Units/kg	Mean	147.0	105.0	120.3	
	SD	41.9	39.1	39.7	
	N	3	3	3	
	%Diff	2.4	10.3	6.9	
Group 3: 110 Units/kg	Mean	148.3	92.3	112.3	
	SD	26.1	7.4	13.2	
	N	3	3	3	
	%Diff	3.3	-3.0	-0.2	
Group 4: 350/225/200 Units/kg	Mean	135.7	87.3	104.7	
	SD	28.1	23.8	24.4	
	N	7	7	7	
	%Diff	-5.5	-8.3	-7.0	

[a] - Anova & Dunnett

Allogenic APOSEC™

TABLE 6-1 Blood Pressure Parameters - Summary Monkey

Day: 11 Relative to Start Date (PreDs)		Blood Pressure			
Sex: Male		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)	
		[a]	[a]	[a]	
Group 1: Control	Mean	155.4	101.0	120.2	
	SD	30.7	21.0	23.0	
	N	5	5	5	
		-	-	-	
Group 2: 35 Units/kg	Mean	161.7	106.7	126.3	
	SD	12.5	52.7	39.1	
	N	3	3	3	
	%Diff	4.0	5.6	5.1	
Group 3: 110 Units/kg	Mean	147.0	103.3	119.0	
	SD	35.1	27.3	27.8	
	N	3	3	3	
	%Diff	-5.4	2.3	-1.0	
Group 4: 350/225/200 Units/kg	Mean	147.6	105.4	120.6	
	SD	17.1	17.3	16.1	
	N	5	5	5	
	%Diff	-5.0	4.4	0.3	

[a] - Anova & Dunnett

Allogenic APOSEC™

TABLE 6-1 Blood Pressure Parameters - Summary Monkey

Day: 11 Relative to Start Date (5minpa)					
Sex: Male		Blood Pressure			
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)	
		[a]	[a]	[a]	
Group 1: Control	Mean	135.2	94.6	109.4	
	SD	9.1	7.6	6.0	
	N	5	5	5	
		-	-	-	
Group 2: 35 Units/kg	Mean	149.7	119.0	130.7	
	SD	18.5	14.7	15.7	
	N	3	3	3	
	%Diff	10.7	25.8	19.4	
Group 3: 110 Units/kg	Mean	143.0	95.0	112.3	
	SD	7.8	6.2	6.4	
	N	3	3	3	
	%Diff	5.8	0.4	2.7	
Group 4: 350/225/ 200 Units/kg	Mean	143.4	95.2	112.6	
	SD	15.8	28.4	23.5	
	N	5	5	5	
	%Diff	6.1	0.6	2.9	

[a] - Anova & Dunnett

Allogenic APOSEC™

TABLE 6-1 Blood Pressure Parameters - Summary Monkey

Day: 25 Relative to Start Date		Blood Pressure		
Sex: Male		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
		[a]	[a]	[a]
Group 1: Control	Mean	138.0n	83.5n	103.0n
	SD	-	-	-
	N	2	2	2
Group 4: 350/225/200 Units/kg	Mean	139.5n	76.5n	98.5n
	SD	-	-	-
	N	2	2	2
		%Diff	1.1	-8.4
				-4.4

[a] - Anova & Dunnett: n - Inappropriate for statistics

Allogenic APOSEC™

TABLE 6-1 Blood Pressure Parameters - Summary Monkey

Day: 1 Relative to Start Date (PreDs)					
Sex: Female		Blood Pressure			
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)	
		[a]	[a1]	[a]	
Group 1: Control	Mean	131.6	83.4	100.8	
	SD	26.4	27.5	26.2	
	N	5	5	5	
Group 2: 35 Units/kg	Mean	129.7	93.7	107.0	
	SD	15.7	14.0	14.5	
	N	3	3	3	
	%Diff	-1.5	12.3	6.2	
Group 3: 110 Units/kg	Mean	142.7	81.0	103.0	
	SD	13.4	2.0	3.5	
	N	3	3	3	
	%Diff	8.4	-2.9	2.2	
Group 4: 350/225/200 Units/kg	Mean	137.8	84.2	103.6	
	SD	24.1	14.9	17.6	
	N	5	5	5	
	%Diff	4.7	1.0	2.8	

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Rank)

Allogenic APOSEC™

TABLE 6-1 Blood Pressure Parameters - Summary Monkey

Day: 1 Relative to Start Date (5minpa)					
Sex: Female		Blood Pressure			
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)	
		[a]	[a]	[a]	
Group 1: Control	Mean	152.6	87.2	110.6	
	SD	19.0	14.5	13.5	
	N	5	5	5	
		-	-	-	
Group 2: 35 Units/kg	Mean	117.0	67.7	85.7	
	SD	31.5	17.4	21.8	
	N	3	3	3	
	%Diff	-23.3	-22.4	-22.5	
Group 3: 110 Units/kg	Mean	139.7	79.3	100.7	
	SD	8.4	7.4	3.5	
	N	3	3	3	
	%Diff	-8.5	-9.0	-9.0	
Group 4: 350/225/200 Units/kg	Mean	125.4	68.4	88.8	
	SD	23.0	10.0	12.9	
	N	5	5	5	
	%Diff	-17.8	-21.6	-19.7	

[a] - Anova & Dunnett

Allogenic APOSEC™

TABLE 6-1 Blood Pressure Parameters - Summary Monkey

Day: 11 Relative to Start Date (PreDs)		Blood Pressure			
Sex: Female		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)	
		[a]	[a]	[a]	
Group 1: Control	Mean	161.0	106.2	125.8	
	SD	24.1	18.8	19.3	
	N	5	5	5	
		-	-	-	
Group 2: 35 Units/kg	Mean	163.3	119.0	135.3	
	SD	18.8	22.5	21.4	
	N	3	3	3	
	%Diff	1.4	12.1	7.6	
Group 3: 110 Units/kg	Mean	139.3	87.7	106.3	
	SD	15.0	19.0	17.8	
	N	3	3	3	
	%Diff	-13.5	-17.5	-15.5	
Group 4: 350/225/200 Units/kg	Mean	153.8	94.2	115.2	
	SD	26.8	26.3	21.5	
	N	5	5	5	
	%Diff	-4.5	-11.3	-8.4	

[a] - Anova & Dunnett

Allogenic APOSEC™

TABLE 6-1 Blood Pressure Parameters - Summary Monkey

Day: 11 Relative to Start Date (5minpa)					
Sex: Female		Blood Pressure			
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)	
		[a]	[a]	[a]	
Group 1: Control	Mean	146.0	94.2	112.8	
	SD	7.5	20.7	13.9	
	N	5	5	5	
		-	-	-	
Group 2: 35 Units/kg	Mean	141.3	91.0	109.0	
	SD	15.3	8.2	8.9	
	N	3	3	3	
	%Diff	-3.2	-3.4	-3.4	
Group 3: 110 Units/kg	Mean	141.0	80.0	101.3	
	SD	30.0	16.7	19.3	
	N	3	3	3	
	%Diff	-3.4	-15.1	-10.2	
Group 4: 350/225/ 200 Units/kg	Mean	158.2	90.0	114.0	
	SD	14.4	20.8	18.3	
	N	5	5	5	
	%Diff	8.4	-4.5	1.1	

[a] - Anova & Dunnett

Allogenic APOSEC™

TABLE 6-1 Blood Pressure Parameters - Summary Monkey

Day: 25 Relative to Start Date		Blood Pressure		
Sex: Female		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
		[a]	[a]	[a]
Group 1: Control	Mean	146.5n	74.5n	100.0n
	SD	-	-	-
	N	2	2	2
Group 4: 350/225/200 Units/kg	Mean	144.5n	90.5n	110.0n
	SD	-	-	-
	N	2	2	2
	%Diff	-1.4	21.5	10.0

[a] - Anova & Dunnett: n - Inappropriate for statistics

Allogenic APOSEC™

TABLE 6-1

Blood Pressure Parameters - Summary

Monkey

Page	Day	Group	Sex	Measurement	Marker	Comment
	25	1	Male	Systolic Blood Press.	n	Anova & Dunnett: n - Inappropriate for statistics
	25	1	Male	Diastolic Blood Press.	n	Anova & Dunnett: n - Inappropriate for statistics
	25	1	Male	Mean Blood Press.	n	Anova & Dunnett: n - Inappropriate for statistics
	25	4	Male	Systolic Blood Press.	n	Anova & Dunnett: n - Inappropriate for statistics
	25	4	Male	Diastolic Blood Press.	n	Anova & Dunnett: n - Inappropriate for statistics
	25	4	Male	Mean Blood Press.	n	Anova & Dunnett: n - Inappropriate for statistics

Allogenic APOSEC™

TABLE 6-1

Blood Pressure Parameters - Summary

Monkey

Page	Day	Group	Sex	Measurement	Marker	Comment
	25	1	Female	Systolic Blood Press.	n	Anova & Dunnett: n - Inappropriate for statistics
	25	1	Female	Diastolic Blood Press.	n	Anova & Dunnett: n - Inappropriate for statistics
	25	1	Female	Mean Blood Press.	n	Anova & Dunnett: n - Inappropriate for statistics
	25	4	Female	Systolic Blood Press.	n	Anova & Dunnett: n - Inappropriate for statistics
	25	4	Female	Diastolic Blood Press.	n	Anova & Dunnett: n - Inappropriate for statistics
	25	4	Female	Mean Blood Press.	n	Anova & Dunnett: n - Inappropriate for statistics

Allogenic APOSEC™

TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Male	Day: 1 Relative to Start Date (PreDs)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 1: Control	1	144	108	122
	2	179	120	141
	3	142	88	107
	4	124	71	90
	5	152	101	120
	Mean	148.2	97.6	116.0
	SD	20.0	18.8	18.9
	N	5	5	5

Allogenic APOSEC™

TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Male Day: 1 Relative to Start Date (PreDs)		Blood Pressure		
Group 2: 35 Units/kg		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
		188	134	153
		116	78	92
		170	123	140
	Mean	158.0	111.7	128.3
	SD	37.5	29.7	32.1
	N	3	3	3

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Male	Day: 1 Relative to Start Date (PreDs)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 3: 110 Units/kg	17	118	89	100
	18	187	136	154
	19	131	100	112
	Mean	145.3	108.3	122.0
	SD	36.7	24.6	28.4
	N	3	3	3

Allogenic APOSEC™

TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Male	Day: 1 Relative to Start Date (PreDs)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 4: 350/225/ 200 Units/kg	23	156	103	122
	24	83	59	68
	25	144	99	115
	26	163	97	121
	27	189	143	159
	33	169	120	138
	34	105	75	86
	Mean	144.1	99.4	115.6
	SD	37.4	27.6	30.5
	N	7	7	7

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Male	Day: 1 Relative to Start Date (5minpa)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 1: Control	1	134	78	98
	2	157	119	133
	3	163	97	120
	4	143	103	118
	5	121	79	94
	Mean	143.6	95.2	112.6
	SD	17.0	17.2	16.3
	N	5	5	5

Allogenic APOSEC™

TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Male Day: 1 Relative to Start Date (5minpa)		Blood Pressure		
Group 2: 35 Units/kg		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
		195	150	166
		118	80	94
		128	85	101
	Mean	147.0	105.0	120.3
	SD	41.9	39.1	39.7
	N	3	3	3

Allogenic APOSEC™

TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Male	Day: 1 Relative to Start Date (5minpa)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 3: 110 Units/kg	17	121	84	98
	18	151	95	115
	19	173	98	124
	Mean	148.3	92.3	112.3
	SD	26.1	7.4	13.2
	N	3	3	3

Allogenic APOSEC™

TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Male	Day: 1 Relative to Start Date (5minpa)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 4: 350/225/ 200 Units/kg	23	160	100	121
	24	111	80	92
	25	165	114	132
	26	144	86	107
	27	161	112	129
	33	107	72	85
	34	102	47	67
	Mean	135.7	87.3	104.7
	SD	28.1	23.8	24.4
	N	7	7	7

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Male Day: 11 Relative to Start Date (PreDs)

Group 1: Control	Blood Pressure		
	Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
1	159	96	119
2	198	116	144
3	135	80	99
4	118	84	96
5	167	129	143
Mean	155.4	101.0	120.2
SD	30.7	21.0	23.0
N	5	5	5

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Male Day: 11 Relative to Start Date (PreDs)

Group 2: 35 Units/kg	Blood Pressure		
	Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
11	149	48	83
12	162	122	137
13	174	150	159
Mean	161.7	106.7	126.3
SD	12.5	52.7	39.1
N	3	3	3

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Male	Day: 11 Relative to Start Date (PreDs)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 3: 110 Units/kg	17	118	72	89
	18	186	122	144
	19	137	116	124
	Mean	147.0	103.3	119.0
	SD	35.1	27.3	27.8
	N	3	3	3

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Male	Day: 11 Relative to Start Date (PreDs)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 4: 350/225/ 200 Units/kg	23	145	115	126
	24	133	90	105
	25	173	111	133
	33	155	126	137
	34	132	85	102
	Mean	147.6	105.4	120.6
	SD	17.1	17.3	16.1
	N	5	5	5

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Male	Day: 11 Relative to Start Date (5minpa)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 1: Control	1	142	83	104
	2	136	97	111
	3	146	104	119
	4	127	96	108
	5	125	93	105
	Mean	135.2	94.6	109.4
	SD	9.1	7.6	6.0
	N	5	5	5

Allogenic APOSEC™

TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Male	Day: 11 Relative to Start Date (5minpa)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 2: 35 Units/kg	11	131	102	113
	12	150	127	136
	13	168	128	143
	Mean	149.7	119.0	130.7
	SD	18.5	14.7	15.7
	N	3	3	3

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Male	Day: 11 Relative to Start Date (5minpa)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 3: 110 Units/kg	17	134	88	105
	18	148	97	115
	19	147	100	117
	Mean	143.0	95.0	112.3
	SD	7.8	6.2	6.4
	N	3	3	3

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Male Day: 11 Relative to Start Date (5minpa)		Blood Pressure		
Group 4: 350/225/ 200 Units/kg	Systolic Blood Press. (mmHg)		Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
	23	155	129	139
	24	125	70	90
	25	159	99	120
	33	150	115	128
	34	128	63	86
	Mean	143.4	95.2	112.6
SD		15.8	28.4	23.5
N		5	5	5

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Male Day: 25 Relative to Start Date

Group 1: Control	Blood Pressure			Mean Blood Press. (mmHg)
	Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)		
4	122	92		103
5	154	75		103
Mean	138.0	83.5		103.0
SD	-	-		-
N	2	2		2

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Male	Day: 25 Relative to Start Date	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 4: 350/225/ 200 Units/kg	33	145	91	110
	34	134	62	87
Mean		139.5	76.5	98.5
SD		-	-	-
N		2	2	2

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Female	Day: 1 Relative to Start Date (PreDs)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 1: Control	6	178	124	143
	7	124	64	85
	8	124	96	107
	9	120	78	93
	10	112	55	76
Mean		131.6	83.4	100.8
SD		26.4	27.5	26.2
N		5	5	5

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Female	Day: 1 Relative to Start Date (PreDs)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 2: 35 Units/kg	14	142	108	121
	15	112	80	92
	16	135	93	108
	Mean	129.7	93.7	107.0
	SD	15.7	14.0	14.5
	N	3	3	3

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Female	Day: 1 Relative to Start Date (PreDs)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 3: 110 Units/kg	20	137	81	101
	21	133	83	101
	22	158	79	107
	Mean	142.7	81.0	103.0
	SD	13.4	2.0	3.5
	N	3	3	3

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Female	Day: 1 Relative to Start Date (PreDs)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 4: 350/225/ 200 Units/kg	28	170	105	128
	29	132	73	94
	30	103	67	81
	31	144	90	109
	32	140	86	106
	Mean	137.8	84.2	103.6
	SD	24.1	14.9	17.6
	N	5	5	5

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Female	Day: 1 Relative to Start Date (5minpa)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 1: Control	6	147	89	110
	7	147	92	112
	8	144	62	91
	9	139	94	111
	10	186	99	129
Mean		152.6	87.2	110.6
SD		19.0	14.5	13.5
N		5	5	5

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Female		Day: 1 Relative to Start Date (5minpa)		Blood Pressure		
Group 2: 35 Units/kg		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)		
14		86	48	62		
15		149	81	105		
16		116	74	90		
Mean		117.0	67.7	85.7		
SD		31.5	17.4	21.8		
N		3	3	3		

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Female	Day: 1 Relative to Start Date (5minpa)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 3: 110 Units/kg	20	145	82	104
	21	130	85	101
	22	144	71	97
	Mean	139.7	79.3	100.7
	SD	8.4	7.4	3.5
	N	3	3	3

Allogenic APOSEC™

TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Female	Day: 1 Relative to Start Date (5minpa)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 4: 350/225/ 200 Units/kg	28	163	81	110
	29	125	66	87
	30	101	65	78
	31	116	75	90
	32	122	55	79
	Mean	125.4	68.4	88.8
	SD	23.0	10.0	12.9
	N	5	5	5

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Female Day: 11 Relative to Start Date (PreDs)		Blood Pressure		
Group 1: Control		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
	6	148	95	114
	7	128	87	102
	8	169	131	145
	9	192	121	146
	10	168	97	122
Mean		161.0	106.2	125.8
SD		24.1	18.8	19.3
N		5	5	5

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Female	Day: 11 Relative to Start Date (PreDs)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 2: 35 Units/kg	14	154	107	124
	15	151	105	122
	16	185	145	160
	Mean	163.3	119.0	135.3
	SD	18.8	22.5	21.4
	N	3	3	3

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Female	Day: 11 Relative to Start Date (PreDs)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 3: 110 Units/kg	20	122	68	87
	21	147	89	110
	22	149	106	122
	Mean	139.3	87.7	106.3
	SD	15.0	19.0	17.8
	N	3	3	3

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Female	Day: 11 Relative to Start Date (PreDs)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 4: 350/225/ 200 Units/kg	28	186	69	109
	29	152	93	114
	30	120	75	91
	31	137	98	112
	32	174	136	150
	Mean	153.8	94.2	115.2
	SD	26.8	26.3	21.5
	N	5	5	5

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Female		Day: 11 Relative to Start Date (5minpa)				
Group 1: Control	Blood Pressure					
	Systolic Blood Press. (mmHg)		Diastolic Blood Press. (mmHg)		Mean Blood Press. (mmHg)	
	6	154	93		115	
	7	149	68		96	
	8	138	81		101	
	9	151	111		126	
	10	138	118		126	
	Mean	146.0	94.2		112.8	
	SD	7.5	20.7		13.9	
	N	5	5		5	

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Female		Day: 11 Relative to Start Date (5minpa)			
Group 2: 35 Units/kg	Blood Pressure				Mean Blood Press. (mmHg)
	Systolic Blood Press. (mmHg)		Diastolic Blood Press. (mmHg)		
14	153	100		119	
15	147	84		106	
16	124	89		102	
Mean	141.3	91.0		109.0	
SD	15.3	8.2		8.9	
N	3	3		3	

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Female		Day: 11 Relative to Start Date (5minpa)			
Group 3: 110 Units/kg	Blood Pressure				Mean Blood Press. (mmHg)
	Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)			
20	110	62			79
21	143	95			112
22	170	83			113
Mean	141.0	80.0			101.3
SD	30.0	16.7			19.3
N	3	3			3

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Female	Day: 11 Relative to Start Date (5minpa)	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 4: 350/225/ 200 Units/kg	28	146	69	96
	29	171	104	127
	30	145	77	101
	31	153	81	107
	32	176	119	139
	Mean	158.2	90.0	114.0
	SD	14.4	20.8	18.3
	N	5	5	5

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TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Female Day: 25 Relative to Start Date

Group 1: Control	Blood Pressure		
	Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
9	142	68	94
10	151	81	106
Mean	146.5	74.5	100.0
SD	-	-	-
N	2	2	2

Allogenic APOSEC™

TABLE 6-2 Blood Pressure Parameters - Individual Data Monkey

Sex: Female	Day: 25 Relative to Start Date	Blood Pressure		
		Systolic Blood Press. (mmHg)	Diastolic Blood Press. (mmHg)	Mean Blood Press. (mmHg)
Group 4: 350/225/ 200 Units/kg	31	156	100	120
	32	133	81	100
	Mean	144.5	90.5	110.0
	SD	-	-	-
	N	2	2	2

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day(s): Predose Relative to Start Date		Haematological Parameters					
Sex: Male		HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
		[a]	[a]	[a1]	[a]	[a]	[a]
Group 1: Control	Mean	8.44	6.152	9.732	1.26	400.0	47.00
	SD	0.50	0.457	1.776	0.37	41.6	3.23
	N	5	5	5	5	5	5
		-	-	-	-	-	-
Group 2: 35 Units/kg	Mean	8.93	6.443	12.717	1.13	378.7	49.93
	SD	0.15	0.252	1.278	0.38	156.9	2.03
	N	3	3	3	3	3	3
Group 3: 110 Units/kg	%Diff	5.8	4.7	30.7	-10.1	-5.3	6.2
	Mean	8.57	6.227	9.440	0.97	401.0	46.70
	SD	0.49	0.146	1.722	0.12	69.3	0.72
Group 4: 350/225/ 200 Units/kg	N	3	3	3	3	3	3
	%Diff	1.5	1.2	-3.0	-23.3	0.3	-0.6
	Mean	8.44	5.997	11.570	1.17	420.0	46.29
Group 4: 350/225/ 200 Units/kg	SD	0.26	0.183	4.843	0.45	72.6	2.23
	N	7	7	7	7	7	7
	%Diff	0.0	-2.5	18.9	-7.0	5.0	-1.5

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Log)

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day: 12 Relative to Start Date		Haematological Parameters					
Sex: Male		HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
		[a]	[a]	[a]	[a]	[a]	[a]
Group 1: Control	Mean	8.16	5.930	11.558	1.72	461.8	45.92
	SD	0.43	0.514	3.317	0.55	66.1	3.20
	N	5	5	5	5	5	5
Group 2: 35 Units/kg	Mean	-	-	-	-	-	-
	SD	8.57	6.183	12.137	1.63	522.3	48.40
	N	0.50	0.386	3.685	0.70	140.6	1.14
Group 3: 110 Units/kg	%Diff	3	3	3	3	3	3
		5.0	4.3	5.0	-5.0	13.1	5.4
		8.23	5.960	10.837	1.30	495.7	45.93
Group 4: 350/225/ 200 Units/kg	Mean	0.81	0.165	1.699	0.44	97.5	3.43
	SD	3	3	3	3	3	3
	%Diff	0.9	0.5	-6.2	-24.4	7.3	0.0
Group 4: 350/225/ 200 Units/kg	Mean	7.94	5.636	15.374	1.50	462.8	44.58
	SD	0.55	0.365	4.391	0.39	86.0	3.49
	N	5	5	5	5	5	5
Group 4: 350/225/ 200 Units/kg	%Diff	-2.7	-5.0	33.0	-12.8	0.2	-2.9

[a] - Anova & Dunnett

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day: 26 Relative to Start Date							
Sex: Male		Haematological Parameters					
		HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
Group 1: Control	Mean	7.75n	5.565n	8.815n	1.25n	431.5n	42.10n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	7.70n	5.605n	17.980n	1.25n	424.5n	41.55n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
	%Diff	-0.6	0.7	104.0	0.0	-1.6	-1.3

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day(s): Predose Relative to Start Date		Haematological Parameters					
Sex: Male		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
Group 1: Control	Mean	48.70	45.54	3.58	0.46	1.28	0.46
	SD	10.15	10.06	0.54	0.50	0.33	0.09
	N	5	5	5	5	5	5
		-	-	-	-	-	-
Group 2: 35 Units/kg	Mean	63.73	31.13	3.53	0.43	0.80	0.33
	SD	11.21	9.28	1.17	0.40	0.20	0.15
	N	3	3	3	3	3	3
	%Diff	30.9	-31.6	-1.3	-5.8	-37.5	-27.5
Group 3: 110 Units/kg	Mean	41.43	52.83	4.27	0.27	0.80	0.40
	SD	12.11	12.30	0.61	0.15	0.10	0.10
	N	3	3	3	3	3	3
	%Diff	-14.9	16.0	19.2	-42.0	-37.5	-13.0
Group 4: 350/225/ 200 Units/kg	Mean	40.69	52.01	5.06	0.64	1.09	0.51
	SD	8.96	7.81	2.37	0.49	0.22	0.18
	N	7	7	7	7	7	7
	%Diff	-16.5	14.2	41.3	39.8	-15.2	11.8

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day: 12 Relative to Start Date		Haematological Parameters					
Sex: Male		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
Group 1: Control	Mean	48.10	46.52	3.50	0.40	1.00	0.48
	SD	8.89	8.45	0.84	0.14	0.39	0.16
	N	5	5	5	5	5	5
		-	-	-	-	-	-
Group 2: 35 Units/kg	Mean	44.10	49.60	4.00	0.67	1.17	0.43
	SD	6.17	6.24	0.44	0.25	0.32	0.06
	N	3	3	3	3	3	3
	%Diff	-8.3	6.6	14.3	66.7	16.7	-9.7
Group 3: 110 Units/kg	Mean	45.63	49.80	3.10	0.53	0.60	0.33
	SD	10.39	10.48	0.53	0.42	0.10	0.06
	N	3	3	3	3	3	3
	%Diff	-5.1	7.1	-11.4	33.3	-40.0	-30.6
Group 4: 350/225/ 200 Units/kg	Mean	45.04	48.98	3.74	0.62	1.18	0.52
	SD	12.87	12.34	0.77	0.50	0.43	0.19
	N	5	5	5	5	5	5
	%Diff	-6.4	5.3	6.9	55.0	18.0	8.3

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TABLE 7-1		Haematological Parameters - Summary			Monkey		
Day: 26 Relative to Start Date							
Sex: Male		Haematological Parameters					
		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
Group 1: Control	Mean	35.70	56.20	5.55	0.50	1.65	0.45
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
Group 4: 350/225/200 Units/kg	Mean	27.10	65.70	4.40	0.65	1.30	0.75
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
	%Diff	-24.1	16.9	-20.7	30.0	-21.2	66.7

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day(s): Predose Relative to Start Date		Haematological Parameters					
Sex: Male		Neut (x10E3/μL)	Lym (x10E3/μL)	Mono (x10E3/μL)	Eos (x10E3/μL)	LUC (x10E3/μL)	Baso (x10E3/μL)
		[a]	[a1]	[a1]	[a]	[a]	[a1]
Group 1: Control	Mean	4.826	4.346	0.346	0.040	0.126	0.044
	SD	1.770	0.741	0.069	0.044	0.038	0.011
	N	5	5	5	5	5	5
		-	-	-	-	-	-
Group 2: 35 Units/kg	Mean	8.193*	3.890	0.447	0.053	0.097	0.040
	SD	2.113	0.767	0.111	0.049	0.023	0.010
	N	3	3	3	3	3	3
	%Diff	69.8	-10.5	29.1	33.3	-23.3	-9.1
Group 3: 110 Units/kg	Mean	3.810	5.097	0.393	0.023	0.080	0.037
	SD	0.799	1.846	0.042	0.012	0.017	0.015
	N	3	3	3	3	3	3
	%Diff	-21.1	17.3	13.7	-41.7	-36.5	-16.7
Group 4: 350/225/ 200 Units/kg	Mean	4.574	6.164	0.571	0.066	0.129	0.064
	SD	1.711	3.128	0.337	0.045	0.064	0.040
	N	7	7	7	7	7	7
	%Diff	-5.2	41.8	65.2	64.3	2.0	46.1

[a] - Anova & Dunnett: * = p ≤ 0.05
[a1] - Anova & Dunnett(Log)

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TABLE 7-1Haematological Parameters - SummaryMonkey

Day: 12 Relative to Start Date		Haematological Parameters					
Sex: Male		Neut	Lym	Mono	Eos	LUC	Baso
		(x10E3/μL)	(x10E3/μL)	(x10E3/μL)	(x10E3/μL)	(x10E3/μL)	(x10E3/μL)
		[a]	[a1]	[a2]	[a]	[a1]	[a]
Group 1: Control	Mean	5.768	5.192	0.386	0.048	0.108	0.054
	SD	2.561	0.839	0.074	0.016	0.038	0.018
	N	5	5	5	5	5	5
		-	-	-	-	-	-
Group 2: 35 Units/kg	Mean	5.503	5.867	0.493	0.087	0.133	0.053
	SD	2.509	0.940	0.176	0.057	0.006	0.015
	N	3	3	3	3	3	3
Group 3: 110 Units/kg	%Diff	-4.6	13.0	27.8	80.6	23.5	-1.2
	Mean	4.967	5.377	0.330	0.057	0.070	0.033
	SD	1.455	1.386	0.010	0.047	0.017	0.006
Units/kg	N	3	3	3	3	3	3
	%Diff	-13.9	3.6	-14.5	18.1	-35.2	-38.3
	Mean	6.740	7.690	0.572	0.098	0.188	0.080
Group 4: 350/225/ 200 Units/kg	SD	2.140	2.930	0.178	0.089	0.097	0.037
	N	5	5	5	5	5	5
	%Diff	16.9	48.1	48.2	104.2	74.1	48.1

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Rank)
[a2] - Anova & Dunnett(Log)

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day: 26 Relative to Start Date		Haematological Parameters					
Sex: Male		Neut (x10E3/μL)	Lym (x10E3/μL)	Mono (x10E3/μL)	Eos (x10E3/μL)	LUC (x10E3/μL)	Baso (x10E3/μL)
		[a]	[a]	[a]	[a]	[a]	[a]
Group 1: Control	Mean	3.345n	4.775n	0.485n	0.045n	0.135n	0.035n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	4.880n	11.820n	0.805n	0.105n	0.235n	0.140n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
	%Diff	45.9	147.5	66.0	133.3	74.1	300.0

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day(s): Predose Relative to Start Date		Haematological Parameters					
Sex: Male		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
		[a]	[a]	[a1]	[a]	[a]	[a]
Group 1: Control	Mean	9.84	21.10	0.0	76.38	1.376	18.016
	SD	0.32	1.68	0.0	2.49	0.043	0.475
	N	5	5	5	5	5	5
		-	-	-	-	-	-
Group 2: 35 Units/kg	Mean	9.67	19.93	0.7	77.53	1.390	17.937
	SD	0.29	0.90	1.2	3.95	0.070	0.771
	N	3	3	3	3	3	3
	%Diff	-1.8	-5.5	-	1.5	1.0	-0.4
Group 3: 110 Units/kg	Mean	9.63	21.10	0.0	75.07	1.373	18.293
	SD	0.47	2.31	0.0	2.92	0.107	0.783
	N	3	3	3	3	3	3
	%Diff	-2.1	0.0	-	-1.7	-0.2	1.5
Group 4: 350/225/ 200 Units/kg	Mean	9.77	20.84	0.1	77.24	1.410	18.256
	SD	0.31	0.87	0.4	3.70	0.043	0.480
	N	7	7	7	7	7	7
	%Diff	-0.7	-1.2	-	1.1	2.5	1.3

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Rank)

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day: 12 Relative to Start Date

Sex: Male		Haematological Parameters						
		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)	
Group 1: Control	Mean	[a]	[a]	[a1]	[a]	[a]	[a]	
	SD	9.60	21.06	0.2	77.52	1.382	17.816	
	N	0.45 5	1.34 5	0.4 5	2.94 5	0.061 5	0.479 5	
Group 2: 35 Units/kg	Mean	9.47	20.67	0.3	78.50	1.383	17.660	
	SD	0.15	0.76	0.6	5.01	0.070	0.792	
	N	3	3	3	3	3	3	
Group 3: 110 Units/kg	%Diff	-1.4	-1.9	66.7	1.3	0.1	-0.9	
	Mean	9.53	21.67	0.7	77.00	1.380	17.873	
	SD	0.47	2.32	1.2	3.75	0.104	0.528	
Group 4: 350/225/ 200 Units/kg	N	3	3	3	3	3	3	
	%Diff	-0.7	2.9	233.3	-0.7	-0.1	0.3	
	Mean	9.64	20.98	0.2	79.10	1.410	17.814	
Group 4: 350/225/ 200 Units/kg	SD	0.26	1.92	0.4	3.45	0.047	0.386	
	N	5	5	5	5	5	5	
	%Diff	0.4	-0.4	0.0	2.0	2.0	0.0	

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Rank)

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day: 26 Relative to Start Date							
Sex: Male		Haematological Parameters					
		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
Group 1: Control	Mean	9.40n	19.10n	0.5n	75.60n	1.395n	18.430n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	9.90n	20.35n	0.0n	74.10n	1.375n	18.535n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
	%Diff	5.3	6.5	-100.0	-2.0	-1.4	0.6

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day(s): Predose Relative to Start Date		Haematological Parameters					
Sex: Female		HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
		[a]	[a]	[a]	[a1]	[a]	[a]
Group 1: Control	Mean	8.74	6.066	13.330	1.14	400.6	47.22
	SD	0.18	0.238	3.554	0.15	64.0	1.85
	N	5	5	5	5	5	5
		-	-	-	-	-	-
Group 2: 35 Units/kg	Mean	8.83	6.350	16.963	0.87	443.0	49.13
	SD	0.68	0.679	1.267	0.15	59.4	4.32
	N	3	3	3	3	3	3
	%Diff	1.1	4.7	27.3	-24.0	10.6	4.1
Group 3: 110 Units/kg	Mean	9.00	6.453	12.613	1.00	369.7	49.13
	SD	0.26	0.530	5.449	0.00	59.4	0.86
	N	3	3	3	3	3	3
	%Diff	3.0	6.4	-5.4	-12.3	-7.7	4.1
Group 4: 350/225/ 200 Units/kg	Mean	8.58	6.272	9.688	1.30	443.6	48.18
	SD	0.28	0.267	1.633	0.78	72.5	1.77
	N	5	5	5	5	5	5
	%Diff	-1.8	3.4	-27.3	14.0	10.7	2.0

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Rank)

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day: 12 Relative to Start Date		Haematological Parameters					
Sex: Female		HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
		[a]	[a]	[a]	[a]	[a]	[a]
Group 1: Control	Mean	8.60	5.972	13.244	1.76	490.4	47.58
	SD	0.46	0.389	3.409	0.43	71.5	2.16
	N	5	5	5	5	5	5
Group 2: 35 Units/kg	Mean	-	-	-	-	-	-
	SD	8.17	5.840	11.957	1.87	480.7	46.10
	N	1.03	0.863	1.651	0.12	59.5	5.63
Group 3: 110 Units/kg	%Diff	3	3	3	3	3	3
	Mean	-5.0	-2.2	-9.7	6.1	-2.0	-3.1
	SD	8.47	6.087	13.243	1.80	474.0	47.50
Group 4: 350/225/ 200 Units/kg	%Diff	0.35	0.526	0.647	0.69	38.3	1.18
	Mean	3	3	3	3	3	3
	SD	-1.6	1.9	0.0	2.3	-3.3	-0.2
Group 4: 350/225/ 200 Units/kg	%Diff	7.84	5.808	15.150	1.70	535.8	45.24
	Mean	0.40	0.253	0.940	0.40	99.2	2.82
	SD	5	5	5	5	5	5
Group 4: 350/225/ 200 Units/kg	%Diff	-8.8	-2.7	14.4	-3.4	9.3	-4.9
	Mean						
	SD						

[a] - Anova & Dunnett

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day: 26 Relative to Start Date		Haematological Parameters - Summary						
Sex: Female		Haematological Parameters						
		HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)	
Group 1: Control	Mean	8.60n	6.075n	13.825n	2.20n	532.0n	46.50n	
	SD	-	-	-	-	-	-	
	N	2	2	2	2	2	2	
Group 4: 350/225/ 200 Units/kg	Mean	8.50n	6.025n	16.950n	2.15n	494.0n	47.15n	
	SD	-	-	-	-	-	-	
	N	2	2	2	2	2	2	
	%Diff	-1.2	-0.8	22.6	-2.3	-7.1	1.4	

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day(s): Predose Relative to Start Date		Haematological Parameters					
Sex: Female		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
Group 1: Control	Mean	53.74	40.64	4.06	0.44	0.64	0.46
	SD	11.49	10.04	1.28	0.44	0.25	0.05
	N	5	5	5	5	5	5
		-	-	-	-	-	-
Group 2: 35 Units/kg	Mean	60.83	34.13	3.63	0.43	0.57	0.47
	SD	14.11	13.56	0.12	0.21	0.32	0.15
	N	3	3	3	3	3	3
	%Diff	13.2	-16.0	-10.5	-1.5	-11.5	1.4
Group 3: 110 Units/kg	Mean	60.13	35.70	2.83	0.50	0.50	0.37
	SD	20.88	19.57	0.81	0.46	0.26	0.06
	N	3	3	3	3	3	3
	%Diff	11.9	-12.2	-30.2	13.6	-21.9	-20.3
Group 4: 350/225/ 200 Units/kg	Mean	41.92	51.78	4.34	0.68	0.72	0.58
	SD	10.21	10.14	1.38	0.54	0.11	0.11
	N	5	5	5	5	5	5
	%Diff	-22.0	27.4	6.9	54.5	12.5	26.1

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day: 12 Relative to Start Date		Haematological Parameters				
Sex: Female		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)
		Baso (%)				
Group 1: Control	Mean	41.88	51.66	4.60	0.50	0.80
	SD	6.56	6.44	1.27	0.32	0.23
	N	5	5	5	5	5
Group 2: 35 Units/kg	Mean	43.87	49.83	4.00	1.03	0.83
	SD	7.00	7.17	0.72	0.38	0.31
	N	3	3	3	3	3
Group 3: 110 Units/kg	%Diff	4.7	-3.5	-13.0	106.7	4.2
	Mean	46.10	48.40	3.50	0.83	0.77
	SD	12.82	12.58	0.61	0.55	0.15
Group 4: 350/225/ 200 Units/kg	N	3	3	3	3	3
	%Diff	10.1	-6.3	-23.9	66.7	-4.2
	Mean	53.80	40.82	3.40	0.48	0.98
	SD	7.77	8.32	1.30	0.22	0.27
	N	5	5	5	5	5
	%Diff	28.5	-21.0	-26.1	-4.0	22.5
						-3.8

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day: 26 Relative to Start Date		Haematological Parameters				
Sex: Female		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)
		Baso (%)				
Group 1: Control	Mean	46.25	46.70	5.20	0.30	1.00
	SD	-	-	-	-	-
	N	2	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	42.65	51.45	4.35	0.30	0.75
	SD	-	-	-	-	-
	N	2	2	2	2	2
		%Diff	10.2	-16.3	0.0	-25.0
						22.2

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day(s): Predose Relative to Start Date		Haematological Parameters					
Sex: Female		Neut (x10E3/μL)	Lym (x10E3/μL)	Mono (x10E3/μL)	Eos (x10E3/μL)	LUC (x10E3/μL)	Baso (x10E3/μL)
		[a]	[a]	[a1]	[a2]	[a]	[a]
Group 1: Control	Mean	7.432	5.202	0.504	0.050	0.080	0.060
	SD	3.319	1.059	0.054	0.046	0.024	0.016
	N	5	5	5	5	5	5
		-	-	-	-	-	-
Group 2: 35 Units/kg	Mean	10.367	5.740	0.617	0.073	0.093	0.077
	SD	2.908	2.243	0.061	0.031	0.057	0.021
	N	3	3	3	3	3	3
	%Diff	39.5	10.3	22.4	46.7	16.7	27.8
Group 3: 110 Units/kg	Mean	8.187	3.947	0.330*	0.050	0.060	0.043
	SD	6.066	1.324	0.026	0.035	0.020	0.006
	N	3	3	3	3	3	3
	%Diff	10.2	-24.1	-34.5	0.0	-25.0	-27.8
Group 4: 350/225/ 200 Units/kg	Mean	4.180	4.896	0.420	0.068	0.066	0.056
	SD	1.613	0.429	0.133	0.064	0.013	0.009
	N	5	5	5	5	5	5
	%Diff	-43.8	-5.9	-16.7	36.0	-17.5	-6.7

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Rank): * = p ≤ 0.05
[a2] - Anova & Dunnett(Log)

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day: 12 Relative to Start Date

Sex: Female		Haematological Parameters						
		Neut (x10E3/μL)	Lym (x10E3/μL)	Mono (x10E3/μL)	Eos (x10E3/μL)	LUC (x10E3/μL)	Baso (x10E3/μL)	
		[a]	[a1]	[a]	[a]	[a]	[a]	
Group 1: Control	Mean	5.720	6.686	0.590	0.072	0.104	0.068	
	SD	2.348	1.029	0.166	0.062	0.018	0.016	
	N	5	5	5	5	5	5	
Group 2: 35 Units/kg	Mean	-	-	-	-	-	-	
	SD	5.177	6.037	0.467	0.120	0.097	0.057	
	N	0.337	1.727	0.038	0.056	0.040	0.015	
Group 3: 110 Units/kg	%Diff	3	3	3	3	3	3	
	Mean	-9.5	-9.7	-20.9	66.7	-7.1	-16.7	
	SD	6.050	6.467	0.463	0.110	0.100	0.053	
Group 4: 350/225/ 200 Units/kg	N	1.455	2.023	0.068	0.075	0.020	0.012	
	%Diff	3	3	3	3	3	3	
	Mean	5.8	-3.3	-21.5	52.8	-3.8	-21.6	
Group 5: 350/225/ 200 Units/kg	SD	8.122	6.218	0.514	0.072	0.148	0.078	
	N	1.007	1.521	0.193	0.035	0.040	0.023	
	%Diff	5	5	5	5	5	5	
Group 6: 350/225/ 200 Units/kg	Mean	42.0	-7.0	-12.9	0.0	42.3	14.7	
	SD							
	N							

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Rank)

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day: 26 Relative to Start Date

Sex: Female		Haematological Parameters					
		Neut (x10E3/μL)	Lym (x10E3/μL)	Mono (x10E3/μL)	Eos (x10E3/μL)	LUC (x10E3/μL)	Baso (x10E3/μL)
Group 1: Control	Mean	7.030n	5.925n	0.650n	0.035n	0.120n	0.065n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	7.270n	8.665n	0.745n	0.050n	0.125n	0.090n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
	%Diff	3.4	46.2	14.6	42.9	4.2	38.5

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day(s): Predose Relative to Start Date		Haematological Parameters					
Sex: Female		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
		[a]	[a]	[a1]	[a]	[a]	[a1]
Group 1: Control	Mean	10.14	23.50	0.0	77.92	1.440	18.482
	SD	0.29	1.72	0.0	3.18	0.040	0.415
	N	5	5	5	5	5	5
		-	-	-	-	-	-
Group 2: 35 Units/kg	Mean	10.00	23.27	0.0n	77.53	1.397	18.003
	SD	0.36	0.81	0.0	2.75	0.042	0.299
	N	3	3	3	3	3	3
	%Diff	-1.4	-1.0	-	-0.5	-3.0	-2.6
Group 3: 110 Units/kg	Mean	10.17	23.73	0.0n	76.37	1.400	18.333
	SD	0.25	1.39	0.0	4.93	0.082	0.437
	N	3	3	3	3	3	3
	%Diff	0.3	1.0	-	-2.0	-2.8	-0.8
Group 4: 350/225/ 200 Units/kg	Mean	9.90	22.14	0.0n	76.86	1.372	17.832
	SD	0.12	1.44	0.0	2.31	0.056	0.426
	N	5	5	5	5	5	5
	%Diff	-2.4	-5.8	-	-1.4	-4.7	-3.5

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Rank); n - Inappropriate for statistics

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TABLE 7-1
Haematological Parameters - Summary
Monkey

Day: 12 Relative to Start Date									
Sex: Female		Haematological Parameters							
		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)		
Group 1: Control	Mean	[a]	[a]	[a1]	[a]	[a]	[a]		
	SD	9.90	20.96	0.4	79.76	1.444	18.096		
	N	0.40	0.57	0.9	3.28	0.044	0.462		
Group 2: 35 Units/kg	Mean	-	-	-	-	-	-		
	SD	9.63	21.00	0.7	79.10	1.410	17.787		
	N	0.31	0.75	0.6	2.82	0.046	0.064		
Group 3: 110 Units/kg	%Diff	3	3	3	3	3	3		
	Mean	-2.7	0.2	66.7	-0.8	-2.4	-1.7		
	SD	9.97	21.63	0.0	78.40	1.397	17.797		
Group 4: 350/225/ 200 Units/kg	%Diff	0.21	1.25	0.0	6.22	0.067	0.670		
	Mean	0.7	3.2	-100.0	-1.7	-3.3	-1.7		
	SD	9.80	20.70	0.4	77.90	1.350	17.348		
	%Diff	0.28	0.97	0.9	2.15	0.037	0.432		
	Mean	5	5	5	5	5	5		
	%Diff	-1.0	-1.2	0.0	-2.3	-6.5	-4.1		

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Rank)

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TABLE 7-1 Haematological Parameters - Summary Monkey

Day: 26 Relative to Start Date		Haematological Parameters						
Sex: Female		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)	
		[a]	[a]	[a]	[a]	[a]	[a]	
Group 1: Control	Mean	10.15n	21.65n	0.0n	76.60n	1.415n	18.485n	
	SD	-	-	-	-	-	-	
	N	2	2	2	2	2	2	
Group 4: 350/225/ 200 Units/kg	Mean	9.50n	21.10n	0.0n	78.20n	1.405n	18.010n	
	SD	-	-	-	-	-	-	
	N	2	2	2	2	2	2	
	%Diff	-6.4	-2.5	-	2.1	-0.7	-2.6	

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 7-1 Haematological Parameters - Summary Monkey

Comments and Markers						
Page	Day	Group	Sex	Measurement	Marker	Comment
26	26	1	Male	HGB	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	RBC	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	WBC	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Reticulocyte (Relative)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	PLT	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	HCT	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	HGB	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	RBC	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	WBC	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Reticulocyte (Relative)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	PLT	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	HCT	n	Anova & Dunnett: n - Inappropriate for statistics

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TABLE 7-1		Haematological Parameters - Summary		Monkey
<u>Comments and Markers</u>				
<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>
	Predose	2	Male	Neutrophils (Absolute)
				<u>Marker</u>
				*
				<u>Comment</u>
				Anova & Dunnett: * = p ≤ 0.05

Marker	Comment
*	Anova & Dunnett: * = $p \leq 0.05$

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TABLE 7-1 Haematological Parameters - Summary Monkey

Comments and Markers

<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker</u>	<u>Comment</u>
26	26	1	Male	Neutrophils (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Lymphocytes (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Monocytes (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Eosinophils (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Large Unclassified Cells	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Basophils (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Neutrophils (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Lymphocytes (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Monocytes (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Eosinophils (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Large Unclassified Cells	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Basophils (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics

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TABLE 7-1 Haematological Parameters - Summary Monkey

Comments and Markers

<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker</u>	<u>Comment</u>
26	26	1	Male	PT	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	aPTT	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	ESR	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	MCV	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	MCH	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	_MCHC	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	PT	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	aPTT	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	ESR	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	MCV	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	MCH	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	_MCHC	n	Anova & Dunnett: n - Inappropriate for statistics

TABLE 7-1
Haematological Parameters - Summary

Page	Day	Group	Sex	Measurement	Marker	Comment
	26	1	Female	HGB	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	RBC	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	WBC	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	Reticulocyte (Relative)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	PLT	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	HCT	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	HGB	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	RBC	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	WBC	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Reticulocyte (Relative)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	PLT	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	HCT	n	Anova & Dunnett: n - Inappropriate for statistics

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TABLE 7-1		Haematological Parameters - Summary			Monkey	
<u>Comments and Markers</u>						
<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker</u>	<u>Comment</u>
Predose		3	Female	Monocytes (Absolute)	*	Anova & Dunnett(Rank): * = p ≤ 0.05

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TABLE 7-1 Haematological Parameters - Summary Monkey

Comments and Markers

<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker</u>	<u>Comment</u>
26	26	1	Female	Neutrophils (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Lymphocytes (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Monocytes (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Eosinophils (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Large Unclassified Cells	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Basophils (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Neutrophils (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Lymphocytes (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Monocytes (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Eosinophils (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Large Unclassified Cells	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Basophils (Absolute)	n	Anova & Dunnett: n - Inappropriate for statistics

Allogenic APOSEC™						
TABLE 7-1		Haematological Parameters - Summary			Monkey	
<u>Comments and Markers</u>						
<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker</u>	<u>Comment</u>
	Predose	2	Female	ESR	n	Anova & Dunnett(Rank): n - Inappropriate for statistics
	Predose	3	Female	ESR	n	Anova & Dunnett(Rank): n - Inappropriate for statistics
	Predose	4	Female	ESR	n	Anova & Dunnett(Rank): n - Inappropriate for statistics

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TABLE 7-1 Haematological Parameters - Summary Monkey

Comments and Markers

<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker</u>	<u>Comment</u>
26	26	1	Female	PT	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	aPTT	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	ESR	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	MCV	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	MCH	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	_MCHC	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	PT	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	aPTT	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	ESR	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	MCV	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	MCH	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	_MCHC	n	Anova & Dunnett: n - Inappropriate for statistics

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Haematological Parameters					
		HGB (mmol/L)	RBC ($\times 10^6/\mu\text{L}$)	WBC ($\times 10^3/\mu\text{L}$)	Reti (%)	PLT ($\times 10^3/\mu\text{L}$)	HCT (%)
Group 1: Control	1	8.6	5.98	9.19	1.8	397	48.2
	2	8.0	5.89	12.86	1.2	438	45.2
	3	9.2	6.87	8.49	0.8	335	51.1
	4	8.4	6.31	9.28	1.1	435	47.9
	5	8.0	5.71	8.84	1.4	395	42.6
Mean	8.44	6.152	9.732	1.26	400.0	47.00	
SD	0.50	0.457	1.776	0.37	41.6	3.23	
N	5	5	5	5	5	5	5

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Haematological Parameters					
		HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
Group 2: 35 Units/kg	11	8.8	6.71	13.19	1.4	558	51.3
	12	9.1	6.21	11.27	1.3	311	50.9
	13	8.9	6.41	13.69	0.7	267	47.6
	Mean	8.93	6.443	12.717	1.13	378.7	49.93
	SD	0.15	0.252	1.278	0.38	156.9	2.03
	N	3	3	3	3	3	3

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Haematological Parameters					
		HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
Group 3: 110 Units/kg	17	8.8	6.11	10.71	0.9	393	46.9
	18	8.0	6.39	10.13	1.1	336	45.9
	19	8.9	6.18	7.48	0.9	474	47.3
	Mean	8.57	6.227	9.440	0.97	401.0	46.70
	SD	0.49	0.146	1.722	0.12	69.3	0.72
	N	3	3	3	3	3	3

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Haematological Parameters					
		HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
Group 4: 350/225/ 200 Units/kg	23	8.5	6.03	9.72	1.4	376	47.5
	24	8.5	5.83	6.59	1.0	341	45.3
	25	8.8	5.99	11.54	1.1	474	50.3
	26	8.5	6.04	9.51	0.9	453	46.9
	27	8.6	6.36	7.98	0.8	542	46.0
	33	8.0	5.91	14.90	0.9	356	44.4
	34	8.2	5.82	20.75	2.1	398	43.6
	Mean	8.44	5.997	11.570	1.17	420.0	46.29
	SD	0.26	0.183	4.843	0.45	72.6	2.23
	N	7	7	7	7	7	7

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male Day: 12 Relative to Start Date		Haematological Parameters - Individual Data					
Group 1: Control		Haematological Parameters					
		HGB (mmol/L)	RBC (x10E6/µL)	WBC (x10E3/µL)	Reti (%)	PLT (x10E3/µL)	HCT (%)
	1	7.9	5.41	16.57	1.7	438	44.8
	2	8.1	6.08	8.30	2.1	522	46.8
	3	8.9	6.69	12.64	1.0	367	50.6
	4	8.1	5.97	11.38	1.4	527	45.6
	5	7.8	5.50	8.90	2.4	455	41.8
Mean		8.16	5.930	11.558	1.72	461.8	45.92
SD		0.43	0.514	3.317	0.55	66.1	3.20
N		5	5	5	5	5	5

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male Day: 12 Relative to Start Date		Haematological Parameters					
Group 2: 35 Units/kg	HGB (mmol/L)	RBC (x10E6/μL)	WBC (x10E3/μL)	Reti (%)	PLT (x10E3/μL)	HCT (%)	
11	8.1	6.16	16.39	2.3	680	47.1	
12	8.5	5.81	10.13	1.7	477	48.9	
13	9.1	6.58	9.89	0.9	410	49.2	
Mean	8.57	6.183	12.137	1.63	522.3	48.40	
SD	0.50	0.386	3.685	0.70	140.6	1.14	
N	3	3	3	3	3	3	

Monkey

Sex: Male Day: 12 Relative to Start Date							
Group 3: 110 Units/kg	Haematological Parameters						
	HGB (mmol/L)	RBC (x10E6/μL)	WBC (x10E3/μL)	Reti (%)	PLT (x10E3/μL)	HCT (%)	
	17	8.6	5.97	9.01	1.0	421	47.0
	18	7.3	5.79	12.37	1.8	460	42.1
	19	8.8	6.12	11.13	1.1	606	48.7
Mean	8.23	5.960	10.837	1.30	495.7	45.93	
SD	0.81	0.165	1.699	0.44	97.5	3.43	
N	3	3	3	3	3	3	

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Sex: Male		Day: 12 Relative to Start Date	TABLE 7-2 Haematological Parameters - Individual Data					Monkey
Group 4: 350/225/ 200 Units/kg		Haematological Parameters						
		HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)	
23		8.5	6.05	13.76	2.0	452	49.6	
24		8.4	5.83	8.91	1.1	390	46.0	
25		7.6	5.16	15.37	1.4	586	42.9	
33		8.0	5.78	19.24	1.8	507	44.1	
34		7.2	5.36	19.59	1.2	379	40.3	
Mean		7.94	5.636	15.374	1.50	462.8	44.58	
SD		0.55	0.365	4.391	0.39	86.0	3.49	
N		5	5	5	5	5	5	

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male		Day: 26 Relative to Start Date						
				Haematological Parameters				
Group 1: Control		HGB (mmol/L)	RBC (x10E6/µL)	WBC (x10E3/µL)	Reti (%)	PLT (x10E3/µL)	HCT (%)	
4		7.7	5.65	10.07	1.4	415	42.5	
5		7.8	5.48	7.56	1.1	448	41.7	
Mean		7.75	5.565	8.815	1.25	431.5	42.10	
SD		-	-	-	-	-	-	
N		2	2	2	2	2	2	

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day: 26 Relative to Start Date	Haematological Parameters					
		HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
Group 4: 350/225/ 200 Units/kg	33	8.1	5.74	20.60	1.1	442	42.9
	34	7.3	5.47	15.36	1.4	407	40.2
Mean		7.70	5.605	17.980	1.25	424.5	41.55
SD		-	-	-	-	-	-
N		2	2	2	2	2	2

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male		Day(s): Predose Relative to Start Date		Haematological Parameters						
Group 1: Control		Neut (%)	Lym (%)	Mono (%)			Eos (%)	LUC (%)	Baso (%)	
1		38.4	55.8	3.9			0.5	0.8	0.5	
2		59.9	34.8	3.4			0.1	1.4	0.5	
3		50.9	43.2	3.9			0.3	1.2	0.5	
4		56.4	37.6	4.0			0.1	1.7	0.3	
5		37.9	56.3	2.7			1.3	1.3	0.5	
Mean		48.70	45.54	3.58			0.46	1.28	0.46	
SD		10.15	10.06	0.54			0.50	0.33	0.09	
N		5	5	5			5	5	5	

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male		Day(s): Predose Relative to Start Date				
Group 2: 35 Units/kg	Haematological Parameters					
	Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
	11	72.5	23.9	2.5	0.2	0.6
	12	51.1	41.6	4.8	0.9	1.0
	13	67.6	27.9	3.3	0.2	0.8
Mean	63.73	31.13	3.53	0.43	0.80	0.33
SD	11.21	9.28	1.17	0.40	0.20	0.15
N	3	3	3	3	3	3

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Haematological Parameters					
Group 3: 110 Units/kg		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
	17	42.1	52.7	3.6	0.3	0.9	0.5
	18	29.0	65.2	4.4	0.1	0.8	0.4
	19	53.2	40.6	4.8	0.4	0.7	0.3
	Mean	41.43	52.83	4.27	0.27	0.80	0.40
	SD	12.11	12.30	0.61	0.15	0.10	0.10
	N	3	3	3	3	3	3

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male Day(s): Predose Relative to Start Date							
Group 4: 350/225/ 200 Units/kg	Haematological Parameters						
	Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)	
23	27.7	64.8	5.7	0.0	1.2	0.6	
24	50.8	43.9	3.8	0.5	0.7	0.3	
25	51.7	44.1	2.6	0.3	1.0	0.3	
26	35.6	52.1	9.4	1.2	1.2	0.4	
27	44.4	46.8	5.7	1.4	1.0	0.7	
33	41.0	53.8	2.6	0.6	1.4	0.7	
34	33.6	58.6	5.6	0.5	1.1	0.6	
Mean	40.69	52.01	5.06	0.64	1.09	0.51	
SD	8.96	7.81	2.37	0.49	0.22	0.18	
N	7	7	7	7	7	7	

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male Day: 12 Relative to Start Date		Haematological Parameters - Individual Data				
Group 1: Control		Haematological Parameters				
		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)
						Baso (%)
	1	56.5	40.1	2.1	0.2	0.6
	2	36.3	57.9	4.1	0.5	0.9
	3	54.1	40.8	3.6	0.5	0.7
	4	52.6	40.5	4.2	0.5	1.5
	5	41.0	53.3	3.5	0.3	1.3
	Mean	48.10	46.52	3.50	0.40	1.00
	SD	8.89	8.45	0.84	0.14	0.39
	N	5	5	5	5	5

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male Day: 12 Relative to Start Date		Haematological Parameters										
Group 2: 35 Units/kg	Neut (%)		Lym (%)		Mono (%)		Eos (%)		LUC (%)		Baso (%)	
	11	51.2	42.4	4.2	0.9	0.8	0.4					
	12	40.1	53.2	4.3	0.7	1.3	0.4					
	13	41.0	53.2	3.5	0.4	1.4	0.5					
	Mean	44.10	49.60	4.00	0.67	1.17	0.43					
	SD	6.17	6.24	0.44	0.25	0.32	0.06					
	N	3	3	3	3	3	3					

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male Day: 12 Relative to Start Date		Haematological Parameters						
Group 3: 110 Units/kg		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)	
	17	38.9	55.9	3.7	0.4	0.6	0.4	
	18	40.4	55.8	2.7	0.2	0.7	0.3	
	19	57.6	37.7	2.9	1.0	0.5	0.3	
Mean		45.63	49.80	3.10	0.53	0.60	0.33	
SD		10.39	10.48	0.53	0.42	0.10	0.06	
N		3	3	3	3	3	3	

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male Day: 12 Relative to Start Date		Haematological Parameters					
Group 4: 350/225/ 200 Units/kg		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
23		26.2	67.4	4.8	0.2	0.9	0.7
24		61.8	33.9	3.2	0.3	0.6	0.2
25		49.8	42.8	3.9	1.3	1.7	0.5
33		43.1	50.7	4.0	0.3	1.4	0.6
34		44.3	50.1	2.8	1.0	1.3	0.6
Mean		45.04	48.98	3.74	0.62	1.18	0.52
SD		12.87	12.34	0.77	0.50	0.43	0.19
N		5	5	5	5	5	5

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male		Day: 26 Relative to Start Date					
				Haematological Parameters			
Group 1: Control		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
	4	51.1	41.9	5.3	0.4	1.1	0.3
	5	20.3	70.5	5.8	0.6	2.2	0.6
Mean		35.70	56.20	5.55	0.50	1.65	0.45
SD		-	-	-	-	-	-
N		2	2	2	2	2	2

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male		Day: 26 Relative to Start Date					
				Haematological Parameters			
		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
Group 4: 350/225/ 200 Units/kg	33	27.3	65.8	4.5	0.4	1.1	0.8
	34	26.9	65.6	4.3	0.9	1.5	0.7
	Mean	27.10	65.70	4.40	0.65	1.30	0.75
SD		-	-	-	-	-	-
N		2	2	2	2	2	2

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Haematological Parameters				
		Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)
Group 1: Control						Baso (x10E3/ μ L)
	1	3.53	5.12	0.36	0.05	0.08
	2	7.70	4.48	0.43	0.01	0.17
	3	4.32	3.67	0.33	0.03	0.10
	4	5.23	3.49	0.37	0.00	0.16
	5	3.35	4.97	0.24	0.11	0.12
	Mean	4.826	4.346	0.346	0.040	0.126
	SD	1.770	0.741	0.069	0.044	0.038
	N	5	5	5	5	5
						5

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Haematological Parameters				
		Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)
Group 2: 35 Units/kg						Baso (x10E3/ μ L)
	11	9.57	3.16	0.33	0.02	0.07
	12	5.76	4.69	0.55	0.11	0.11
	13	9.25	3.82	0.46	0.03	0.11
Mean SD N		8.193	3.890	0.447	0.053	0.097
		2.113	0.767	0.111	0.049	0.023
		3	3	3	3	3

Monkey

Sex: Male	Day(s): Predose	Relative to Start Date	Haematological Parameters					
Group 3: 110 Units/kg	Neut (x10E3/μL)	Lym (x10E3/μL)	Mono (x10E3/μL)	Eos (x10E3/μL)	LUC (x10E3/μL)	Baso (x10E3/μL)		
	17	4.51	5.64	0.38	0.03	0.09	0.05	
	18	2.94	6.61	0.44	0.01	0.09	0.04	
	19	3.98	3.04	0.36	0.03	0.06	0.02	
Mean	3.810	5.097	0.393	0.023	0.080	0.037		
SD	0.799	1.846	0.042	0.012	0.017	0.015		
N	3	3	3	3	3	3		

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Haematological Parameters				
		Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)
Group 4: 350/225/ 200 Units/kg						Baso (x10E3/ μ L)
	23	2.69	6.30	0.55	0.00	0.11
	24	3.35	2.89	0.25	0.03	0.05
	25	5.97	5.08	0.30	0.03	0.12
	26	3.39	4.96	0.90	0.11	0.11
	27	3.54	3.74	0.46	0.11	0.08
	33	6.11	8.01	0.38	0.08	0.21
	34	6.97	12.17	1.16	0.10	0.22
	Mean	4.574	6.164	0.571	0.066	0.129
	SD	1.711	3.128	0.337	0.045	0.064
	N	7	7	7	7	7

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Haematological Parameters				
		Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)
Group 1: Control						Baso (x10E3/ μ L)
	1	9.37	6.65	0.35	0.04	0.10
	2	3.01	4.81	0.34	0.04	0.07
	3	6.83	5.15	0.45	0.07	0.09
	4	5.98	4.61	0.48	0.06	0.17
	5	3.65	4.74	0.31	0.03	0.11
Mean		5.768	5.192	0.386	0.048	0.108
SD		2.561	0.839	0.074	0.016	0.038
N		5	5	5	5	5

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male Day: 12 Relative to Start Date		Haematological Parameters					
Group 2: 35 Units/kg	Neut (x10E3/μL)	Lym (x10E3/μL)	Mono (x10E3/μL)	Eos (x10E3/μL)	LUC (x10E3/μL)	Baso (x10E3/μL)	
11	8.40	6.95	0.69	0.15	0.13	0.07	
12	4.06	5.39	0.44	0.07	0.13	0.04	
13	4.05	5.26	0.35	0.04	0.14	0.05	
Mean	5.503	5.867	0.493	0.087	0.133	0.053	
SD	2.509	0.940	0.176	0.057	0.006	0.015	
N	3	3	3	3	3	3	

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Haematological Parameters				
		Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)
Group 3: 110 Units/kg						Baso (x10E3/ μ L)
	17	3.50	5.04	0.33	0.04	0.06
	18	4.99	6.90	0.34	0.02	0.09
	19	6.41	4.19	0.32	0.11	0.06
Mean SD N		4.967	5.377	0.330	0.057	0.070
		1.455	1.386	0.010	0.047	0.017
		3	3	3	3	3

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Haematological Parameters				
		Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)
Group 4: 350/225/ 200 Units/kg						Baso (x10E3/ μ L)
	23	3.60	9.28	0.65	0.02	0.12
	24	5.50	3.02	0.29	0.03	0.05
	25	7.65	6.58	0.60	0.20	0.26
	33	8.28	9.76	0.77	0.05	0.26
	34	8.67	9.81	0.55	0.19	0.25
Mean		6.740	7.690	0.572	0.098	0.188
SD		2.140	2.930	0.178	0.089	0.097
N		5	5	5	5	5

Monkey

Sex: Male Day: 26 Relative to Start Date						
Group 1: Control	Haematological Parameters					
	Neut (x10E3/μL)	Lym (x10E3/μL)	Mono (x10E3/μL)	Eos (x10E3/μL)	LUC (x10E3/μL)	Baso (x10E3/μL)
4	5.15	4.22	0.53	0.04	0.11	0.03
5	1.54	5.33	0.44	0.05	0.16	0.04
Mean	3.345	4.775	0.485	0.045	0.135	0.035
SD	-	-	-	-	-	-
N	2	2	2	2	2	2

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day: 26 Relative to Start Date	Haematological Parameters				
		Neut (x10E3/µL)	Lym (x10E3/µL)	Mono (x10E3/µL)	Eos (x10E3/µL)	LUC (x10E3/µL)
Group 4: 350/225/ 200 Units/kg	33	5.63	13.55	0.94	0.08	0.23
	34	4.13	10.09	0.67	0.13	0.24
Mean		4.880	11.820	0.805	0.105	0.235
SD		-	-	-	-	-
N		2	2	2	2	2
						0.140
						-
						2

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Haematological Parameters - Individual Data				
		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)
Group 1: Control						MCHC (mmol/L)
	1	10.2	22.5	0	80.5	1.44
	2	10.0	20.2	0	76.6	1.36
	3	9.5	23.0	0	74.3	1.34
	4	10.0	18.9	0	75.9	1.34
	5	9.5	20.9	0	74.6	1.40
	Mean	9.84	21.10	0.0	76.38	1.376
	SD	0.32	1.68	0.0	2.49	0.043
	N	5	5	5	5	5
						5

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Haematological Parameters					
		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
Group 2: 35 Units/kg	11	10.0	20.4	0	76.5	1.32	17.25
	12	9.5	20.5	0	81.9	1.46	17.79
	13	9.5	18.9	2	74.2	1.39	18.77
	Mean	9.67	19.93	0.7	77.53	1.390	17.937
	SD	0.29	0.90	1.2	3.95	0.070	0.771
	N	3	3	3	3	3	3

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Haematological Parameters				
		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)
Group 3: 110 Units/kg						MCHC (mmol/L)
	17	10.0	23.7	0	76.8	1.44
	18	9.8	19.3	0	71.7	1.25
	19	9.1	20.3	0	76.7	1.43
Mean SD N		9.63	21.10	0.0	75.07	1.373
		0.47	2.31	0.0	2.92	0.107
		3	3	3	3	3

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Haematological Parameters					
		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
Group 4: 350/225/ 200 Units/kg	23	10.1	19.9	0	78.8	1.41	17.94
	24	9.7	20.4	0	77.7	1.46	18.74
	25	10.2	22.0	1	84.0	1.47	17.54
	26	9.9	20.3	0	77.7	1.41	18.09
	27	9.6	20.8	0	72.3	1.36	18.75
	33	9.6	20.4	0	75.2	1.36	18.02
	34	9.3	22.1	0	75.0	1.40	18.71
	Mean	9.77	20.84	0.1	77.24	1.410	18.256
	SD	0.31	0.87	0.4	3.70	0.043	0.480
	N	7	7	7	7	7	7

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male Day: 12 Relative to Start Date		Haematological Parameters					
Group 1: Control		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
1		10.2	22.4	0	82.7	1.47	17.75
2		9.7	20.5	0	77.0	1.34	17.40
3		9.1	22.3	1	75.6	1.33	17.61
4		9.8	19.2	0	76.3	1.35	17.68
5		9.2	20.9	0	76.0	1.42	18.64
Mean		9.60	21.06	0.2	77.52	1.382	17.816
SD		0.45	1.34	0.4	2.94	0.061	0.479
N		5	5	5	5	5	5

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Haematological Parameters					
		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
Group 2: 35 Units/kg	11	9.5	21.0	0	76.5	1.31	17.13
	12	9.6	21.2	1	84.2	1.45	17.28
	13	9.3	19.8	0	74.8	1.39	18.57
	Mean	9.47	20.67	0.3	78.50	1.383	17.660
	SD	0.15	0.76	0.6	5.01	0.070	0.792
	N	3	3	3	3	3	3

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male Day: 12 Relative to Start Date		Haematological Parameters					
Group 3: 110 Units/kg	PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)	
17	9.9	24.3	0	78.7	1.44	18.25	
18	9.7	19.9	2	72.7	1.26	17.27	
19	9.0	20.8	0	79.6	1.44	18.10	
Mean	9.53	21.67	0.7	77.00	1.380	17.873	
SD	0.47	2.32	1.2	3.75	0.104	0.528	
N	3	3	3	3	3	3	

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Haematological Parameters				
		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)
Group 4: 350/225/ 200 Units/kg						MCHC (mmol/L)
	23	9.9	19.7	0	82.0	1.41
	24	9.3	20.6	0	78.9	1.44
	25	9.9	23.1	1	83.1	1.47
	33	9.5	22.8	0	76.3	1.38
	34	9.6	18.7	0	75.2	1.35
Mean SD N		9.64	20.98	0.2	79.10	1.410
		0.26	1.92	0.4	3.45	0.047
		5	5	5	5	5

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male		Day: 26 Relative to Start Date						
Group 1: Control		PT (Seconds)	aPTT (Seconds)	Haematological Parameters				
				ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)	
	4	9.6	18.5	0	75.1	1.37	18.20	
	5	9.2	19.7	1	76.1	1.42	18.66	
Mean		9.40	19.10	0.5	75.60	1.395	18.430	
SD		-	-	-	-	-	-	
N		2	2	2	2	2	2	

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Male		Day: 26 Relative to Start Date						
				Haematological Parameters				
Group 4: 350/225/ 200 Units/kg		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)	
33		9.8	21.3	0	74.7	1.41	18.89	
34		10.0	19.4	0	73.5	1.34	18.18	
Mean		9.90	20.35	0.0	74.10	1.375	18.535	
SD		-	-	-	-	-	-	
N		2	2	2	2	2	2	

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female		Day(s): Predose Relative to Start Date						
Group 1: Control	Haematological Parameters							
	HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)		
6	8.7	5.80	13.14	1.3	415	46.1		
7	8.5	5.82	16.45	1.2	346	46.3		
8	9.0	6.21	9.46	0.9	336	50.5		
9	8.7	6.19	17.36	1.2	495	46.5		
10	8.8	6.31	10.24	1.1	411	46.7		
Mean	8.74	6.066	13.330	1.14	400.6	47.22		
SD	0.18	0.238	3.554	0.15	64.0	1.85		
N	5	5	5	5	5	5		

TABLE 7-2	Haematological Parameters - Individual Data	Monkey
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Sex: Female	Day(s): Predose Relative to Start Date	Haematological Parameters					
Group 2: 35 Units/kg	HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)	
	14	8.6	6.03	18.12	0.9	464	48.6
	15	8.3	5.89	17.16	0.7	489	45.1
	16	9.6	7.13	15.61	1.0	376	53.7
	Mean	8.83	6.350	16.963	0.87	443.0	49.13
SD	0.68	0.679	1.267	0.15	59.4	4.32	
N	3	3	3	3	3	3	

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female		Day(s): Predose Relative to Start Date					
Group 3: 110 Units/kg	Haematological Parameters						
	HGB (mmol/L)	RBC (x10E6/μL)	WBC (x10E3/μL)	Reti (%)	PLT (x10E3/μL)	HCT (%)	
	20	9.3	7.02	9.69	1.0	355	49.9
	21	8.9	5.97	9.25	1.0	319	48.2
	22	8.8	6.37	18.90	1.0	435	49.3
Mean	9.00	6.453	12.613	1.00	369.7	49.13	
SD	0.26	0.530	5.449	0.00	59.4	0.86	
N	3	3	3	3	3	3	

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female	Day(s): Predose Relative to Start Date	Haematological Parameters				
Group 4: 350/225/ 200 Units/kg	HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
	8.8	6.38	10.88	1.1	515	48.5
	8.3	6.48	8.11	0.6	376	47.5
	8.6	6.29	11.80	1.6	371	50.0
	8.9	6.40	9.46	0.7	435	49.4
	8.3	5.81	8.19	2.5	521	45.5
	Mean	6.272	9.688	1.30	443.6	48.18
SD		0.267	1.633	0.78	72.5	1.77
N		5	5	5	5	5

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female Day: 12 Relative to Start Date		Haematological Parameters - Individual Data					
Group 1: Control		Haematological Parameters					
		HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
	6	8.9	5.98	17.07	1.3	417	48.1
	7	7.8	5.33	12.44	2.2	511	44.4
	8	8.8	6.06	16.57	1.3	429	50.0
	9	8.9	6.38	10.05	1.9	594	48.8
	10	8.6	6.11	10.09	2.1	501	46.6
Mean		8.60	5.972	13.244	1.76	490.4	47.58
SD		0.46	0.389	3.409	0.43	71.5	2.16
N		5	5	5	5	5	5

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Sex: Female		Day: 12 Relative to Start Date		TABLE 7-2 Haematological Parameters - Individual Data				Monkey
Group 2: 35 Units/kg		Haematological Parameters						
		HGB (mmol/L)	RBC (x10E6/μL)	WBC (x10E3/μL)	Reti (%)	PLT (x10E3/μL)	HCT (%)	
14		7.9	5.44	11.10	1.8	518	44.7	
15		7.3	5.25	13.86	2.0	512	41.3	
16		9.3	6.83	10.91	1.8	412	52.3	
Mean		8.17	5.840	11.957	1.87	480.7	46.10	
SD		1.03	0.863	1.651	0.12	59.5	5.63	
N		3	3	3	3	3	3	

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female		Day: 12 Relative to Start Date					
Group 3: 110 Units/kg			Haematological Parameters				
	HGB (mmol/L)	RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)	
20	8.8	6.56	13.99	1.4	456	47.2	
21	8.1	5.52	12.86	2.6	448	46.5	
22	8.5	6.18	12.88	1.4	518	48.8	
Mean	8.47	6.087	13.243	1.80	474.0	47.50	
SD	0.35	0.526	0.647	0.69	38.3	1.18	
N	3	3	3	3	3	3	

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Sex: Female		Day: 12 Relative to Start Date	TABLE 7-2 Haematological Parameters - Individual Data					Monkey
Group 4: 350/225/ 200 Units/kg		Haematological Parameters						
		HGB (mmol/L)	RBC (x10E6/μL)	WBC (x10E3/μL)	Reti (%)	PLT (x10E3/μL)	HCT (%)	
28	7.5	5.42	15.06	2.0	652	41.5		
29	7.4	5.75	13.90	1.5	402	43.0		
30	8.0	5.88	14.79	1.6	506	46.9		
31	8.4	6.11	16.44	1.2	505	48.0		
32	7.9	5.88	15.56	2.2	614	46.8		
Mean	7.84	5.808	15.150	1.70	535.8	45.24		
SD	0.40	0.253	0.940	0.40	99.2	2.82		
N	5	5	5	5	5	5		

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female		Day: 26 Relative to Start Date					
			Haematological Parameters				
Group 1: Control	HGB (mmol/L)		RBC (x10E6/ μ L)	WBC (x10E3/ μ L)	Reti (%)	PLT (x10E3/ μ L)	HCT (%)
	9	8.8	6.25	18.36	2.0	609	47.3
	10	8.4	5.90	9.29	2.4	455	45.7
	Mean	8.60	6.075	13.825	2.20	532.0	46.50
SD		-	-	-	-	-	-
N		2	2	2	2	2	2

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female		Day: 26 Relative to Start Date		Haematological Parameters								
Group 4: 350/225/ 200 Units/kg	HGB (mmol/L)		RBC (x10E6/μL)		WBC (x10E3/μL)		Reti (%)		PLT (x10E3/μL)		HCT (%)	
	31	8.6	6.14	18.03	1.8	489	47.7					
	32	8.4	5.91	15.87	2.5	499	46.6					
Mean	8.50	6.025	16.950	2.15	494.0	47.15						
SD	-	-	-	-	-	-						
N	2	2	2	2	2	2						

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Sex: Female		Day(s): Predose Relative to Start Date	TABLE 7-2 Haematological Parameters - Individual Data					Monkey
Group 1: Control	Haematological Parameters							
	Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)		
6	59.7	34.1	4.3	0.7	0.7	0.5		
7	53.2	42.6	3.1	0.1	0.6	0.5		
8	45.8	47.6	5.3	0.2	0.6	0.5		
9	69.6	27.1	2.4	0.1	0.3	0.4		
10	40.4	51.8	5.2	1.1	1.0	0.4		
Mean	53.74	40.64	4.06	0.44	0.64	0.46		
SD	11.49	10.04	1.28	0.44	0.25	0.05		
N	5	5	5	5	5	5		

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Sex: Female		Day(s): Predose Relative to Start Date		TABLE 7-2 Haematological Parameters - Individual Data				Monkey
Group 2: 35 Units/kg		Haematological Parameters						
		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)	
14		75.3	20.3	3.7	0.2	0.2	0.3	
15		47.1	47.4	3.7	0.6	0.8	0.6	
16		60.1	34.7	3.5	0.5	0.7	0.5	
Mean		60.83	34.13	3.63	0.43	0.57	0.47	
SD		14.11	13.56	0.12	0.21	0.32	0.15	
N		3	3	3	3	3	3	

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TABLE 7-2						Haematological Parameters - Individual Data		Monkey
Sex: Female	Day(s): Predose Relative to Start Date		Haematological Parameters					
Group 3: 110 Units/kg	Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)		
	20	38.3	56.4	3.2	1.0	0.8	0.4	
	21	62.2	33.2	3.4	0.4	0.4	0.4	
	22	79.9	17.5	1.9	0.1	0.3	0.3	
	Mean	60.13	35.70	2.83	0.50	0.50	0.37	
SD	20.88	19.57	0.81	0.46	0.26	0.06		
N	3	3	3	3	3	3	3	

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Sex: Female		Day(s): Predose Relative to Start Date	TABLE 7-2 Haematological Parameters - Individual Data					Monkey	
Group 4: 350/225/ 200 Units/kg			Haematological Parameters						
			Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)		Baso (%)
28			55.5	38.9	4.4	0.2	0.6	0.4	
29			30.9	60.8	6.2	0.7	0.8	0.6	
30			47.3	45.5	4.3	1.6	0.8	0.6	
31			43.0	50.8	4.5	0.4	0.6	0.7	
32			32.9	62.9	2.3	0.5	0.8	0.6	
Mean			41.92	51.78	4.34	0.68	0.72	0.58	
SD			10.21	10.14	1.38	0.54	0.11	0.11	
N			5	5	5	5	5	5	

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female Day: 12 Relative to Start Date		Haematological Parameters					
Group 1: Control		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
	6	49.9	44.0	4.0	1.0	0.6	0.5
	7	37.7	58.1	2.8	0.1	0.8	0.5
	8	48.1	45.6	4.7	0.4	0.7	0.5
	9	36.2	56.4	5.4	0.5	0.7	0.6
	10	37.5	54.2	6.1	0.5	1.2	0.5
	Mean	41.88	51.66	4.60	0.50	0.80	0.52
SD	6.56	6.44	1.27	0.32	0.23	0.04	
N	5	5	5	5	5	5	5

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female		Day: 12 Relative to Start Date					
			Haematological Parameters				
Group 2: 35 Units/kg	Neut (%)		Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
	14	50.1	43.9	4.6	0.6	0.5	0.3
	15	36.3	57.8	3.2	1.3	0.9	0.5
	16	45.2	47.8	4.2	1.2	1.1	0.6
	Mean	43.87	49.83	4.00	1.03	0.83	0.47
SD		7.00	7.17	0.72	0.38	0.31	0.15
N		3	3	3	3	3	3

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female		Day: 12 Relative to Start Date		Haematological Parameters								
Group 3: 110 Units/kg	Neut (%)		Lym (%)		Mono (%)		Eos (%)		LUC (%)		Baso (%)	
	20	31.3	62.9	3.1	1.4	0.9	0.5					
	21	53.5	40.4	4.2	0.8	0.8	0.3					
	22	53.5	41.9	3.2	0.3	0.6	0.5					
	Mean	46.10	48.40	3.50	0.83	0.77	0.43					
	SD	12.82	12.58	0.61	0.55	0.15	0.12					
	N	3	3	3	3	3	3					

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Sex: Female			Day: 12 Relative to Start Date		TABLE 7-2				Haematological Parameters - Individual Data			Monkey
Group 4: 350/225/ 200 Units/kg			Haematological Parameters									
			Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)				
28			64.3	31.0	3.3	0.2	0.8	0.3				
29			56.6	37.0	4.4	0.6	1.0	0.4				
30			55.5	38.2	3.9	0.3	1.4	0.7				
31			48.3	45.3	4.2	0.7	1.0	0.6				
32			44.3	52.6	1.2	0.6	0.7	0.5				
Mean			53.80	40.82	3.40	0.48	0.98	0.50				
SD			7.77	8.32	1.30	0.22	0.27	0.16				
N			5	5	5	5	5	5				

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female		Day: 26 Relative to Start Date					
			Haematological Parameters				
Group 1: Control		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)
	9	60.2	34.9	3.7	0.1	0.5	0.5
	10	32.3	58.5	6.7	0.5	1.5	0.4
	Mean	46.25	46.70	5.20	0.30	1.00	0.45
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female		Day: 26 Relative to Start Date		Haematological Parameters				
Group 4: 350/225/ 200 Units/kg		Neut (%)	Lym (%)	Mono (%)	Eos (%)	LUC (%)	Baso (%)	
31		46.8	46.5	5.2	0.3	0.7	0.5	
32		38.5	56.4	3.5	0.3	0.8	0.6	
Mean		42.65	51.45	4.35	0.30	0.75	0.55	
SD		-	-	-	-	-	-	
N		2	2	2	2	2	2	

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Sex: Female		Day(s): Predose Relative to Start Date	TABLE 7-2 Haematological Parameters - Individual Data					Monkey
Group 1: Control	Haematological Parameters							
	Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)	Baso (x10E3/ μ L)		
6	7.85	4.49	0.56	0.09	0.09	0.06		
7	8.75	7.00	0.50	0.02	0.09	0.08		
8	4.33	4.50	0.50	0.02	0.06	0.05		
9	12.09	4.71	0.42	0.01	0.05	0.07		
10	4.14	5.31	0.54	0.11	0.11	0.04		
Mean	7.432	5.202	0.504	0.050	0.080	0.060		
SD	3.319	1.059	0.054	0.046	0.024	0.016		
N	5	5	5	5	5	5		

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TABLE 7-2							
Sex: Female	Day(s): Predose Relative to Start Date	Haematological Parameters - Individual Data				Monkey	
Group 2: 35 Units/kg	Haematological Parameters						
	Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)	Baso (x10E3/ μ L)	
	14	13.64	3.68	0.67	0.04	0.03	0.06
	15	8.08	8.13	0.63	0.10	0.14	0.10
	16	9.38	5.41	0.55	0.08	0.11	0.07
Mean	10.367	5.740	0.617	0.073	0.093	0.077	
SD	2.908	2.243	0.061	0.031	0.057	0.021	
N	3	3	3	3	3	3	

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female	Day(s): Predose Relative to Start Date	Haematological Parameters				
		Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)
Group 3: 110 Units/kg						Baso (x10E3/ μ L)
	20	3.71	5.47	0.31	0.09	0.08
	21	5.76	3.07	0.32	0.03	0.04
	22	15.09	3.30	0.36	0.03	0.06
	Mean	8.187	3.947	0.330	0.050	0.060
	SD	6.066	1.324	0.026	0.035	0.020
	N	3	3	3	3	3

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female	Day(s): Predose Relative to Start Date	Haematological Parameters				
		Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)
Group 4: 350/225/ 200 Units/kg						Baso (x10E3/ μ L)
	28	6.04	4.23	0.48	0.02	0.06
	29	2.51	4.94	0.50	0.06	0.06
	30	5.58	5.36	0.51	0.18	0.09
	31	4.07	4.80	0.42	0.04	0.06
	32	2.70	5.15	0.19	0.04	0.06
Mean SD N		4.180	4.896	0.420	0.068	0.066
		1.613	0.429	0.133	0.064	0.013
		5	5	5	5	5

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female Day: 12 Relative to Start Date		Haematological Parameters					
Group 1: Control		Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)	Baso (x10E3/ μ L)
	6	8.52	7.50	0.68	0.18	0.10	0.09
	7	4.69	7.23	0.34	0.02	0.10	0.06
	8	7.97	7.56	0.78	0.06	0.11	0.08
	9	3.64	5.67	0.54	0.05	0.08	0.06
	10	3.78	5.47	0.61	0.05	0.13	0.05
Mean SD N	Mean	5.720	6.686	0.590	0.072	0.104	0.068
	SD	2.348	1.029	0.166	0.062	0.018	0.016
	N	5	5	5	5	5	5

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female	Day: 12 Relative to Start Date	Haematological Parameters				
		Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)
Group 2: 35 Units/kg						Baso (x10E3/ μ L)
	14	5.56	4.87	0.51	0.06	0.05
	15	5.04	8.02	0.44	0.17	0.12
	16	4.93	5.22	0.45	0.13	0.12
Mean SD N		5.177	6.037	0.467	0.120	0.097
		0.337	1.727	0.038	0.056	0.040
		3	3	3	3	3

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female		Day: 12 Relative to Start Date		Haematological Parameters								
Group 3: 110 Units/kg	Neut (x10E3/μL)		Lym (x10E3/μL)		Mono (x10E3/μL)		Eos (x10E3/μL)		LUC (x10E3/μL)		Baso (x10E3/μL)	
	20	4.37	8.80	0.44	0.19	0.12	0.06					
	21	6.88	5.20	0.54	0.10	0.10	0.04					
	22	6.90	5.40	0.41	0.04	0.08	0.06					
	Mean	6.050	6.467	0.463	0.110	0.100	0.053					
	SD	1.455	2.023	0.068	0.075	0.020	0.012					
	N	3	3	3	3	3	3					

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female		Day: 12 Relative to Start Date					
			Haematological Parameters				
			Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)
			Baso (x10E3/ μ L)				
Group 4: 350/225/ 200 Units/kg	28		9.69	4.67	0.50	0.03	0.12
	29		7.87	5.14	0.61	0.09	0.14
	30		8.21	5.65	0.58	0.04	0.21
	31		7.94	7.45	0.69	0.11	0.16
	32		6.90	8.18	0.19	0.09	0.11
	Mean		8.122	6.218	0.514	0.072	0.148
			SD	1.007	0.193	0.035	0.040
			N	5	5	5	5

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female		Day: 26 Relative to Start Date					
			Haematological Parameters				
Group 1: Control	Neut (x10E3/µL)		Lym (x10E3/µL)	Mono (x10E3/µL)	Eos (x10E3/µL)	LUC (x10E3/µL)	Baso (x10E3/µL)
	9	11.06	6.41	0.68	0.02	0.10	0.09
	10	3.00	5.44	0.62	0.05	0.14	0.04
	Mean	7.030	5.925	0.650	0.035	0.120	0.065
SD		-	-	-	-	-	-
N		2	2	2	2	2	2

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female		Day: 26 Relative to Start Date		Haematological Parameters				
Group 4: 350/225/ 200 Units/kg		Neut (x10E3/ μ L)	Lym (x10E3/ μ L)	Mono (x10E3/ μ L)	Eos (x10E3/ μ L)	LUC (x10E3/ μ L)	Baso (x10E3/ μ L)	
31		8.44	8.38	0.94	0.05	0.13	0.09	
32		6.10	8.95	0.55	0.05	0.12	0.09	
Mean		7.270	8.665	0.745	0.050	0.125	0.090	
SD		-	-	-	-	-	-	
N		2	2	2	2	2	2	

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Sex: Female		Day(s): Predose Relative to Start Date		TABLE 7-2 Haematological Parameters - Individual Data				Monkey
Group 1: Control		PT (Seconds)	aPTT (Seconds)	Haematological Parameters				
				ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)	
	6	9.7	24.6	0	79.6	1.49	18.78	
	7	10.5	25.3	0	79.6	1.46	18.37	
	8	10.2	20.8	0	81.3	1.45	17.80	
	9	10.1	23.3	0	75.1	1.41	18.72	
	10	10.2	23.5	0	74.0	1.39	18.74	
Mean		10.14	23.50	0.0	77.92	1.440	18.482	
SD		0.29	1.72	0.0	3.18	0.040	0.415	
N		5	5	5	5	5	5	

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female	Day(s): Predose Relative to Start Date	Haematological Parameters				
		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)
Group 2: 35 Units/kg						MCHC (mmol/L)
	14	10.1	24.2	0	80.6	1.43
	15	10.3	22.8	0	76.7	1.41
	16	9.6	22.8	0	75.3	1.35
Mean SD N		10.00	23.27	0.0	77.53	1.397
		0.36	0.81	0.0	2.75	0.042
		3	3	3	3	3

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female	Day(s): Predose Relative to Start Date	Haematological Parameters				
Group 3: 110 Units/kg	PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
	20	22.2	0	71.0	1.33	18.72
	21	10.4	0	80.7	1.49	18.42
	22	9.9	0	77.4	1.38	17.86
	Mean	10.17	0.0	76.37	1.400	18.333
	SD	0.25	0.0	4.93	0.082	0.437
	N	3	3	3	3	3

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female	Day(s): Predose Relative to Start Date	Haematological Parameters				
		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)
Group 4: 350/225/ 200 Units/kg						MCHC (mmol/L)
	28	9.9	21.4	0	76.1	1.38
	29	9.9	21.7	0	73.4	1.28
	30	9.8	20.5	0	79.5	1.37
	31	10.1	24.2	0	77.1	1.40
	32	9.8	22.9	0	78.2	1.43
Mean SD N		9.90	22.14	0.0	76.86	1.372
		0.12	1.44	0.0	2.31	0.056
		5	5	5	5	5

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female Day: 12 Relative to Start Date		Haematological Parameters - Individual Data					
Group 1: Control		Haematological Parameters					
		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
	6	9.3	20.9	0	80.4	1.50	18.60
	7	10.0	21.7	0	83.2	1.47	17.64
	8	10.4	20.1	0	82.5	1.45	17.58
	9	9.8	21.1	2	76.5	1.40	18.24
	10	10.0	21.0	0	76.2	1.40	18.42
Mean		9.90	20.96	0.4	79.76	1.444	18.096
SD		0.40	0.57	0.9	3.28	0.044	0.462
N		5	5	5	5	5	5

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TABLE 7-2 Haematological Parameters - Individual Data

Sex: Female Day: 12 Relative to Start Date

Monkey

Group 2: 35 Units/kg	Haematological Parameters						
	PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)	
14	9.7	21.7	0	82.1	1.46	17.76	
15	9.9	21.1	1	78.7	1.40	17.74	
16	9.3	20.2	1	76.5	1.37	17.86	
Mean	9.63	21.00	0.7	79.10	1.410	17.787	
SD	0.31	0.75	0.6	2.82	0.046	0.064	
N	3	3	3	3	3	3	

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female		Day: 12 Relative to Start Date					
Group 3: 110 Units/kg			Haematological Parameters				
	PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)	
	20	9.8	20.2	71.9	1.34	18.57	
	21	10.2	22.5	84.3	1.47	17.41	
	22	9.9	22.2	79.0	1.38	17.41	
Mean	9.97	21.63	0.0	78.40	1.397	17.797	
SD	0.21	1.25	0.0	6.22	0.067	0.670	
N	3	3	3	3	3	3	

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female		Day: 12 Relative to Start Date					
Group 4: 350/225/ 200 Units/kg		PT (Seconds)	aPTT (Seconds)	Haematological Parameters			
				ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
28		10.0	20.9	0	76.6	1.38	17.98
29		9.5	19.7	0	74.8	1.29	17.29
30		10.1	21.4	0	79.7	1.35	16.99
31		9.9	21.8	0	78.7	1.38	17.55
32		9.5	19.7	2	79.7	1.35	16.93
Mean		9.80	20.70	0.4	77.90	1.350	17.348
SD		0.28	0.97	0.9	2.15	0.037	0.432
N		5	5	5	5	5	5

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TABLE 7-2 Haematological Parameters - Individual Data

Monkey

Sex: Female		Day: 26 Relative to Start Date						
				Haematological Parameters				
Group 1: Control		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)	
	9	10.2	21.9	0	75.8	1.41	18.61	
	10	10.1	21.4	0	77.4	1.42	18.36	
Mean SD N	10.15		21.65	0.0	76.60	1.415	18.485	
	-		-	-	-	-	-	
	2		2	2	2	2	2	

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TABLE 7-2 Haematological Parameters - Individual Data Monkey

Sex: Female		Day: 26 Relative to Start Date					
			Haematological Parameters				
Group 4: 350/225/ 200 Units/kg		PT (Seconds)	aPTT (Seconds)	ESR (mm/1h)	MCV (fL)	MCH (fmol)	MCHC (mmol/L)
31		9.7	22.1	0	77.7	1.39	17.96
32		9.3	20.1	0	78.7	1.42	18.06
Mean		9.50	21.10	0.0	78.20	1.405	18.010
SD		-	-	-	-	-	-
N		2	2	2	2	2	2

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day(s): Predose Relative to Start Date		Biochemical Parameters							
Sex: Male		Bile Acids (µmol/L)	Bilirubin (total) (µmol/L)	Cholesterol (total) (mmol/L)	Creatinine (µmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)	
Group 1: Control		[a]	[a1]	[a1]	[a1]	[a1]	[a1]	[a1]	
	Mean	5.68	5.22	3.886	83.6	3.198	2.344	78.0	
	SD	1.41	0.61	1.100	5.0	0.519	0.460	2.8	
	N	5	5	5	5	5	5	5	
Group 2: 35 Units/kg									
	Mean	4.43	6.10	4.390	78.3	2.977	2.613	81.3	
	SD	0.55	1.54	0.548	9.0	0.418	0.235	2.1	
	N	3	3	3	3	3	3	3	
Group 3: 110 Units/kg									
	%Diff	-21.9	16.9	13.0	-6.3	-6.9	11.5	4.3	
	Mean	6.60	6.30	3.093	78.0	3.217	2.317	78.7	
	SD	3.30	0.72	0.684	6.9	1.029	0.050	4.0	
Group 4: 350/225/200 Units/kg									
	N	3	3	3	3	3	3	3	
	%Diff	16.2	20.7	-20.4	-6.7	0.6	-1.2	0.9	
	Mean	12.37	4.53	3.993	73.1	3.323	2.331	78.7	
	SD	12.80	1.12	0.525	4.5	0.837	0.497	4.6	
	N	7	7	7	7	7	7	7	
	%Diff	117.8	-13.2	2.7	-12.5	3.9	-0.5	0.9	

[a] - Anova & Dunnett(Rank)
[a1] - Anova & Dunnett

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day: 12 Relative to Start Date		Biochemical Parameters						
Sex: Male		Bile Acids (μmol/L)	Bilirubin (total) (μmol/L)	Cholesterol (total) (mmol/L)	Creatinine (μmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)
Group 1: Control		[a]	[a1]	[a]	[a]	[a]	[a]	[a]
	Mean	5.84	4.04	3.182	72.2	4.070	2.022	77.2
	SD	0.47	0.63	0.806	5.0	0.332	0.461	3.2
	N	5	5	5	5	5	5	5
Group 2: 35 Units/kg								
	Mean	5.20	4.53	3.647	68.0	4.353	2.123	79.3
	SD	0.92	0.85	0.293	2.0	0.456	0.287	3.2
	N	3	3	3	3	3	3	3
Group 3: 110 Units/kg								
	%Diff	-11.0	12.2	14.6	-5.8	7.0	5.0	2.8
	Mean	4.43	4.07	2.427	65.7	4.103	2.063	77.0
	SD	0.86	1.16	0.220	7.6	0.379	0.193	1.0
Group 4: 350/225/200 Units/kg								
	N	3	3	3	3	3	3	3
	%Diff	-24.1	0.7	-23.7	-9.0	0.8	2.0	-0.3
	Mean	5.58	4.72	3.198	74.2	4.480	2.040	82.2
	SD	0.79	1.17	0.471	4.8	0.375	0.334	5.5
	N	5	5	5	5	5	5	5
	%Diff	-4.5	16.8	0.5	2.8	10.1	0.9	6.5

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Log)

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day: 26 Relative to Start Date		Biochemical Parameters						
Sex: Male		Bile Acids (μmol/L)	Bilirubin (total) (μmol/L)	Cholesterol (total) (mmol/L)	Creatinine (μmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)
Group 1: Control	Mean	[a] 6.65n	[a] 3.80n	[a] 4.830n	[a] 90.0n	[a] 4.860n	[a] 1.545n	[a] 77.0n
	SD	-	-	-	-	-	-	-
	N	2	2	2	2	2	2	2
Group 4: 350/225/200 Units/kg	Mean	5.50n	4.20n	3.580n	89.0n	4.935n	1.790n	80.0n
	SD	-	-	-	-	-	-	-
	N	2	2	2	2	2	2	2
		%Diff	10.5	-25.9	-1.1	1.5	15.9	3.9

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day(s): Predose Relative to Start Date		Electrophoresis						
Sex: Male		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)
		[a]	[a1]	[a]	[a]	[a2]	[a]	[a]
Group 1: Control	Mean	50.84	27.16	1.882	2.36	7.00	9.88	7.96
	SD	1.61	2.23	0.156	0.32	1.25	1.64	1.81
	N	5	5	5	5	5	5	5
Group 2: 35 Units/kg	Mean	53.00	28.37	1.887	1.87	7.00	9.60	9.93
	SD	2.69	2.86	0.261	0.21	0.26	1.06	2.31
	N	3	3	3	3	3	3	3
Group 3: 110 Units/kg	%Diff	4.2	4.4	0.2	-20.9	0.0	-2.8	24.8
	Mean	51.37	27.30	1.890	2.13	6.17	9.60	9.43
	SD	1.88	2.69	0.151	0.32	0.93	1.23	0.68
Group 4: 350/225/ 200 Units/kg	N	3	3	3	3	3	3	3
	%Diff	1.0	0.5	0.4	-9.6	-11.9	-2.8	18.5
	Mean	49.51	29.21	1.703	2.40	7.30	9.79	9.76
	SD	4.66	1.84	0.203	0.25	1.92	2.13	1.56
	N	7	7	7	7	7	7	7
	%Diff	-2.6	7.6	-9.5	1.7	4.3	-1.0	22.6

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Rank)
[a2] - Anova & Dunnett(Log)

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day: 12 Relative to Start Date									
Sex: Male		Electrophoresis							
		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)	
Group 1: Control		[a]	[a]	[a]	[a]	[a1]	[a2]	[a]	
	Mean	49.00	28.20	1.740	2.54	7.22	10.70	7.76	
	SD	2.66	1.18	0.105	0.30	1.43	1.53	1.81	
	N	5	5	5	5	5	5	5	
Group 2: 35 Units/kg			-	-	-	-	-	-	
	Mean	47.67	31.67	1.510	2.50	7.63	11.23	10.30	
	SD	1.26	2.02	0.062	0.40	0.12	0.32	2.02	
	N	3	3	3	3	3	3	3	
Group 3: 110 Units/kg	%Diff	-2.7	12.3	-13.2	-1.6	5.7	5.0	32.7	
	Mean	48.63	28.37	1.710	2.43	6.93	9.90	9.13	
	SD	1.07	0.86	0.078	0.32	0.72	0.17	0.51	
	N	3	3	3	3	3	3	3	
Group 4: 350/225/ 200 Units/kg	%Diff	-0.7	0.6	-1.7	-4.2	-4.0	-7.5	17.7	
	Mean	50.00	32.22	1.566	3.18	7.50	11.82	9.68	
	SD	2.91	3.64	0.162	0.46	1.64	1.40	2.45	
	N	5	5	5	5	5	5	5	
	%Diff	2.0	14.3	-10.0	25.2	3.9	10.5	24.7	

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Log)
[a2] - Anova & Dunnett(Rank)

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day: 26 Relative to Start Date		Electrophoresis						
Sex: Male		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)
Group 1: Control	Mean	50.05n	27.00n	1.855n	2.00n	8.65n	9.10n	7.30n
	SD	-	-	-	-	-	-	-
	N	2	2	2	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	47.65n	32.35n	1.480n	2.35n	8.20n	9.95n	11.80n
	SD	-	-	-	-	-	-	-
	N	2	2	2	2	2	2	2
		-4.8	19.8	-20.2	17.5	-5.2	9.3	61.6

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day(s): Predose Relative to Start Date		Biochemical Parameters							
Sex: Male		Triglycerides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potassium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)	
Group 1: Control	Mean	[a]	[a]	[a]	[a]	[a]	[a]	[a]	
	SD	0.716	9.302	2.636	106.2	4.978	148.0	62.2	
	N	0.168	0.858	0.160	1.3	0.466	1.6	7.9	
		5	5	5	5	5	5	5	
Group 2: 35 Units/kg	Mean	-	-	-	-	-	-	-	
	SD	0.890	9.003	2.560	106.0	5.177	147.0	59.0	
	N	0.062	1.502	0.075	1.7	0.337	1.7	15.6	
	%Diff	3	3	3	3	3	3	3	
Group 3: 110 Units/kg	Mean	24.3	-3.2	-2.9	-0.2	4.0	-0.7	-5.1	
	SD	0.747	7.397	2.560	105.7	4.720	146.7	79.7	
	N	0.097	0.957	0.040	1.5	0.260	1.5	12.1	
	%Diff	3	3	3	3	3	3	3	
Group 4: 350/225/ 200 Units/kg	Mean	4.3	-20.5	-2.9	-0.5	-5.2	-0.9	28.1	
	SD	0.680	9.617	2.630	106.7	5.066	146.9	67.1	
	N	0.210	1.034	0.052	1.6	0.517	1.8	13.0	
	%Diff	7	7	7	7	7	7	7	
	Mean	-5.0	3.4	-0.2	0.5	1.8	-0.8	7.9	
	%Diff								

[a] - Anova & Dunnett

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day: 12 Relative to Start Date									
Sex: Male		Biochemical Parameters							
		Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)	
Group 1: Control	Mean	[a]	[a]	[a]	[a]	[a]	[a]	[a]	
	SD	0.468	4.838	2.602	103.6	5.566	146.2	96.8	
	N	0.217	0.490	0.038	0.9	0.456	2.0	15.4	
		5	5	5	5	5	5	5	
Group 2: 35 Units/kg	Mean	-	-	-	-	-	-	-	
	SD	0.423	3.893	2.537	103.0	5.350	145.3	91.0	
	N	0.047	0.253	0.055	1.0	0.130	3.1	17.3	
	%Diff	3	3	3	3	3	3	3	
Group 3: 110 Units/kg	Mean	-9.5	-19.5	-2.5	-0.6	-3.9	-0.6	-6.0	
	SD	0.433	4.153	2.563	104.7	5.510	146.0	130.3	
	N	0.258	0.800	0.097	0.6	0.417	1.0	20.2	
	%Diff	3	3	3	3	3	3	3	
Group 4: 350/225/ 200 Units/kg	Mean	-7.4	-14.2	-1.5	1.0	-1.0	-0.1	34.6	
	SD	0.468	5.486	2.620	105.0*	5.528	146.2	128.4	
	N	0.134	0.898	0.062	0.7	0.583	1.8	68.5	
	%Diff	5	5	5	5	5	5	5	
		0.0	13.4	0.7	1.4	-0.7	0.0	32.6	

[a] - Anova & Dunnett: * = $p \leq 0.05$

[a1] - Anova & Dunnett(Rank)

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day: 26 Relative to Start Date		Biochemical Parameters						
Sex: Male		Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)
Group 1: Control	Mean	0.555n	7.265n	2.495n	105.0n	5.165n	147.0n	70.0n
	SD	-	-	-	-	-	-	-
	N	2	2	2	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	0.345n	6.840n	2.565n	105.0n	5.305n	144.5n	50.0n
	SD	-	-	-	-	-	-	-
	N	2	2	2	2	2	2	2
		%Diff	-5.8	2.8	0.0	2.7	-1.7	-28.6

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day(s): Predose Relative to Start Date		Biochemical Parameters			
Sex: Male		aP (U/L)	ASAT (U/L)	LDH (U/L)	Gamma-GT (U/L)
		[a]	[a]	[a1]	[a2]
Group 1: Control	Mean	689.2	58.2	406.8	111.30
	SD	129.0	7.3	61.3	23.64
	N	5	5	5	5
		-	-	-	-
Group 2: 35 Units/kg	Mean	799.7	64.7	478.0	90.57
	SD	44.5	9.1	80.8	23.17
	N	3	3	3	3
	%Diff	16.0	11.1	17.5	-18.6
Group 3: 110 Units/kg	Mean	717.0	74.3	702.7	100.33
	SD	128.6	8.7	442.0	28.04
	N	3	3	3	3
	%Diff	4.0	27.7	72.7	-9.9
Group 4: 350/225/ 200 Units/kg	Mean	791.4	67.4	519.4	101.36
	SD	230.0	11.9	122.5	22.45
	N	7	7	7	7
	%Diff	14.8	15.9	27.7	-8.9

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Log)
[a2] - Anova & Dunnett(Rank)

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TABLE 8-1

Biochemical Parameters - Summary

Monkey

Day: 12 Relative to Start Date		Biochemical Parameters			
Sex: Male		aP (U/L)	ASAT (U/L)	LDH (U/L)	Gamma-GT (U/L)
		[a]	[a1]	[a2]	[a]
Group 1: Control	Mean	529.0	103.8	631.8	94.54
	SD	117.9	30.7	192.0	21.48
	N	5	5	5	5
		-	-	-	-
Group 2: 35 Units/kg	Mean	608.3	122.7	652.7	72.90
	SD	51.9	32.7	103.1	17.85
	N	3	3	3	3
	%Diff	15.0	18.2	3.3	-22.9
Group 3: 110 Units/kg	Mean	524.0	128.7	737.0	86.57
	SD	114.1	21.5	166.3	14.89
	N	3	3	3	3
	%Diff	-0.9	24.0	16.7	-8.4
Group 4: 350/225/ 200 Units/kg	Mean	588.4	126.4	865.8	84.22
	SD	157.5	82.9	630.4	10.75
	N	5	5	5	5
	%Diff	11.2	21.8	37.0	-10.9

[a] - Anova & Dunnett

[a1] - Anova & Dunnett(Log)

[a2] - Anova & Dunnett(Rank)

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TABLE 8-1

Biochemical Parameters - Summary

Monkey

Day: 26 Relative to Start Date		Biochemical Parameters			
Sex: Male		aP (U/L)	ASAT (U/L)	LDH (U/L)	Gamma-GT (U/L)
		[a]	[a]	[a]	[a]
Group 1: Control	Mean	531.5n	52.5n	443.5n	102.60n
	SD	-	-	-	-
	N	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	712.0n	61.0n	397.5n	90.55n
	SD	-	-	-	-
	N	2	2	2	2
	%Diff	34.0	16.2	-10.4	-11.7

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day(s): Predose Relative to Start Date		Biochemical Parameters							
Sex: Female		Bile Acids (μmol/L)	Bilirubin (total) (μmol/L)	Cholesterol (total) (mmol/L)	Creatinine (μmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)	
		[a]	[a]	[a]	[a]	[a1]	[a]	[a]	
Group 1: Control	Mean	5.74	5.36	3.512	66.4	3.050	2.214	74.8	
	SD	1.72	1.07	0.736	9.8	0.430	0.169	5.1	
	N	5	5	5	5	5	5	5	
Group 2: 35 Units/kg	Mean	9.77*	5.87	3.767	64.7	2.987	2.213	73.7	
	SD	2.74	1.07	0.225	12.7	0.595	0.198	5.5	
	N	3	3	3	3	3	3	3	
	%Diff	70.2	9.5	7.3	-2.6	-2.1	0.0	-1.5	
Group 3: 110 Units/kg	Mean	4.60	5.93	3.933	71.3	2.903	2.237	71.3	
	SD	0.26	0.97	0.327	5.8	0.116	0.180	2.1	
	N	3	3	3	3	3	3	3	
	%Diff	-19.9	10.7	12.0	7.4	-4.8	1.0	-4.6	
Group 4: 350/225/200 Units/kg	Mean	5.46	5.86	3.686	72.8	3.294	2.252	78.2	
	SD	0.93	1.39	0.426	5.8	0.547	0.250	2.6	
	N	5	5	5	5	5	5	5	
	%Diff	-4.9	9.3	5.0	9.6	8.0	1.7	4.5	

[a] - Anova & Dunnett: * = $p \leq 0.05$

[a1] - Anova & Dunnett(Rank)

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day: 12 Relative to Start Date		Biochemical Parameters							
Sex: Female		Bile Acids (μmol/L)	Bilirubin (total) (μmol/L)	Cholesterol (total) (mmol/L)	Creatinine (μmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)	
Group 1: Control		[a]	[a1]	[a1]	[a2]	[a]	[a]	[a1]	
	Mean	6.36	4.58	3.238	65.8	4.270	2.270	81.4	
	SD	1.63	0.93	0.862	5.3	0.646	0.126	2.1	
	N	5	5	5	5	5	5	5	
Group 2: 35 Units/kg		-	-	-	-	-	-	-	
	Mean	6.93	4.60	3.257	64.0	4.287	2.103	77.7	
	SD	0.35	0.26	0.382	8.0	0.300	0.112	12.4	
	N	3	3	3	3	3	3	3	
Group 3: 110 Units/kg		9.0	0.4	0.6	-2.7	0.4	-7.3	-4.6	
	%Diff								
	Mean	5.67	4.63	3.357	67.3	3.890	2.133	78.7	
	SD	1.02	1.17	0.374	7.6	0.948	0.091	4.0	
Group 4: 350/225/ 200 Units/kg		-10.9	1.2	3.7	2.3	-8.9	-6.0	-3.4	
	%Diff								
	Mean	6.60	6.74	2.852	77.6	4.074	1.774**	79.0	
	SD	0.40	5.86	0.117	14.3	1.236	0.339	2.9	
	N	5	5	5	5	5	5	5	
	%Diff	3.8	47.2	-11.9	17.9	-4.6	-21.9	-2.9	

[a] - Anova & Dunnett: ** = p ≤ 0.01

[a1] - Anova & Dunnett(Rank)

[a2] - Anova & Dunnett(Log)

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day: 26 Relative to Start Date		Biochemical Parameters						
Sex: Female		Bile Acids (μmol/L)	Bilirubin (total) (μmol/L)	Cholesterol (total) (mmol/L)	Creatinine (μmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)
Group 1: Control	Mean	[a] 5.50n	[a] 3.45n	[a] 4.105n	[a] 74.5n	[a] 5.440n	[a] 2.250n	[a] 73.5n
	SD	-	-	-	-	-	-	-
	N	2	2	2	2	2	2	2
Group 4: 350/225/200 Units/kg	Mean	16.35n	4.25n	3.530n	78.0n	5.015n	1.755n	80.0n
	SD	-	-	-	-	-	-	-
	N	2	2	2	2	2	2	2
		197.3	23.2	-14.0	4.7	-7.8	-22.0	8.8

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day(s): Predose Relative to Start Date		Electrophoresis						
Sex: Female		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)
Group 1: Control		[a]	[a1]	[a1]	[a1]	[a1]	[a1]	[a1]
	Mean	47.48	27.32	1.754	2.06	6.32	10.68	8.26
	SD	2.36	3.50	0.186	0.22	0.52	1.86	2.17
	N	5	5	5	5	5	5	5
Group 2: 35 Units/kg		-	-	-	-	-	-	-
	Mean	46.70	26.97	1.780	1.93	6.43	10.60	8.03
	SD	0.20	5.69	0.342	0.21	1.55	1.45	3.03
	N	3	3	3	3	3	3	3
Group 3: 110 Units/kg		-1.6	-1.3	1.5	-6.1	1.8	-0.7	-2.7
	%Diff							
	Mean	46.70	24.63	1.900	1.87	6.00	9.10	7.77
	SD	0.80	1.33	0.079	0.15	0.40	0.36	1.93
Group 4: 350/225/ 200 Units/kg		3	3	3	3	3	3	3
	%Diff							
	Mean	49.06	29.14	1.698	2.32	7.10	10.64	9.12
	SD	1.63	2.82	0.175	0.49	0.91	1.15	1.68
	N	5	5	5	5	5	5	5
	%Diff	3.3	6.7	-3.2	12.6	12.3	-0.4	10.4

[a] - Anova & Dunnett(Log)

[a1] - Anova & Dunnett

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day: 12 Relative to Start Date		Electrophoresis						
Sex: Female		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)
Group 1: Control		[a]	[a1]	[a]	[a]	[a1]	[a]	[a]
	Mean	49.98	31.42	1.598	2.82	8.06	11.54	9.06
	SD	2.48	2.14	0.177	0.36	0.34	1.47	1.56
	N	5	5	5	5	5	5	5
Group 2: 35 Units/kg		-	-	-	-	-	-	-
	Mean	47.90	29.80	1.663	2.60	8.40	10.37	8.43
	SD	3.98	8.41	0.290	0.36	2.66	2.90	3.87
	N	3	3	3	3	3	3	3
Group 3: 110 Units/kg	%Diff	-4.2	-5.2	4.1	-7.8	4.2	-10.2	-6.9
	Mean	48.10	30.57	1.573	2.67	7.67	10.27	9.97
	SD	3.12	1.72	0.108	0.06	0.06	0.57	1.38
	N	3	3	3	3	3	3	3
Group 4: 350/225/ 200 Units/kg	%Diff	-3.8	-2.7	-1.5	-5.4	-4.9	-11.0	10.0
	Mean	47.32	31.70	1.498	3.32	8.20	11.38	8.82
	SD	3.14	1.42	0.138	0.36	1.41	1.12	1.07
	N	5	5	5	5	5	5	5
	%Diff	-5.3	0.9	-6.3	17.7	1.7	-1.4	-2.6

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Rank)

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TABLE 8-1			Biochemical Parameters - Summary			Monkey		
Day: 26 Relative to Start Date								
Sex: Female		Electrophoresis						
		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)
Group 1: Control	Mean	47.95n	[a]	[a]	[a]	[a]	[a]	[a]
	SD	-	25.55n	1.875n	1.80n	7.00n	8.35n	8.40n
	N	2	2	2	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	48.55n	31.45n	1.550n	2.25n	8.65n	8.85n	11.70n
	SD	-	-	-	-	-	-	-
	N	2	2	2	2	2	2	2
	%Diff	1.3	23.1	-17.3	25.0	23.6	6.0	39.3

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day(s): Predose Relative to Start Date		Biochemical Parameters							
Sex: Female		Triglycerides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potassium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)	
Group 1: Control		[a]	[a]	[a]	[a]	[a]	[a]	[a]	
	Mean	0.776	5.608	2.504	105.6	5.178	146.0	75.6	
	SD	0.198	1.099	0.078	1.8	0.352	3.5	25.7	
	N	5	5	5	5	5	5	5	
Group 2: 35 Units/kg									
	Mean	0.757	5.297	2.587	105.7	4.787	146.3	72.7	
	SD	0.049	2.075	0.040	2.3	0.297	2.9	36.5	
	N	3	3	3	3	3	3	3	
Group 3: 110 Units/kg									
	%Diff	-2.5	-5.6	3.3	0.1	-7.6	0.2	-3.9	
	Mean	0.940	8.273	2.547	105.7	5.457	145.0	66.0	
	SD	0.255	1.698	0.068	1.5	0.366	2.6	34.0	
Group 4: 350/225/200 Units/kg									
	N	3	3	3	3	3	3	3	
	%Diff	21.1	47.5	1.7	0.1	5.4	-0.7	-12.7	
	Mean	0.620	8.142*	2.520	105.4	4.704	146.6	62.8	
	SD	0.189	1.246	0.147	1.1	0.519	1.3	14.4	
	N	5	5	5	5	5	5	5	
	%Diff	-20.1	45.2	0.6	-0.2	-9.2	0.4	-16.9	

[a] - Anova & Dunnett: * = $p \leq 0.05$

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day: 12 Relative to Start Date		Biochemical Parameters						
Sex: Female		Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)
Group 1: Control	Mean	[a]	[a1]	[a1]	[a2]	[a2]	[a2]	[a2]
	SD	0.360	4.942	2.584	103.8	5.194	146.8	104.6
	N	0.114	0.409	0.078	1.3	0.499	1.9	37.2
	%Diff	5	5	5	5	5	5	5
Group 2: 35 Units/kg	Mean	-	-	-	-	-	-	-
	SD	0.433	4.467	2.570	106.7*	4.787	150.7	105.7
	N	0.031	0.410	0.118	2.3	0.414	3.5	47.4
	%Diff	3	3	3	3	3	3	3
Group 3: 110 Units/kg	Mean	20.4	-9.6	-0.5	2.8	-7.8	2.6	1.0
	SD	0.400	5.413	2.633	104.7	5.413	147.0	93.3
	N	0.176	1.298	0.049	0.6	0.490	2.0	13.0
	%Diff	3	3	3	3	3	3	3
Group 4: 350/225/ 200 Units/kg	Mean	11.1	9.5	1.9	0.8	4.2	0.1	-10.8
	SD	0.710	6.408	2.470	103.4	5.214	146.6	119.0
	N	0.428	2.584	0.220	0.5	0.513	1.1	77.9
	%Diff	5	5	5	5	5	5	5
	Mean	97.2	29.7	-4.4	-0.4	0.4	-0.1	13.8
	%Diff							

[a] - Anova & Dunnett(Log)
[a1] - Anova & Dunnett(Rank)
[a2] - Anova & Dunnett: * = p ≤ 0.05

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day: 26 Relative to Start Date		Biochemical Parameters						
Sex: Female		Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)
Group 1: Control	Mean	0.375n	4.140n	2.540n	105.0n	5.655n	143.5n	70.5n
	SD	-	-	-	-	-	-	-
	N	2	2	2	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	0.620n	6.495n	2.695n	102.0n	5.565n	143.0n	82.0n
	SD	-	-	-	-	-	-	-
	N	2	2	2	2	2	2	2
%Diff		65.3	56.9	6.1	-2.9	-1.6	-0.3	16.3

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 8-1

Biochemical Parameters - Summary

Monkey

Day(s): Predose Relative to Start Date		Biochemical Parameters			
Sex: Female		aP (U/L)	ASAT (U/L)	LDH (U/L)	Gamma-GT (U/L)
		[a]	[a]	[a1]	[a]
Group 1: Control	Mean	686.8	46.8	418.6	73.16
	SD	186.3	4.5	70.5	23.06
	N	5	5	5	5
		-	-	-	-
Group 2: 35 Units/kg	Mean	694.0	50.7	522.7	95.83
	SD	245.0	14.6	85.3	8.91
	N	3	3	3	3
	%Diff	1.0	8.3	24.9	31.0
Group 3: 110 Units/kg	Mean	665.0	58.3	460.7	83.13
	SD	64.6	12.1	26.6	9.17
	N	3	3	3	3
	%Diff	-3.2	24.6	10.0	13.6
Group 4: 350/225/ 200 Units/kg	Mean	733.4	61.2	563.4	70.92
	SD	151.6	16.8	224.8	11.56
	N	5	5	5	5
	%Diff	6.8	30.8	34.6	-3.1

[a] - Anova & Dunnett

[a1] - Anova & Dunnett(Log)

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Day: 12 Relative to Start Date		Biochemical Parameters			
Sex: Female		aP (U/L)	ASAT (U/L)	LDH (U/L)	Gamma-GT (U/L)
		[a]	[a1]	[a]	[a]
Group 1: Control	Mean	601.2	122.2	772.0	72.50
	SD	182.9	60.3	91.9	20.37
	N	5	5	5	5
		-	-	-	-
Group 2: 35 Units/kg	Mean	571.7	85.0	758.0	90.93
	SD	268.7	7.9	334.2	7.98
	N	3	3	3	3
	%Diff	-4.9	-30.4	-1.8	25.4
Group 3: 110 Units/kg	Mean	580.0	84.0	622.3	81.53
	SD	82.1	11.8	101.5	7.15
	N	3	3	3	3
	%Diff	-3.5	-31.3	-19.4	12.5
Group 4: 350/225/ 200 Units/kg	Mean	650.6	127.0	759.6	66.78
	SD	172.1	48.2	133.1	10.56
	N	5	5	5	5
	%Diff	8.2	3.9	-1.6	-7.9

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Log)

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TABLE 8-1

Biochemical Parameters - Summary

Monkey

Day: 26 Relative to Start Date		Biochemical Parameters			
Sex: Female		aP (U/L)	ASAT (U/L)	LDH (U/L)	Gamma-GT (U/L)
		[a]	[a]	[a]	[a]
Group 1: Control	Mean	692.0n	44.0n	424.0n	69.55n
	SD	-	-	-	-
	N	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	557.5n	45.5n	371.0n	78.55n
	SD	-	-	-	-
	N	2	2	2	2
	%Diff	-19.4	3.4	-12.5	12.9

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 8-1		Biochemical Parameters - Summary		Monkey	
<u>Comments and Markers</u>					
<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	
	Predose	2	Female	Bile Acids	<u>Marker</u> * Anova & Dunnett: * = p ≤ 0.05
	Predose	4	Female	Urea (in blood)	<u>Comment</u> * Anova & Dunnett: * = p ≤ 0.05

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TABLE 8-1

Biochemical Parameters - Summary

Monkey

Comments and Markers

Page	Day	Group	Sex	Measurement	Marker	Comment
12	12	4	Male	Chloride	*	Anova & Dunnett: * = $p \leq 0.05$
12	12	4	Female	Phosphate	**	Anova & Dunnett: ** = $p \leq 0.01$
12	12	2	Female	Chloride	*	Anova & Dunnett: * = $p \leq 0.05$
26	26	1	Male	Bile Acids	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Bilirubin (total)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Cholest-rol (total)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Crea- tine	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Glucose	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Phosphate	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Protein (total)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Bile Acids	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Bilirubin (total)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Cholest-rol (total)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Crea- tine	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Glucose	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Phosphate	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Protein (total)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Triglyc- erides	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Urea	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Calcium	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Chloride	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Potas- sium	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Sodium	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	ALAT	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Triglyc- erides	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Urea	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Calcium	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Chloride	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Potas- sium	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Sodium	n	Anova & Dunnett: n - Inappropriate for statistics

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Comments and Markers

Page	Day	Group	Sex	Measurement	Marker	Comment
	26	4	Male	ALAT	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Alkaline Phosph'tase	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	ASAT	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Lactate Dehy drogenase	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Gamma-GT	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Alkaline Phosph'tase	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	ASAT	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Lactate Dehy drogenase	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Gamma-GT	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	Bile Acids	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	Bilirubin (total)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	Cholest-rol (total)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	Crea- tinine	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	Glucose	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	Phosphate	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	Protein (total)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Bile Acids	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Bilirubin (total)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Cholest-rol (total)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Crea- tinine	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Glucose	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Phosphate	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Protein (total)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	Triglyc- erides	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	Urea	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	Calcium	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	Chloride	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	Potas- sium	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	Sodium	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	ALAT	n	Anova & Dunnett: n - Inappropriate for statistics

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Comments and Markers

<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker</u>	<u>Comment</u>
	26	4	Female	Triglyc- erides	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Urea	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Calcium	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Chloride	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Potas- sium	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Sodium	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	ALAT	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	Alkaline Phosp'tase	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	ASAT	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	Lactate Dehy drogenase	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Female	Gamma-GT	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Alkaline Phosp'tase	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	ASAT	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Lactate Dehy drogenase	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Gamma-GT	n	Anova & Dunnett: n - Inappropriate for statistics

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TABLE 8-1 Biochemical Parameters - Summary Monkey

Comments and Markers

Page	Day	Group	Sex	Measurement	Marker	Comment
26	26	1	Male	Albumin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Alb./Glob. Ratio	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Alpha1- Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Alpha2- Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Beta- Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Gamma- Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Albumin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Alb./Glob. Ratio	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Alpha1- Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Alpha2- Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Beta- Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Gamma- Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Albumin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Alb./Glob. Ratio	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Alpha1- Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Alpha2- Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Beta- Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Gamma- Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Albumin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Alb./Glob. Ratio	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Alpha1- Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Alpha2- Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Beta- Globulin	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Gamma- Globulin	n	Anova & Dunnett: n - Inappropriate for statistics

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Sex: Male		Day(s): Predose Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 1: Control	Biochemical Parameters							
	Bile Acids (µmol/L)	Bilirubin (total) (µmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (µmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)	
	1	3.8	5.7	3.33	78	2.45	2.66	83
	2	7.5	4.9	2.49	79	3.48	2.18	77
	3	6.5	5.9	3.68	85	3.59	2.98	77
	4	5.6	5.2	5.29	90	3.61	1.99	77
	5	5.0	4.4	4.64	86	2.86	1.91	76
Mean	5.68	5.22	3.886	83.6	3.198	2.344	78.0	
SD	1.41	0.61	1.100	5.0	0.519	0.460	2.8	
N	5	5	5	5	5	5	5	

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Sex: Male		Day(s): Predose Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 2: 35 Units/kg	Biochemical Parameters							
	Bile Acids (µmol/L)	Bilirubin (total) (µmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (µmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)	
	11	4.8	7.8	4.13	83	3.07	2.37	82
	12	3.8	5.7	4.02	68	3.34	2.63	79
	13	4.7	4.8	5.02	84	2.52	2.84	83
Mean	4.43	6.10	4.390	78.3	2.977	2.613	81.3	
SD	0.55	1.54	0.548	9.0	0.418	0.235	2.1	
N	3	3	3	3	3	3	3	

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Sex: Male		Day(s): Predose Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 3: 110 Units/kg	Biochemical Parameters							
	Bile Acids (µmol/L)	Bilirubin (total) (µmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (µmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)	
	17	9.9	6.5	2.91	70	2.53	2.27	75
	18	6.6	6.9	2.52	82	4.40	2.37	78
	19	3.3	5.5	3.85	82	2.72	2.31	83
Mean	6.60	6.30	3.093	78.0	3.217	2.317	78.7	
SD	3.30	0.72	0.684	6.9	1.029	0.050	4.0	
N	3	3	3	3	3	3	3	

Allogenic APOSEC™

Sex: Male		Day(s): Predose Relative to Start Date			TABLE 8-2 Biochemical Parameters - Individual Data			Monkey
Group 4: 350/225/ 200 Units/kg		Biochemical Parameters						
		Bile Acids ($\mu\text{mol/L}$)	Bilirubin (total) ($\mu\text{mol/L}$)	Choleste- rol (total) (mmol/L)	Crea- tinine ($\mu\text{mol/L}$)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)
23		6.2	4.9	4.39	76	3.06	2.54	82
24		5.3	4.6	4.62	72	3.03	2.28	83
25		7.6	6.5	3.29	81	3.40	2.99	81
26		4.1	4.1	4.32	70	2.48	2.83	74
27		4.9	5.0	3.96	72	2.80	2.13	82
33		19.8	3.2	4.08	74	3.42	1.56	78
34		38.7	3.4	3.29	67	5.07	1.99	71
Mean		12.37	4.53	3.993	73.1	3.323	2.331	78.7
SD		12.80	1.12	0.525	4.5	0.837	0.497	4.6
N		7	7	7	7	7	7	7

Allogenic APOSEC™

Sex: Male		Day: 12 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 1: Control	Biochemical Parameters							
	Bile Acids (μmol/L)	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)	
	1	5.4	5.1	2.51	70	3.56	2.73	79
	2	6.4	3.9	2.21	65	4.02	1.71	81
	3	5.3	4.0	3.32	73	4.08	2.21	78
	4	6.0	3.8	4.09	78	4.23	1.88	73
	5	6.1	3.4	3.78	75	4.46	1.58	75
Mean	5.84	4.04	3.182	72.2	4.070	2.022	77.2	
SD	0.47	0.63	0.806	5.0	0.332	0.461	3.2	
N	5	5	5	5	5	5	5	

Allogenic APOSEC™

Sex: Male		Day: 12 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 2: 35 Units/kg	Biochemical Parameters							
	Bile Acids ($\mu\text{mol/L}$)	Bilirubin (total) ($\mu\text{mol/L}$)	Choleste- rol (total) (mmol/L)	Crea- tinine ($\mu\text{mol/L}$)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)	
	11	5.0	5.5	3.57	70	4.88	1.86	77
	12	6.2	4.2	3.40	66	4.10	2.43	78
	13	4.4	3.9	3.97	68	4.08	2.08	83
Mean	5.20	4.53	3.647	68.0	4.353	2.123	79.3	
SD	0.92	0.85	0.293	2.0	0.456	0.287	3.2	
N	3	3	3	3	3	3	3	

Allogenic APOSEC™

Sex: Male		Day: 12 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 3: 110 Units/kg	Biochemical Parameters							
	Bile Acids (μmol/L)	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)	
	17	4.6	5.4	2.42	69	4.37	2.00	78
	18	5.2	3.3	2.21	57	4.27	1.91	76
	19	3.5	3.5	2.65	71	3.67	2.28	77
Mean	4.43	4.07	2.427	65.7	4.103	2.063	77.0	
SD	0.86	1.16	0.220	7.6	0.379	0.193	1.0	
N	3	3	3	3	3	3	3	

Allogenic APOSEC™

Sex: Male			Day: 12 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data					Monkey
Group 4: 350/225/ 200 Units/kg			Biochemical Parameters							
			Bile Acids (μmol/L)	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)	
23			6.4	4.0	3.51	70	4.22	2.42	88	
24			4.6	3.4	3.17	71	5.07	2.06	80	
25			6.4	5.9	2.44	73	4.47	2.21	74	
33			5.3	6.0	3.21	75	4.10	1.99	83	
34			5.2	4.3	3.66	82	4.54	1.52	86	
Mean			5.58	4.72	3.198	74.2	4.480	2.040	82.2	
SD			0.79	1.17	0.471	4.8	0.375	0.334	5.5	
N			5	5	5	5	5	5	5	

Allogenic APOSEC™

Sex: Male		Day: 26 Relative to Start Date	TABLE 8-2 Biochemical Parameters - Individual Data					Monkey
Group 1: Control	Biochemical Parameters							
	Bile Acids (μmol/L)	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)	
4	6.4	3.5	4.82	90	5.06	1.39	79	
5	6.9	4.1	4.84	90	4.66	1.70	75	
Mean	6.65	3.80	4.830	90.0	4.860	1.545	77.0	
SD	-	-	-	-	-	-	-	
N	2	2	2	2	2	2	2	

Allogenic APOSEC™

Sex: Male			Day: 26 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data					Monkey
Group 4: 350/225/ 200 Units/kg			Biochemical Parameters							
			Bile Acids (µmol/L)	Bilirubin (total) (µmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (µmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)	
33	4.8		4.6		3.04	89	5.00	1.90	80	
34	6.2		3.8		4.12	89	4.87	1.68	80	
Mean	5.50		4.20		3.580	89.0	4.935	1.790	80.0	
SD	-		-		-	-	-	-	-	
N	2		2		2	2	2	2	2	

Allogenic APOSEC™

Sex: Male		Day(s): Predose Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data			Monkey	
Group 1: Control		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Electrophoresis			
					Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	
	1	52.6	30.4	1.73	2.6	6.4	11.0	10.4
	2	51.5	25.5	2.02	2.4	5.3	8.5	9.3
	3	48.4	28.6	1.70	2.7	7.7	12.1	6.1
	4	51.5	25.5	2.02	2.2	7.0	9.5	6.9
	5	50.2	25.8	1.94	1.9	8.6	8.3	7.1
Mean		50.84	27.16	1.882	2.36	7.00	9.88	7.96
SD		1.61	2.23	0.156	0.32	1.25	1.64	1.81
N		5	5	5	5	5	5	5

Allogenic APOSEC™

Sex: Male		Day(s): Predose Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data			Monkey	
Group 2: 35 Units/kg		Electrophoresis						
		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)
11		56.1	25.9	2.16	1.8	7.3	8.4	8.5
12		51.4	27.7	1.86	2.1	6.9	10.0	8.7
13		51.5	31.5	1.64	1.7	6.8	10.4	12.6
Mean		53.00	28.37	1.887	1.87	7.00	9.60	9.93
SD		2.69	2.86	0.261	0.21	0.26	1.06	2.31
N		3	3	3	3	3	3	3

Allogenic APOSEC™

Sex: Male		Day(s): Predose Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 3: 110 Units/kg		Electrophoresis						
		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)
17		49.2	25.8	1.91	1.9	5.9	9.1	8.9
18		52.3	25.7	2.03	2.5	5.4	8.7	9.2
19		52.6	30.4	1.73	2.0	7.2	11.0	10.2
Mean		51.37	27.30	1.890	2.13	6.17	9.60	9.43
SD		1.88	2.69	0.151	0.32	0.93	1.23	0.68
N		3	3	3	3	3	3	3

Allogenic APOSEC™

TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Electrophoresis						
		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)
Group 4: 350/225/ 200 Units/kg	23	51.8	30.2	1.72	2.2	6.9	9.3	11.8
	24	54.1	28.9	1.87	2.5	6.1	11.6	8.7
	25	53.5	27.5	1.94	2.8	6.5	10.5	7.8
	26	46.8	27.2	1.72	2.0	6.2	10.5	8.5
	27	52.8	29.2	1.81	2.5	6.1	10.7	10.0
	33	45.3	32.7	1.39	2.4	7.9	10.7	11.7
	34	42.3	28.8	1.47	2.4	11.4	5.2	9.8
	Mean	49.51	29.21	1.703	2.40	7.30	9.79	9.76
	SD	4.66	1.84	0.203	0.25	1.92	2.13	1.56
	N	7	7	7	7	7	7	7

Allogenic APOSEC™

TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Male		Day: 12 Relative to Start Date		Electrophoresis				
Group 1: Control	Albumin	Globulin	Alb./Glob. Ratio	Alpha1- Globulin	Alpha2- Globulin	Beta- Globulin	Gamma- Globulin	
	(g/L)	(g/L)		(g/L)	(g/L)	(g/L)	(g/L)	
	49.6	29.4	1.69	2.5	6.1	11.2	9.6	
	53.2	27.8	1.92	2.5	5.8	9.7	9.7	
	48.6	29.4	1.65	2.9	7.6	12.9	6.0	
	46.3	26.7	1.73	2.7	7.2	10.8	6.1	
	47.3	27.7	1.71	2.1	9.4	8.9	7.4	
Mean	49.00	28.20	1.740	2.54	7.22	10.70	7.76	
SD	2.66	1.18	0.105	0.30	1.43	1.53	1.81	
N	5	5	5	5	5	5	5	

Allogenic APOSEC™

Sex: Male			Day: 12 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 2: 35 Units/kg		Electrophoresis							
		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)	
11	46.5	30.5	1.53	2.9	7.7	11.1	8.8		
12	47.5	30.5	1.56	2.5	7.5	11.0	9.5		
13	49.0	34.0	1.44	2.1	7.7	11.6	12.6		
Mean	47.67	31.67	1.510	2.50	7.63	11.23	10.30		
SD	1.26	2.02	0.062	0.40	0.12	0.32	2.02		
N	3	3	3	3	3	3	3		

Allogenic APOSEC™

Sex: Male		Day: 12 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 3: 110 Units/kg		Electrophoresis						
		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)
17		49.8	28.2	1.76	2.2	7.4	9.7	9.0
18		48.4	27.6	1.75	2.8	6.1	10.0	8.7
19		47.7	29.3	1.62	2.3	7.3	10.0	9.7
Mean		48.63	28.37	1.710	2.43	6.93	9.90	9.13
SD		1.07	0.86	0.078	0.32	0.72	0.17	0.51
N		3	3	3	3	3	3	3

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Electrophoresis						
		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)
Group 4: 350/225/ 200 Units/kg	23	54.0	34.0	1.59	2.7	7.6	12.1	11.5
	24	51.1	28.9	1.77	2.7	6.6	12.2	7.4
	25	46.0	28.0	1.65	3.7	5.6	12.0	6.7
	33	49.4	33.6	1.47	3.3	10.0	9.5	10.8
	34	49.5	36.6	1.35	3.5	7.7	13.3	12.0
Mean SD N	Mean	50.00	32.22	1.566	3.18	7.50	11.82	9.68
	SD	2.91	3.64	0.162	0.46	1.64	1.40	2.45
	N	5	5	5	5	5	5	5

Allogenic APOSEC™

Sex: Male		Day: 26 Relative to Start Date	TABLE 8-2				Biochemical Parameters - Individual Data				Monkey			
Group 1: Control		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Electrophoresis				Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)		
4		51.3	27.7	1.85				1.7	9.3	8.3		8.5		
5		48.8	26.3	1.86				2.3	8.0	9.9		6.1		
Mean		50.05	27.00	1.855				2.00	8.65	9.10		7.30		
SD		-	-	-				-	-	-		-		
N		2	2	2				2	2	2		2		

Allogenic APOSEC™

Sex: Male		Day: 26 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey	
Group 4: 350/225/ 200 Units/kg		Electrophoresis							
		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)	
33		49.5	30.5	1.62	2.2	9.4	7.5	11.4	
34		45.8	34.2	1.34	2.5	7.0	12.4	12.2	
Mean		47.65	32.35	1.480	2.35	8.20	9.95	11.80	
SD		-	-	-	-	-	-	-	-
N		2	2	2	2	2	2	2	2

Allogenic APOSEC™

Sex: Male		Day(s): Predose Relative to Start Date		TABLE 8-2			Biochemical Parameters - Individual Data			Monkey	
Group 1: Control		Biochemical Parameters									
		Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)			
	1	0.78	9.25	2.67	104	5.21	146	64			
	2	0.72	9.66	2.44	106	4.64	147	56			
	3	0.96	10.20	2.78	107	5.59	150	56			
	4	0.54	7.90	2.79	107	5.04	149	60			
	5	0.58	9.50	2.50	107	4.41	148	75			
Mean		0.716	9.302	2.636	106.2	4.978	148.0	62.2			
SD		0.168	0.858	0.160	1.3	0.466	1.6	7.9			
N		5	5	5	5	5	5	5			

Allogenic APOSEC™

Sex: Male		Day(s): Predose Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data			Monkey	
Group 2: 35 Units/kg	Biochemical Parameters							
	Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)	
	11	0.91	10.71	2.57	108	5.33	149	67
	12	0.82	7.88	2.63	105	5.41	146	41
	13	0.94	8.42	2.48	105	4.79	146	69
Mean	0.890	9.003	2.560	106.0	5.177	147.0	59.0	
SD	0.062	1.502	0.075	1.7	0.337	1.7	15.6	
N	3	3	3	3	3	3	3	

Allogenic APOSEC™

Sex: Male		Day(s): Predose Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data			Monkey	
Group 3: 110 Units/kg	Biochemical Parameters							
	Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)	
	17	0.83	8.43	2.52	104	4.87	145	91
	18	0.77	7.22	2.60	107	4.87	148	67
	19	0.64	6.54	2.56	106	4.42	147	81
Mean	0.747	7.397	2.560	105.7	4.720	146.7	79.7	
SD	0.097	0.957	0.040	1.5	0.260	1.5	12.1	
N	3	3	3	3	3	3	3	

Allogenic APOSEC™

Sex: Male		Day(s): Predose Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data		Monkey		
Group 4: 350/225/ 200 Units/kg		Biochemical Parameters						
		Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)
23		0.47	9.66	2.63	108	5.80	147	73
24		0.75	8.97	2.64	106	4.29	147	66
25		0.69	10.47	2.70	108	5.25	150	84
26		0.69	10.45	2.55	105	4.63	146	76
27		1.08	7.59	2.63	105	4.79	145	47
33		0.45	10.19	2.68	109	5.33	148	53
34		0.63	9.99	2.58	106	5.37	145	71
Mean		0.680	9.617	2.630	106.7	5.066	146.9	67.1
SD		0.210	1.034	0.052	1.6	0.517	1.8	13.0
N		7	7	7	7	7	7	7

Allogenic APOSEC™

Sex: Male			Day: 12 Relative to Start Date		TABLE 8-2		Biochemical Parameters - Individual Data			Monkey	
Group 1: Control	Biochemical Parameters										ALAT (U/L)
	Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)					
1	0.48	5.64	2.60	103	5.71	148				84	
2	0.31	4.94	2.61	105	5.18	143				83	
3	0.51	4.63	2.62	103	5.16	148				91	
4	0.80	4.39	2.64	103	6.27	146				109	
5	0.24	4.59	2.54	104	5.51	146				117	
Mean	0.468	4.838	2.602	103.6	5.566	146.2				96.8	
SD	0.217	0.490	0.038	0.9	0.456	2.0				15.4	
N	5	5	5	5	5	5				5	

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Sex: Male		Day: 12 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data			Monkey	
Group 2: 35 Units/kg	Biochemical Parameters							
	Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)	
	11	0.44	3.94	2.51	102	5.20	146	110
	12	0.37	4.12	2.60	104	5.43	148	76
	13	0.46	3.62	2.50	103	5.42	142	87
Mean	0.423	3.893	2.537	103.0	5.350	145.3	91.0	
SD	0.047	0.253	0.055	1.0	0.130	3.1	17.3	
N	3	3	3	3	3	3	3	

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Sex: Male		Day: 12 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 3: 110 Units/kg	Biochemical Parameters							
	Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)	
	17	0.36	4.94	2.48	105	5.99	146	127
	18	0.72	3.34	2.67	105	5.24	147	152
	19	0.22	4.18	2.54	104	5.30	145	112
Mean	0.433	4.153	2.563	104.7	5.510	146.0	130.3	
SD	0.258	0.800	0.097	0.6	0.417	1.0	20.2	
N	3	3	3	3	3	3	3	

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Sex: Male		Day: 12 Relative to Start Date		TABLE 8-2		Biochemical Parameters - Individual Data		Monkey	
Group 4: 350/225/ 200 Units/kg		Biochemical Parameters							
		Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)	
23		0.66	4.31	2.70	106	6.29	149	103	
24		0.45	5.04	2.64	105	4.70	146	247	
25		0.39	6.74	2.53	104	5.34	144	118	
33		0.31	5.63	2.63	105	5.77	146	71	
34		0.53	5.71	2.60	105	5.54	146	103	
Mean		0.468	5.486	2.620	105.0	5.528	146.2	128.4	
SD		0.134	0.898	0.062	0.7	0.583	1.8	68.5	
N		5	5	5	5	5	5	5	

Allogenic APOSEC™

Sex: Male			Day: 26 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 1: Control	Biochemical Parameters								
	Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)		
4	0.30	7.00	2.40	107	4.92	148	80		
5	0.81	7.53	2.59	103	5.41	146	60		
Mean	0.555	7.265	2.495	105.0	5.165	147.0	70.0		
SD	-	-	-	-	-	-	-		
N	2	2	2	2	2	2	2		

Allogenic APOSEC™

Sex: Male		Day: 26 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data			Monkey
Group 4: 350/225/ 200 Units/kg		Biochemical Parameters					
		Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)
33	0.46	8.13	2.66	104	5.28	144	42
34	0.23	5.55	2.47	106	5.33	145	58
Mean	0.345	6.840	2.565	105.0	5.305	144.5	50.0
SD	-	-	-	-	-	-	-
N	2	2	2	2	2	2	2

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Biochemical Parameters		
		aP (U/L)	ASAT (U/L)	LDH (U/L)
Group 1: Control	1	720	52	513
	2	703	55	363
	3	749	67	396
	4	469	52	395
	5	805	65	367
Mean SD N	Mean	689.2	58.2	406.8
	SD	129.0	7.3	61.3
	N	5	5	5

Gamma-GT
(U/L)

101.7
93.8
151.9
97.6
111.5

23.64
5

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Biochemical Parameters		
		aP (U/L)	ASAT (U/L)	LDH (U/L)
Group 2: 35 Units/kg				Gamma-GT (U/L)
	11	840	75	425
	12	752	61	438
	13	807	58	571
Mean SD N		799.7	64.7	478.0
		44.5	9.1	80.8
		3	3	3
				90.57
				23.17
				3

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Biochemical Parameters		
		aP (U/L)	ASAT (U/L)	LDH (U/L)
Group 3: 110 Units/kg				Gamma-GT (U/L)
	17	830	84	1201
	18	744	67	358
	19	577	72	549
Mean		717.0	74.3	702.7
SD		128.6	8.7	442.0
N		3	3	3

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Biochemical Parameters		
		aP (U/L)	ASAT (U/L)	LDH (U/L)
Group 4: 350/225/ 200 Units/kg	23	690	57	557
	24	561	67	767
	25	683	82	417
	26	888	58	481
	27	912	53	404
	33	592	74	476
	34	1214	81	534
	Mean	791.4	67.4	519.4
	SD	230.0	11.9	122.5
	N	7	7	7
		Gamma-GT (U/L)		
		90.2		
		77.2		
		141.4		
		120.9		
		102.7		
		87.7		
		89.4		

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Biochemical Parameters			
		Biochemical Parameters			Gamma-GT
		aP (U/L)	ASAT (U/L)	LDH (U/L)	
Group 1: Control	1	490	72	755	77.5
	2	579	75	436	85.9
	3	561	144	590	127.8
	4	350	107	896	77.6
	5	665	121	482	103.9
	Mean	529.0	103.8	631.8	94.54
	SD	117.9	30.7	192.0	21.48
	N	5	5	5	5

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Biochemical Parameters		
		aP (U/L)	ASAT (U/L)	LDH (U/L)
Group 2: 35 Units/kg				Gamma-GT (U/L)
	11	652	143	720
	12	622	140	704
	13	551	85	534
Mean SD N		608.3	122.7	652.7
		51.9	32.7	103.1
		3	3	3
				72.90
				17.85
				3

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Biochemical Parameters		
		aP (U/L)	ASAT (U/L)	LDH (U/L)
Group 3: 110 Units/kg				Gamma-GT (U/L)
	17	641	143	920
	18	518	139	595
	19	413	104	696
Mean SD N		524.0	128.7	737.0
		114.1	21.5	166.3
		3	3	3
				86.57
				14.89
				3

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Biochemical Parameters			
		aP (U/L)	ASAT (U/L)	LDH (U/L)	Gamma-GT (U/L)
Group 4: 350/225/ 200 Units/kg	23	635	61	594	80.9
	24	446	267	1990	68.4
	25	491	131	662	95.0
	33	841	75	544	83.4
	34	529	98	539	93.4
Mean		588.4	126.4	865.8	84.22
SD		157.5	82.9	630.4	10.75
N		5	5	5	5

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Male		Day: 26 Relative to Start Date				
			Biochemical Parameters			
Group 1: Control	aP (U/L)	ASAT (U/L)	LDH (U/L)	Gamma-GT (U/L)		
	4	699	53	373	119.8	
	5	364	52	514	85.4	
	Mean	531.5	52.5	443.5	102.60	
	SD	-	-	-	-	
	N	2	2	2	2	

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Male	Day: 26 Relative to Start Date	Biochemical Parameters			
		aP (U/L)	ASAT (U/L)	LDH (U/L)	Gamma-GT (U/L)
Group 4: 350/225/ 200 Units/kg	33	953	63	457	86.2
	34	471	59	338	94.9
Mean	712.0	61.0	397.5	90.55	
SD	-	-	-	-	-
N	2	2	2	2	2

Allogenic APOSEC™

Sex: Female		Day(s): Predose Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data			Monkey	
Group 1: Control		Biochemical Parameters						
		Bile Acids (μmol/L)	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)
6		4.3	6.6	2.76	79	3.02	2.05	74
7		7.7	5.8	3.81	54	2.38	2.24	79
8		4.3	5.9	2.71	64	3.22	2.28	81
9		4.9	4.5	3.94	73	3.07	2.45	71
10		7.5	4.0	4.34	62	3.56	2.05	69
Mean		5.74	5.36	3.512	66.4	3.050	2.214	74.8
SD		1.72	1.07	0.736	9.8	0.430	0.169	5.1
N		5	5	5	5	5	5	5

Allogenic APOSEC™

Sex: Female		Day(s): Predose Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 2: 35 Units/kg	Biochemical Parameters							
	Bile Acids (μmol/L)	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)	
	14	10.3	4.7	3.55	60	3.30	2.00	71
	15	6.8	6.8	4.00	55	3.36	2.39	70
	16	12.2	6.1	3.75	79	2.30	2.25	80
Mean	9.77	5.87	3.767	64.7	2.987	2.213	73.7	
SD	2.74	1.07	0.225	12.7	0.595	0.198	5.5	
N	3	3	3	3	3	3	3	

Allogenic APOSEC™

Sex: Female		Day(s): Predose Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 3: 110 Units/kg	Biochemical Parameters							
	Bile Acids (µmol/L)	Bilirubin (total) (µmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (µmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)	
	20	4.8	7.0	4.07	68	2.78	2.42	73
	21	4.7	5.7	4.17	68	3.01	2.06	69
	22	4.3	5.1	3.56	78	2.92	2.23	72
Mean	4.60	5.93	3.933	71.3	2.903	2.237	71.3	
SD	0.26	0.97	0.327	5.8	0.116	0.180	2.1	
N	3	3	3	3	3	3	3	

Allogenic APOSEC™

Sex: Female		Day(s): Predose Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 4: 350/225/ 200 Units/kg		Biochemical Parameters						
		Bile Acids (μmol/L)	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)
28		5.2	5.6	3.87	75	2.34	1.97	76
29		6.0	3.8	4.11	70	3.44	2.10	77
30		6.8	5.6	3.33	77	3.74	2.19	81
31		4.6	7.1	3.98	78	3.50	2.60	81
32		4.7	7.2	3.14	64	3.45	2.40	76
Mean		5.46	5.86	3.686	72.8	3.294	2.252	78.2
SD		0.93	1.39	0.426	5.8	0.547	0.250	2.6
N		5	5	5	5	5	5	5

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Sex: Female		Day: 12 Relative to Start Date		TABLE 8-2		Biochemical Parameters - Individual Data		Monkey	
Group 1: Control		Biochemical Parameters							
		Bile Acids ($\mu\text{mol/L}$)	Bilirubin (total) ($\mu\text{mol/L}$)	Choleste- rol (total) (mmol/L)	Crea- tinine ($\mu\text{mol/L}$)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)	
6		4.8	4.4	2.48	69	4.25	2.09	78	
7		9.0	4.9	3.20	59	3.37	2.44	83	
8		5.3	6.0	2.32	67	4.40	2.24	83	
9		6.5	3.6	3.89	72	5.18	2.27	82	
10		6.2	4.0	4.30	62	4.15	2.31	81	
Mean		6.36	4.58	3.238	65.8	4.270	2.270	81.4	
SD		1.63	0.93	0.862	5.3	0.646	0.126	2.1	
N		5	5	5	5	5	5	5	

Allogenic APOSEC™

Sex: Female		Day: 12 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 2: 35 Units/kg	Biochemical Parameters							
	Bile Acids (µmol/L)	Bilirubin (total) (µmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (µmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)	
	14	7.3	4.5	2.82	64	3.94	2.20	71
	15	6.6	4.9	3.42	56	4.46	2.13	70
	16	6.9	4.4	3.53	72	4.46	1.98	92
Mean	6.93	4.60	3.257	64.0	4.287	2.103	77.7	
SD	0.35	0.26	0.382	8.0	0.300	0.112	12.4	
N	3	3	3	3	3	3	3	

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Sex: Female			Day: 12 Relative to Start Date		TABLE 8-2					Biochemical Parameters - Individual Data			Monkey	
Group 3: 110 Units/kg			Biochemical Parameters										Protein (total) (g/L)	
			Bile Acids (μmol/L)	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)						
20			4.5	4.4	3.78	59	2.99	2.17	83					
21			6.1	5.9	3.22	69	3.80	2.03	75					
22			6.4	3.6	3.07	74	4.88	2.20	78					
Mean			5.67	4.63	3.357	67.3	3.890	2.133	78.7					
SD			1.02	1.17	0.374	7.6	0.948	0.091	4.0					
N			3	3	3	3	3	3	3					

Allogenic APOSEC™

Sex: Female		Day: 12 Relative to Start Date	TABLE 8-2 Biochemical Parameters - Individual Data					Monkey
Group 4: 350/225/ 200 Units/kg		Biochemical Parameters						
		Bile Acids ($\mu\text{mol/L}$)	Bilirubin (total) ($\mu\text{mol/L}$)	Choleste- rol (total) (mmol/L)	Crea- tinine ($\mu\text{mol/L}$)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)
28	6.0	3.8	2.82	69	4.07	1.88	75	
29	6.4	4.7	2.75	68	4.80	1.41	82	
30	6.8	17.2	2.85	102	2.26	2.19	77	
31	7.0	3.8	2.79	70	3.70	1.44	80	
32	6.8	4.2	3.05	79	5.54	1.95	81	
Mean	6.60	6.74	2.852	77.6	4.074	1.774	79.0	
SD	0.40	5.86	0.117	14.3	1.236	0.339	2.9	
N	5	5	5	5	5	5	5	

Allogenic APOSEC™

Sex: Female		Day: 26 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data					Monkey
Group 1: Control		Biochemical Parameters							
		Bile Acids (μmol/L)	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)	
9	5.4	3.3	3.60	79	5.81	2.34	73		
10	5.6	3.6	4.61	70	5.07	2.16	74		
Mean	5.50	3.45	4.105	74.5	5.440	2.250	73.5		
SD	-	-	-	-	-	-	-		
N	2	2	2	2	2	2	2		

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Sex: Female			Day: 26 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey	
Group 4: 350/225/ 200 Units/kg			Biochemical Parameters							
			Bile Acids (μmol/L)	Bilirubin (total) (μmol/L)	Choleste- rol (total) (mmol/L)	Crea- tinine (μmol/L)	Glucose (mmol/L)	Phosphate (mmol/L)	Protein (total) (g/L)	
31	14.5	4.2	3.62	73	4.58	1.76	82			
32	18.2	4.3	3.44	83	5.45	1.75	78			
Mean	16.35	4.25	3.530	78.0	5.015	1.755	80.0			
SD	-	-	-	-	-	-	-			
N	2	2	2	2	2	2	2			

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Sex: Female		Day(s): Predose Relative to Start Date	TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 1: Control		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Electrophoresis		
					Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)
	6	45.8	28.2	1.62	2.1	6.5	11.3
	7	51.1	27.9	1.83	2.3	7.1	11.2
	8	48.6	32.4	1.50	2.1	6.2	12.4
	9	46.4	24.6	1.89	2.1	5.7	11.0
	10	45.5	23.5	1.93	1.7	6.1	7.5
	Mean	47.48	27.32	1.754	2.06	6.32	10.68
	SD	2.36	3.50	0.186	0.22	0.52	1.86
	N	5	5	5	5	5	5
							8.26
							2.17
							5

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TABLE 8-2

Biochemical Parameters - Individual Data

Monkey

Sex: Female	Day(s): Predose Relative to Start Date	Electrophoresis						
		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)
Group 2: 35 Units/kg	14	46.7	24.3	1.92	2.1	5.8	10.5	5.9
	15	46.9	23.1	2.03	2.0	5.3	9.2	6.7
	16	46.5	33.5	1.39	1.7	8.2	12.1	11.5
	Mean	46.70	26.97	1.780	1.93	6.43	10.60	8.03
	SD	0.20	5.69	0.342	0.21	1.55	1.45	3.03
	N	3	3	3	3	3	3	3

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TABLE 8-2

Biochemical Parameters - Individual Data

Monkey

Sex: Female	Day(s): Predose Relative to Start Date	Electrophoresis						
		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)
Group 3: 110 Units/kg								
	20	47.5	25.5	1.87	1.9	5.6	8.8	9.3
	21	45.9	23.1	1.99	1.7	6.4	9.5	5.6
	22	46.7	25.3	1.84	2.0	6.0	9.0	8.4
Mean SD N		46.70	24.63	1.900	1.87	6.00	9.10	7.77
		0.80	1.33	0.079	0.15	0.40	0.36	1.93
		3	3	3	3	3	3	3

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Sex: Female		Day(s): Predose Relative to Start Date				TABLE 8-2 Biochemical Parameters - Individual Data				Monkey			
Group 4: 350/225/ 200 Units/kg		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Electrophoresis				Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)	
28		48.9	27.1	1.81				2.3		6.8	11.6	6.4	
29		49.5	27.5	1.80				1.9		6.7	10.2	8.6	
30		47.1	33.9	1.39				3.1		8.7	12.1	10.1	
31		51.5	29.5	1.75				2.4		6.9	9.9	10.4	
32		48.3	27.7	1.74				1.9		6.4	9.4	10.1	
Mean		49.06	29.14	1.698				2.32		7.10	10.64	9.12	
SD		1.63	2.82	0.175				0.49		0.91	1.15	1.68	
N		5	5	5				5		5	5	5	

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Sex: Female		Day: 12 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data					Monkey
Group 1: Control		Electrophoresis							
		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)	
6		46.3	31.7	1.46	3.0	8.3	11.8	8.7	
7		50.9	32.1	1.58	3.2	8.5	12.1	8.4	
8		49.0	34.0	1.44	2.6	7.8	12.0	11.6	
9		50.8	31.2	1.63	3.0	8.0	12.8	7.4	
10		52.9	28.1	1.88	2.3	7.7	9.0	9.2	
Mean		49.98	31.42	1.598	2.82	8.06	11.54	9.06	
SD		2.48	2.14	0.177	0.36	0.34	1.47	1.56	
N		5	5	5	5	5	5	5	

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Sex: Female		Day: 12 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 2: 35 Units/kg		Electrophoresis						
		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)
14	45.7	25.4	1.80	2.9	5.9	10.5	6.0	
15	45.5	24.5	1.86	2.7	8.1	7.4	6.4	
16	52.5	39.5	1.33	2.2	11.2	13.2	12.9	
Mean	47.90	29.80	1.663	2.60	8.40	10.37	8.43	
SD	3.98	8.41	0.290	0.36	2.66	2.90	3.87	
N	3	3	3	3	3	3	3	

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TABLE 8-2

Biochemical Parameters - Individual Data

Monkey

Sex: Female Day: 12 Relative to Start Date

Group 3: 110 Units/kg	Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Electrophoresis			
				Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)
20	51.7	31.3	1.65	2.7	7.6	10.1	11.0
21	46.4	28.6	1.62	2.6	7.7	9.8	8.4
22	46.2	31.8	1.45	2.7	7.7	10.9	10.5
Mean	48.10	30.57	1.573	2.67	7.67	10.27	9.97
SD	3.12	1.72	0.108	0.06	0.06	0.57	1.38
N	3	3	3	3	3	3	3

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TABLE 8-2

Biochemical Parameters - Individual Data

Monkey

Sex: Female Day: 12 Relative to Start Date

Group 4: 350/225/ 200 Units/kg	Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Electrophoresis			
				Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)
28	44.3	30.8	1.44	3.1	8.0	12.8	7.0
29	50.3	31.7	1.58	3.5	7.0	12.1	9.1
30	44.7	32.3	1.39	3.5	8.0	11.4	9.3
31	46.3	33.7	1.38	3.7	10.6	10.6	8.9
32	51.0	30.0	1.70	2.8	7.4	10.0	9.8
Mean	47.32	31.70	1.498	3.32	8.20	11.38	8.82
SD	3.14	1.42	0.138	0.36	1.41	1.12	1.07
N	5	5	5	5	5	5	5

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Sex: Female		Day: 26 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 1: Control	Electrophoresis							
	Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)	
9	47.6	25.4	1.87	1.9	6.9	9.3	7.3	
10	48.3	25.7	1.88	1.7	7.1	7.4	9.5	
Mean	47.95	25.55	1.875	1.80	7.00	8.35	8.40	
SD	-	-	-	-	-	-	-	
N	2	2	2	2	2	2	2	

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Sex: Female		Day: 26 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data					Monkey	
Group 4: 350/225/ 200 Units/kg		Electrophoresis								
		Albumin (g/L)	Globulin (g/L)	Alb./Glob. Ratio	Alpha1- Globulin (g/L)	Alpha2- Globulin (g/L)	Beta- Globulin (g/L)	Gamma- Globulin (g/L)		
31	48.5	33.5	1.45	2.5	9.7	9.0	12.3			
32	48.6	29.4	1.65	2.0	7.6	8.7	11.1			
Mean	48.55	31.45	1.550	2.25	8.65	8.85	11.70			
SD	-	-	-	-	-	-	-	-		
N	2	2	2	2	2	2	2	2		

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Sex: Female		Day(s): Predose Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 1: Control		Biochemical Parameters						
		Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)
6		0.60	7.56	2.40	104	5.11	143	65
7		0.98	5.07	2.56	104	5.79	143	95
8		0.94	5.29	2.56	108	5.05	151	63
9		0.82	5.19	2.44	105	4.89	145	109
10		0.54	4.93	2.56	107	5.05	148	46
Mean		0.776	5.608	2.504	105.6	5.178	146.0	75.6
SD		0.198	1.099	0.078	1.8	0.352	3.5	25.7
N		5	5	5	5	5	5	5

Allogenic APOSEC™

Sex: Female		Day(s): Predose Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data			Monkey
Group 2: 35 Units/kg	Biochemical Parameters						
	Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)
	14	0.79	4.00	2.55	107	5.10	148
	15	0.78	4.20	2.63	103	4.75	143
	16	0.70	7.69	2.58	107	4.51	148
Mean	0.757	5.297	2.587	105.7	4.787	146.3	72.7
SD	0.049	2.075	0.040	2.3	0.297	2.9	36.5
N	3	3	3	3	3	3	3

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Sex: Female		Day(s): Predose Relative to Start Date	TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 3: 110 Units/kg	Triglyc- erides (mmol/L)		Biochemical Parameters				
	Urea (in blood) (mmol/L)		Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)
	20	0.93					
	21	0.69	2.60	104	5.42	142	43
	22	1.20	2.47	107	5.11	147	105
			2.57	106	5.84	146	50
Mean	0.940	8.273	2.547	105.7	5.457	145.0	66.0
SD	0.255	1.698	0.068	1.5	0.366	2.6	34.0
N	3	3	3	3	3	3	3

Allogenic APOSEC™

Sex: Female		Day(s): Predose Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 4: 350/225/ 200 Units/kg		Biochemical Parameters						
		Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)
28		0.57	9.16	2.57	105	4.81	145	68
29		0.40	6.58	2.28	104	4.41	146	42
30		0.87	7.91	2.68	107	4.07	148	61
31		0.51	7.44	2.52	106	4.77	148	82
32		0.75	9.62	2.55	105	5.46	146	61
Mean		0.620	8.142	2.520	105.4	4.704	146.6	62.8
SD		0.189	1.246	0.147	1.1	0.519	1.3	14.4
N		5	5	5	5	5	5	5

Allogenic APOSEC™

Sex: Female		Day: 12 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data					Monkey
Group 1: Control		Biochemical Parameters							
		Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)	
6		0.31	4.60	2.48	102	4.42	145	147	
7		0.52	4.68	2.70	104	5.80	147	131	
8		0.21	5.63	2.59	105	5.36	150	79	
9		0.40	4.96	2.58	103	5.21	146	110	
10		0.36	4.84	2.57	105	5.18	146	56	
Mean		0.360	4.942	2.584	103.8	5.194	146.8	104.6	
SD		0.114	0.409	0.078	1.3	0.499	1.9	37.2	
N		5	5	5	5	5	5	5	

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Sex: Female		Day: 12 Relative to Start Date	TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 2: 35 Units/kg	Triglyc- erides (mmol/L)		Biochemical Parameters				
	Urea (in blood) (mmol/L)		Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)
	14	0.40	2.54	108	5.26	154	142
	15	0.44	2.47	104	4.61	147	123
	16	0.46	2.70	108	4.49	151	52
Mean	0.433	4.467	2.570	106.7	4.787	150.7	105.7
SD	0.031	0.410	0.118	2.3	0.414	3.5	47.4
N	3	3	3	3	3	3	3

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Sex: Female		Day: 12 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data			Monkey
Group 3: 110 Units/kg	Biochemical Parameters						
	Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)
	20	0.27					
	21	0.33	4.38	2.69	104	5.22	145
	22	0.60	4.99	2.60	105	5.05	149
		6.87	2.61	105	5.97	147	80
Mean	0.400	5.413	2.633	104.7	5.413	147.0	93.3
SD	0.176	1.298	0.049	0.6	0.490	2.0	13.0
N	3	3	3	3	3	3	3

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Sex: Female		Day: 12 Relative to Start Date	TABLE 8-2 Biochemical Parameters - Individual Data					Monkey
Group 4: 350/225/ 200 Units/kg		Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Biochemical Parameters				ALAT (U/L)
				Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	
28		0.52	4.86	2.60	103	5.69	145	126
29		0.24	5.12	2.49	103	5.03	146	58
30		1.40	10.98	2.09	104	4.41	148	77
31		0.69	5.19	2.53	103	5.39	147	251
32		0.70	5.89	2.64	104	5.55	147	83
Mean		0.710	6.408	2.470	103.4	5.214	146.6	119.0
SD		0.428	2.584	0.220	0.5	0.513	1.1	77.9
N		5	5	5	5	5	5	5

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Female		Day: 26 Relative to Start Date		Biochemical Parameters				Monkey			
Group 1: Control		Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)			
9	0.35	3.75	2.48	104	6.00	142	97				
10	0.40	4.53	2.60	106	5.31	145	44				
Mean	0.375	4.140	2.540	105.0	5.655	143.5	70.5				
SD	-	-	-	-	-	-	-				
N	2	2	2	2	2	2	2				

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Sex: Female		Day: 26 Relative to Start Date		TABLE 8-2 Biochemical Parameters - Individual Data				Monkey
Group 4: 350/225/ 200 Units/kg		Biochemical Parameters						
		Triglyc- erides (mmol/L)	Urea (in blood) (mmol/L)	Calcium (mmol/L)	Chloride (mmol/L)	Potas- sium (mmol/L)	Sodium (mmol/L)	ALAT (U/L)
31	0.78		4.45	2.65	101	5.60	142	120
32	0.46		8.54	2.74	103	5.53	144	44
Mean	0.620		6.495	2.695	102.0	5.565	143.0	82.0
SD	-		-	-	-	-	-	-
N	2		2	2	2	2	2	2

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Female	Day(s): Predose Relative to Start Date	Biochemical Parameters		
		aP (U/L)	ASAT (U/L)	LDH (U/L)
Group 1: Control				Gamma-GT (U/L)
	6	483	53	348
	7	877	44	412
	8	557	45	484
	9	628	50	497
	10	889	42	352
Mean SD N	Mean	686.8	46.8	418.6
	SD	186.3	4.5	70.5
	N	5	5	5

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Female	Day(s): Predose Relative to Start Date	Biochemical Parameters		
		aP (U/L)	ASAT (U/L)	LDH (U/L)
Group 2: 35 Units/kg				Gamma-GT (U/L)
	14	463	46	591
	15	668	39	550
	16	951	67	427
Mean SD N		694.0	50.7	522.7
		245.0	14.6	85.3
		3	3	3
				95.83
				8.91
				3

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Female	Day(s): Predose Relative to Start Date	Biochemical Parameters		
		aP (U/L)	ASAT (U/L)	LDH (U/L)
Group 3: 110 Units/kg				Gamma-GT (U/L)
	20	612	54	430
	21	737	72	478
	22	646	49	474
Mean SD N		665.0	58.3	460.7
		64.6	12.1	26.6
		3	3	3
				83.13
				9.17
				3

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Female	Day(s): Predose Relative to Start Date	Biochemical Parameters		
		aP (U/L)	ASAT (U/L)	LDH (U/L)
Group 4: 350/225/ 200 Units/kg	28	672	68	512
	29	548	49	390
	30	962	84	669
	31	769	64	348
	32	716	41	898
Mean SD N	Mean	733.4	61.2	563.4
	SD	151.6	16.8	224.8
	N	5	5	5
		Gamma-GT (U/L)		
		67.0		
		69.9		
		65.8		
		90.8		
		61.1		

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Female	Day: 12 Relative to Start Date	Biochemical Parameters			
		Biochemical Parameters			Gamma-GT (U/L)
		aP (U/L)	ASAT (U/L)	LDH (U/L)	
Group 1: Control	6	390	197	781	51.5
	7	750	175	890	65.2
	8	455	79	702	100.2
	9	596	99	825	86.9
	10	815	61	662	58.7
Mean SD N	Mean	601.2	122.2	772.0	72.50
	SD	182.9	60.3	91.9	20.37
	N	5	5	5	5

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Female Day: 12 Relative to Start Date

Group 2: 35 Units/kg	Biochemical Parameters			Gamma-GT (U/L)
	aP (U/L)	ASAT (U/L)	LDH (U/L)	
14	322	91	1124	87.2
15	537	88	681	100.1
16	856	76	469	85.5
Mean	571.7	85.0	758.0	90.93
SD	268.7	7.9	334.2	7.98
N	3	3	3	3

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Female	Day: 12 Relative to Start Date	Biochemical Parameters		
		aP (U/L)	ASAT (U/L)	LDH (U/L)
Group 3: 110 Units/kg				Gamma-GT (U/L)
	20	496	71	507
	21	660	87	698
	22	584	94	662
Mean SD N		580.0	84.0	622.3
		82.1	11.8	101.5
		3	3	3
				81.53
				7.15
				3

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Female	Day: 12 Relative to Start Date	Biochemical Parameters		
		aP (U/L)	ASAT (U/L)	LDH (U/L)
Group 4: 350/225/ 200 Units/kg	28	691	126	695
	29	461	58	572
	30	915	161	925
	31	640	182	817
	32	546	108	789
Mean SD N	Mean	650.6	127.0	759.6
	SD	172.1	48.2	133.1
	N	5	5	5

Biochemical Parameters			Gamma-GT (U/L)
aP (U/L)	ASAT (U/L)	LDH (U/L)	
691	126	695	58.0
461	58	572	57.1
915	161	925	77.3
640	182	817	78.9
546	108	789	62.6
Mean	127.0	759.6	66.78
SD	48.2	133.1	10.56
N	5	5	5

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Female Day: 26 Relative to Start Date

Group 1: Control	Biochemical Parameters			
	aP (U/L)	ASAT (U/L)	LDH (U/L)	Gamma-GT (U/L)
9	563	50	507	84.0
10	821	38	341	55.1
Mean	692.0	44.0	424.0	69.55
SD	-	-	-	-
N	2	2	2	2

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TABLE 8-2 Biochemical Parameters - Individual Data Monkey

Sex: Female	Day: 26 Relative to Start Date	Biochemical Parameters			
		aP (U/L)	ASAT (U/L)	LDH (U/L)	Gamma-GT (U/L)
Group 4: 350/225/ 200 Units/kg	31	602	46	339	90.9
	32	513	45	403	66.2
Mean	557.5	45.5	371.0	78.55	
SD	-	-	-	-	-
N	2	2	2	2	2

Allogenic APOSEC™

Urinalysis - Summary

Monkey

TABLE 9-1

Day(s): Predose Relative to Start Date		Urinalysis	
Sex: Male		Specific Gravity (g/mL)	pH
		[a]	[a]
Group 1: Control	Mean	1.0038	7.84
	SD	0.0008	0.34
	N	5	5
		-	-
Group 2: 35 Units/kg	Mean	1.0033	7.67
	SD	0.0012	0.45
	N	3	3
	%Diff	0.0	-2.2
Group 3: 110 Units/kg	Mean	1.0040	7.97
	SD	0.0010	0.31
	N	3	3
	%Diff	0.0	1.6
Group 4: 350/225/200 Units/kg	Mean	1.0031	7.81
	SD	0.0012	0.57
	N	7	7
	%Diff	-0.1	-0.3

[a] - Anova & Dunnett

Allogenic APOSEC™

Urinalysis - Summary

Monkey

TABLE 9-1

Day: 10 Relative to Start Date

Sex: Male		Urinalysis	
		Specific Gravity (g/mL)	pH
Group 1: Control		[a]	[a]
	Mean	1.0040	7.86
	SD	0.0010	0.45
	N	5	5
Group 2: 35 Units/kg		-	-
	Mean	1.0030	7.37
	SD	0.0010	0.25
	N	3	3
Group 3: 110 Units/kg	%Diff	-0.1	-6.3
	Mean	1.0037	7.97
	SD	0.0012	0.42
	N	3	3
Group 4: 350/225/ 200 Units/kg	%Diff	0.0	1.4
	Mean	1.0046	8.16
	SD	0.0011	0.30
	N	5	5
	%Diff	0.1	3.8

[a] - Anova & Dunnett

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Urinalysis - Summary

Monkey

TABLE 9-1

Day: 25 Relative to Start Date

Sex: Male		Urinalysis	
		Specific Gravity (g/mL)	pH
Group 1: Control	Mean	1.0035n	[a]
	SD	-	7.80n
	N	2	2
Group 4: 350/225/200 Units/kg	Mean	1.0035n	8.00n
	SD	-	-
	N	2	2
	%Diff	0.0	2.6

[a] - Anova & Dunnett: n - Inappropriate for statistics

Allogenic APOSEC™

Urinalysis - Summary

Monkey

TABLE 9-1

Day(s): Predose Relative to Start Date		Urinalysis	
Sex: Female		Specific Gravity (g/mL)	pH
		[a]	[a]
Group 1: Control	Mean	1.0034	7.04
	SD	0.0009	0.63
	N	5	5
		-	-
Group 2: 35 Units/kg	Mean	1.0023	7.67
	SD	0.0006	0.21
	N	3	3
	%Diff	-0.1	8.9
Group 3: 110 Units/kg	Mean	1.0037	7.47
	SD	0.0006	0.40
	N	3	3
	%Diff	0.0	6.1
Group 4: 350/225/ 200 Units/kg	Mean	1.0038	7.46
	SD	0.0008	0.66
	N	5	5
	%Diff	0.0	6.0

[a] - Anova & Dunnett

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Urinalysis - Summary

Monkey

TABLE 9-1

Day: 10 Relative to Start Date		Urinalysis	
Sex: Female		Specific Gravity (g/mL)	pH
		[a]	[a]
Group 1: Control	Mean	1.0030	8.12
	SD	0.0007	0.60
	N	5	5
		-	-
Group 2: 35 Units/kg	Mean	1.0043*	8.37
	SD	0.0006	0.31
	N	3	3
	%Diff	0.1	3.0
Group 3: 110 Units/kg	Mean	1.0043*	7.80
	SD	0.0006	0.20
	N	3	3
	%Diff	0.1	-3.9
Group 4: 350/225/ 200 Units/kg	Mean	1.0040	8.22
	SD	0.0007	0.44
	N	5	5
	%Diff	0.1	1.2

[a] - Anova & Dunnett: * = p ≤ 0.05

Allogenic APOSEC™

Urinalysis - Summary

Monkey

TABLE 9-1

Day: 25 Relative to Start Date

Sex: Female		Urinalysis	
		Specific Gravity (g/mL)	pH
Group 1: Control		[a]	[a]
	Mean	1.0035n	8.75n
	SD	-	-
	N	2	2
Group 4: 350/225/200 Units/kg			
	Mean	1.0030n	7.05n
	SD	-	-
	N	2	2
	%Diff	0.0	-19.4

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 9-1Urinalysis - SummaryMonkey

Comments and Markers

Page	Day	Group	Sex	Measurement	Marker	Comment
	10	2	Female	Specific Gravity	*	Anova & Dunnett: * = $p \leq 0.05$
	10	3	Female	Specific Gravity	*	Anova & Dunnett: * = $p \leq 0.05$
	25	1	Male	Specific Gravity	n	Anova & Dunnett: n - Inappropriate for statistics
	25	1	Male	pH	n	Anova & Dunnett: n - Inappropriate for statistics
	25	4	Male	Specific Gravity	n	Anova & Dunnett: n - Inappropriate for statistics
	25	4	Male	pH	n	Anova & Dunnett: n - Inappropriate for statistics
	25	1	Female	Specific Gravity	n	Anova & Dunnett: n - Inappropriate for statistics
	25	1	Female	pH	n	Anova & Dunnett: n - Inappropriate for statistics
	25	4	Female	Specific Gravity	n	Anova & Dunnett: n - Inappropriate for statistics
	25	4	Female	pH	n	Anova & Dunnett: n - Inappropriate for statistics

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TABLE 9-2 Urinalysis - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Urinalysis		
		Colour	Specific Gravity (g/mL)	pH
Group 1: Control	1	SC	1.003	7.8
	2	SC	1.004	7.9
	3	SC	1.005	8.2
	4	SC	1.004	7.3
	5	SC	1.003	8.0
	Mean	-	1.0038	7.84
	SD	-	0.0008	0.34
	N	-	5	5

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TABLE 9-2 Urinalysis - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Urinalysis		
Group 2: 35 Units/kg		Colour	Specific Gravity (g/mL)	pH
	11	SC	1.004	7.7
	12	SC	1.002	7.2
	13	SC	1.004	8.1
Mean		-	1.0033	7.67
SD		-	0.0012	0.45
N		-	3	3

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TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Male Day(s): Predose Relative to Start Date

Group 3: 110 Units/kg	Urinalysis		
	Colour	Specific Gravity (g/mL)	pH
17	SC	1.005	8.3
18	SC	1.004	7.7
19	SC	1.003	7.9
Mean	-	1.0040	7.97
SD	-	0.0010	0.31
N	-	3	3

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TABLE 9-2 Urinalysis - Individual Data Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Urinalysis		
		Colour	Specific Gravity (g/mL)	pH
Group 4: 350/225/ 200 Units/kg	23	SC	1.004	8.0
	24	SC	1.002	8.0
	25	SC	1.004	7.2
	26	SC	1.004	8.8
	27	SC	1.003	7.8
	33	SC	1.001	7.8
	34	SC	1.004	7.1
	Mean	-	1.0031	7.81
	SD	-	0.0012	0.57
	N	-	7	7

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TABLE 9-2 Urinalysis - Individual Data Monkey

Sex: Male Day: 10 Relative to Start Date

Group 1: Control	Urinalysis		
	Colour	Specific Gravity (g/mL)	pH
1	SC	1.004	7.8
2	SC	1.005	8.5
3	SC	1.005	7.4
4	SC	1.003	7.5
5	SC	1.003	8.1
Mean	-	1.0040	7.86
SD	-	0.0010	0.45
N	-	5	5

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TABLE 9-2 Urinalysis - Individual Data Monkey

Sex: Male Day: 10 Relative to Start Date

Group 2: 35 Units/kg	Urinalysis		
	Colour	Specific Gravity (g/mL)	pH
11	SC	1.003	7.4
12	SC	1.002	7.1
13	SC	1.004	7.6
Mean	-	1.0030	7.37
SD	-	0.0010	0.25
N	-	3	3

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TABLE 9-2 Urinalysis - Individual Data Monkey

Sex: Male Day: 10 Relative to Start Date

Group 3: 110 Units/kg	Urinalysis		
	Colour	Specific Gravity (g/mL)	pH
17	SC	1.005	8.3
18	SC	1.003	8.1
19	SC	1.003	7.5
Mean	-	1.0037	7.97
SD	-	0.0012	0.42
N	-	3	3

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TABLE 9-2 Urinalysis - Individual Data Monkey

Sex: Male Day: 10 Relative to Start Date

Group 4: 350/225/ 200 Units/kg	Urinalysis		
	Colour	Specific Gravity (g/mL)	pH
23	SC	1.003	7.7
24	SC	1.004	8.2
25	SC	1.005	8.1
33	SC	1.006	8.5
34	SC	1.005	8.3
Mean	-	1.0046	8.16
SD	-	0.0011	0.30
N	-	5	5

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TABLE 9-2 Urinalysis - Individual Data Monkey

Sex: Male Day: 25 Relative to Start Date

Group 1: Control	Urinalysis		
	Colour	Specific Gravity (g/mL)	pH
4	SC	1.003	7.6
5	SC	1.004	8.0
Mean	-	1.0035	7.80
SD	-	-	-
N	-	2	2

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TABLE 9-2 Urinalysis - Individual Data Monkey

Sex: Male Day: 25 Relative to Start Date

Group 4: 350/225/ 200 Units/kg	Urinalysis		
	Colour	Specific Gravity (g/mL)	pH
33	SC	1.005	7.9
34	SC	1.002	8.1
Mean	-	1.0035	8.00
SD	-	-	-
N	-	2	2

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TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Male Day(s): Predose Relative to Start Date

		Urinalysis					Further constituents
		Leucocytes	Erythrocytes	Crystalluria	Epithelial cells	Organisms	
Group 1: Control	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0

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TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Male Day(s): Predose Relative to Start Date

Group 2: 35 Units/kg	Leucocytes	Erythrocytes	Crystalluria	Urinalysis		
				Epithelial cells	Organisms	Further constituents
11	+	0	0	0	0	0
12	0	0	0	0	0	0
13	0	0	0	0	0	0

Allogenic APOSEC™

TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Male Day(s): Predose Relative to Start Date

Group 3: 110 Units/kg	Urinalysis					Organisms	Further constituents
	Leucocytes	Erythrocytes	Crystalluria	Epithelial cells			
17	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0

Allogenic APOSEC™

TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Male Day(s): Predose Relative to Start Date

Group 4: 350/225/ 200 Units/kg	Urinalysis					
	Leucocytes	Erythrocytes	Crystalluria	Epithelial cells	Organisms	Further constituents
23	0	0	0	+	0	0
24	0	0	0	0	0	0
25	0	0	0	0	0	0
26	0	0	0	0	0	0
27	0	0	0	0	0	0
33	0	0	0	0	0	0
34	0	0	0	0	0	0

Allogenic APOSEC™

TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Male Day: 10 Relative to Start Date

Group 1: Control	Urinalysis					Organisms	Further constituents
	Leucocytes	Erythrocytes	Crystalluria	Epithelial cells			
1	0	0	0	0	0		
2	0	0	0	0	0		
3	0	0	0	0	0		
4	0	++	0	0	0		
5	0	0	0	0	0		

Allogenic APOSEC™

TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Male Day: 10 Relative to Start Date

Group 2: 35 Units/kg	Urinalysis					Further constituents
	Leucocytes	Erythrocytes	Crystalluria	Epithelial cells	Organisms	
11	0	0	0	0	0	0
12	0	0	0	0	0	0
13	0	0	0	0	0	0

Allogenic APOSEC™

TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Male Day: 10 Relative to Start Date

Group 3: 110 Units/kg	Urinalysis					Further constituents
	Leucocytes	Erythrocytes	Crystalluria	Epithelial cells	Organisms	
17	0	0	0	+	0	0
18	0	0	0	0	0	0
19	0	+	0	+	0	0

Allogenic APOSEC™

TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Male Day: 10 Relative to Start Date

Group 4: 350/225/ 200 Units/kg	Urinalysis					Further constituents
	Leucocytes	Erythrocytes	Crystalluria	Epithelial cells	Organisms	
23	0	0	0	0	0	0
24	0	0	0	0	0	0
25	0	0	0	0	0	0
33	0	0	0	0	0	0
34	+	0	0	++	0	0

Allogenic APOSEC™							
TABLE 9-2		Urinalysis - Individual Data			Monkey		
Sex: Male	Day: 25 Relative to Start Date	Urinalysis					
Group 1: Control		Leucocytes	Erythrocytes	Crystalluria	Epithelial cells	Organisms	Further constituents
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0

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TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Male Day: 25 Relative to Start Date

Group 4: 350/225/ 200 Units/kg	Urinalysis					Organisms	Further constituents
	Leucocytes	Erythrocytes	Crystalluria	Epithelial cells			
33	+	0	0	+		0	0
34	0	0	0	0		0	0

Monkey

Sex: Male	Day(s): Predose Relative to Start Date
-----------	--

Group 1: Control	Urinalysis						
	Nitrite	Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (μmol/L)	Bilirubin	Haemoglobin (ery/μL)
1	neg	neg	normal	neg	normal	neg	10
2	pos	neg	normal	neg	normal	neg	neg
3	neg	neg	normal	neg	normal	neg	neg
4	neg	neg	normal	neg	normal	neg	neg
5	neg	neg	normal	neg	normal	neg	25

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TABLE 9-2

Sex: Male		Day(s): Predose Relative to Start Date		Urinalysis - Individual Data				Monkey
		Urinalysis						
Group 2: 35 Units/kg	Nitrite	Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (μmol/L)	Bilirubin	Haemoglobin (ery/μL)	
	11	neg	neg	normal	neg	neg	10	
	12	pos	neg	normal	neg	neg	neg	
	13	neg	neg	normal	neg	neg	10	

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TABLE 9-2

Monkey

Sex: Male	Day(s): Predose Relative to Start Date	Urinalysis - Individual Data					
		Urinalysis					
Group 3: 110 Units/kg		Nitrite	Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (µmol/L)	Bilirubin
							Haemoglobin (ery/µL)
	17	neg	neg	normal	neg	normal	neg
	18	neg	neg	normal	neg	normal	neg
	19	pos	neg	normal	neg	normal	10

Allogenic APOSEC™

TABLE 9-2		Urinalysis - Individual Data					Monkey
Sex: Male	Day(s): Predose Relative to Start Date	Urinalysis					
Group 4: 350/225/ 200 Units/kg	Nitrite	Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (µmol/L)	Bilirubin	Haemoglobin (ery/µL)
	23	pos	neg	normal	neg	neg	250
	24	neg	neg	normal	neg	neg	neg
	25	pos	neg	normal	neg	neg	neg
	26	pos	normal	neg	normal	neg	10
	27	pos	normal	neg	normal	neg	neg
	33	neg	normal	neg	normal	neg	neg
	34	neg	normal	neg	normal	neg	neg

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TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Male Day: 10 Relative to Start Date

Group 1: Control	Urinalysis					
	Nitrite	Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (µmol/L)	Bilirubin
1	neg	neg	normal	neg	normal	neg
2	pos	neg	normal	neg	normal	neg
3	neg	neg	normal	neg	normal	neg
4	neg	neg	normal	neg	normal	250
5	neg	neg	normal	neg	normal	neg

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TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Male Day: 10 Relative to Start Date

Group 2: 35 Units/kg	Urinalysis						
	Nitrite	Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (µmol/L)	Bilirubin	Haemoglobin (ery/µL)
	11	neg	neg	neg	normal	neg	neg
	12	neg	normal	neg	normal	neg	neg
13	neg	neg	normal	neg	normal	neg	neg

Allogenic APOSEC™

TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Male Day: 10 Relative to Start Date

Group 3: 110 Units/kg	Urinalysis					
	Nitrite	Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (µmol/L)	Bilirubin
17	pos	neg	normal	neg	normal	neg
18	pos	neg	normal	neg	normal	neg
19	pos	neg	normal	neg	normal	250

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TABLE 9-2

Monkey

Sex: Male Day: 10 Relative to Start Date

Group 4: 350/225/ 200 Units/kg	Urinalysis					
	Nitrite	Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (µmol/L)	Bilirubin
23	pos	neg	normal	neg	normal	neg
24	neg	neg	normal	neg	normal	neg
25	neg	neg	normal	neg	normal	neg
33	pos	neg	normal	neg	normal	neg
34	pos	neg	normal	neg	normal	neg

Haemoglobin
(ery/µL)

neg

neg

10

neg

neg

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TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Male Day: 25 Relative to Start Date

Group 1: Control	Urinalysis					
	Nitrite	Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (µmol/L)	Bilirubin
						Haemoglobin (ery/µL)
4	neg	neg	normal	neg	normal	neg
5	neg	neg	normal	neg	normal	neg

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TABLE 9-2

Monkey

Sex: Male Day: 25 Relative to Start Date

Group 4: 350/225/ 200 Units/kg	Urinalysis						
	Nitrite	Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (µmol/L)	Bilirubin	Haemoglobin (ery/µL)
	33 34	neg neg	normal normal	neg neg	normal normal	neg neg	neg 10

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TABLE 9-2 Urinalysis - Individual Data Monkey

Sex: Female	Day(s): Predose Relative to Start Date	Urinalysis		
		Colour	Specific Gravity (g/mL)	pH
Group 1: Control	6	SC	1.003	6.9
	7	SC	1.002	7.8
	8	SC	1.004	6.8
	9	SC	1.004	6.2
	10	SC	1.004	7.5
	Mean	-	1.0034	7.04
	SD	-	0.0009	0.63
	N	-	5	5

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TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Female Day(s): Predose Relative to Start Date

Group 2: 35 Units/kg	Urinalysis		
	Colour	Specific Gravity (g/mL)	pH
14	SC	1.002	7.5
15	SC	1.002	7.6
16	SC	1.003	7.9
Mean	-	1.0023	7.67
SD	-	0.0006	0.21
N	-	3	3

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TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Female Day(s): Predose Relative to Start Date

Group 3: 110 Units/kg	Urinalysis		
	Colour	Specific Gravity (g/mL)	pH
20	SC	1.003	7.7
21	SC	1.004	7.0
22	SC	1.004	7.7
Mean	-	1.0037	7.47
SD	-	0.0006	0.40
N	-	3	3

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TABLE 9-2 Urinalysis - Individual Data Monkey

Sex: Female	Day(s): Predose Relative to Start Date	Urinalysis		
Group 4: 350/225/ 200 Units/kg		Colour	Specific Gravity (g/mL)	pH
		SC	1.003	7.2
		SC	1.003	7.7
		SC	1.004	6.6
		SC	1.005	8.4
		SC	1.004	7.4
	Mean	-	1.0038	7.46
SD		-	0.0008	0.66
N		-	5	5

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TABLE 9-2 Urinalysis - Individual Data Monkey

Sex: Female Day: 10 Relative to Start Date

Group 1: Control	Urinalysis		
	Colour	Specific Gravity (g/mL)	pH
6	SC	1.002	8.5
7	SC	1.003	8.1
8	SC	1.003	7.1
9	SC	1.004	8.6
10	SC	1.003	8.3
Mean	-	1.0030	8.12
SD	-	0.0007	0.60
N	-	5	5

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TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Female Day: 10 Relative to Start Date

Group 2: 35 Units/kg	Urinalysis		
	Colour	Specific Gravity (g/mL)	pH
14	SC	1.004	8.3
15	SC	1.005	8.7
16	SC	1.004	8.1
Mean	-	1.0043	8.37
SD	-	0.0006	0.31
N	-	3	3

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TABLE 9-2 Urinalysis - Individual Data Monkey

Sex: Female Day: 10 Relative to Start Date

Group 3: 110 Units/kg	Urinalysis		
	Colour	Specific Gravity (g/mL)	pH
20	SC	1.004	8.0
21	SC	1.004	7.6
22	SC	1.005	7.8
Mean	-	1.0043	7.80
SD	-	0.0006	0.20
N	-	3	3

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TABLE 9-2 Urinalysis - Individual Data Monkey

Sex: Female Day: 10 Relative to Start Date

Group 4: 350/225/ 200 Units/kg	Urinalysis		
	Colour	Specific Gravity (g/mL)	pH
28	SC	1.005	8.2
29	SC	1.004	8.3
30	SC	1.004	7.5
31	SC	1.003	8.4
32	SC	1.004	8.7
Mean	-	1.0040	8.22
SD	-	0.0007	0.44
N	-	5	5

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TABLE 9-2 Urinalysis - Individual Data Monkey

Sex: Female Day: 25 Relative to Start Date

Group 1: Control	Colour	Urinalysis	
		Specific Gravity (g/mL)	pH
9	LC	1.004	9.0
10	SC	1.003	8.5
Mean	-	1.0035	8.75
SD	-	-	-
N	-	2	2

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TABLE 9-2 Urinalysis - Individual Data Monkey

Sex: Female Day: 25 Relative to Start Date

Group 4: 350/225/ 200 Units/kg	Urinalysis		
	Colour	Specific Gravity (g/mL)	pH
31	SC	1.003	6.9
32	SC	1.003	7.2
Mean	-	1.0030	7.05
SD	-	-	-
N	-	2	2

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TABLE 9-2		Urinalysis - Individual Data			Monkey		
Sex: Female	Day(s): Predose Relative to Start Date	Urinalysis					
Group 1: Control		Leucocytes	Erythrocytes	Crystalluria	Epithelial cells	Organisms	Further constituents
	6	0	0	0	+	0	0
	7	0	0	0	0	0	0
	8	0	0	0	0	0	0
	9	0	0	0	+	0	0
	10	0	0	0	0	0	0

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TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Female Day(s): Predose Relative to Start Date

Group 2: 35 Units/kg	Urinalysis					Further constituents
	Leucocytes	Erythrocytes	Crystalluria	Epithelial cells	Organisms	
14	0	0	0	0	0	0
15	0	0	0	0	0	0
16	0	0	0	0	0	0

Allogenic APOSEC™

TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Female Day(s): Predose Relative to Start Date

Group 3: 110 Units/kg	Urinalysis					
	Leucocytes	Erythrocytes	Crystalluria	Epithelial cells	Organisms	Further constituents
20	0	0	0	0	0	0
21	0	0	0	+++	0	0
22	0	0	0	+	0	0

Allogenic APOSEC™						
TABLE 9-2		Urinalysis - Individual Data			Monkey	
Sex: Female	Day(s): Predose Relative to Start Date	Urinalysis				
Group 4: 350/225/ 200 Units/kg	Leucocytes	Erythrocytes	Crystalluria	Epithelial cells	Organisms	Further constituents
	0	0	0	0	0	0
	++	++	0	+	0	0
	0	0	0	+	0	0
	++	0	0	+++	0	0
	+	0	0	+++	0	0
	28					
29						
30						
31						
32						

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TABLE 9-2		Urinalysis - Individual Data			Monkey	
Sex: Female	Day: 10 Relative to Start Date	Urinalysis				
Group 1: Control	Leucocytes	Erythrocytes	Crystalluria	Epithelial cells	Organisms	Further constituents
	6	+	0	0	+	0
	7	0	0	0	0	0
	8	0	0	0	0	0
	9	0	0	0	+++	0
	10	0	0	0	++	0

Allogenic APOSEC™						
TABLE 9-2		Urinalysis - Individual Data			Monkey	
Sex: Female	Day: 10 Relative to Start Date	Urinalysis				
Group 2: 35 Units/kg	Leucocytes	Erythrocytes	Crystalluria	Epithelial cells	Organisms	Further constituents
	14	+	0	0	+++	0
	15	0	0	0	0	0
	16	0	0	0	0	0

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TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Female Day: 10 Relative to Start Date

Group 3: 110 Units/kg	Urinalysis					Organisms	Further constituents
	Leucocytes	Erythrocytes	Crystalluria	Epithelial cells			
20	+	0	0	+++	0	0	
21	0	0	0	++	0	0	
22	0	0	0	0	0	0	

Allogenic APOSEC™							
TABLE 9-2		Urinalysis - Individual Data			Monkey		
Sex: Female	Day: 10 Relative to Start Date	Urinalysis					
Group 4: 350/225/ 200 Units/kg	Leucocytes	Erythrocytes	Crystalluria	Epithelial cells	Organisms	Further constituents	
	28	0			+	0	0
	29	0	0	0	0	0	0
	30	0	0	0	++	0	0
	31	0	0	0	+	0	0
	32	0	0	0	0	0	0

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TABLE 9-2

Monkey

Urinalysis - Individual Data

Sex: Female Day: 25 Relative to Start Date

Group 1: Control	Urinalysis					Organisms	Further constituents
	Leucocytes	Erythrocytes	Crystalluria	Epithelial cells			
9	0	0	0	0		0	0
10	0	0	0	+++		0	0

Allogenic APOSEC™							
TABLE 9-2		Urinalysis - Individual Data			Monkey		
Sex: Female	Day: 25 Relative to Start Date	Urinalysis					
Group 4: 350/225/ 200 Units/kg		Leucocytes	Erythrocytes	Crystalluria	Epithelial cells	Organisms	Further constituents
		++	0	0	+++	0	0
		0	0	0	++	0	0

Allogenic APOSEC™

TABLE 9-2

Monkey

Sex: Female	Day(s): Predose Relative to Start Date	Urinalysis						
Group 1: Control		Nitrite	Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (μmol/L)	Bilirubin	Haemoglobin (ery/μL)
	6	neg	neg	normal	neg	normal	neg	neg
	7	pos	neg	normal	neg	normal	neg	neg
	8	neg	neg	normal	neg	normal	neg	neg
	9	pos	neg	normal	neg	normal	neg	neg
	10	pos	neg	normal	neg	normal	neg	neg

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TABLE 9-2

Monkey

Sex: Female Day(s): Predose Relative to Start Date

Group 2: 35 Units/kg	Urinalysis					
	Nitrite	Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (µmol/L)	Bilirubin
14	neg	neg	normal	neg	normal	neg
15	neg	neg	normal	neg	normal	neg
16	pos	neg	normal	neg	normal	neg
						Haemoglobin (ery/µL)
						10
						50
						neg

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TABLE 9-2

Monkey

Sex: Female	Day(s): Predose Relative to Start Date	Urinalysis - Individual Data					
		Urinalysis					
Group 3: 110 Units/kg		Nitrite	Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (µmol/L)	Bilirubin
							Haemoglobin (ery/µL)
		20	neg	normal	neg	normal	neg
		21	neg	normal	neg	normal	250
	22	neg	neg	normal	neg	normal	10

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TABLE 9-2

Sex: Female	Day(s): Predose Relative to Start Date	Urinalysis						
Group 4: 350/225/ 200 Units/kg		Nitrite	Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (μmol/L)	Bilirubin	Haemoglobin (ery/μL)
	28	neg	neg	normal	neg	normal	neg	neg
	29	neg	neg	normal	neg	normal	neg	250
	30	neg	neg	normal	neg	normal	neg	neg
	31	pos	neg	normal	neg	normal	neg	10
	32	pos	neg	normal	neg	normal	neg	10

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TABLE 9-2

Sex: Female		Day: 10 Relative to Start Date	Urinalysis - Individual Data					Monkey
			Urinalysis					
Group 2: 35 Units/kg	Nitrite		Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (µmol/L)	Bilirubin	Haemoglobin (ery/µL)
	14	pos	neg	normal	neg	normal	neg	neg
	15	pos	neg	normal	neg	normal	neg	25
	16	neg	neg	normal	neg	normal	neg	10

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TABLE 9-2

Monkey

Sex: Female		Day: 10 Relative to Start Date		Urinalysis - Individual Data				
Group 3: 110 Units/kg		Nitrite	Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (µmol/L)	Bilirubin	Haemoglobin (ery/µL)
20		neg	neg	normal	neg	normal	neg	neg
21		neg	neg	normal	neg	normal	neg	neg
22		pos	neg	normal	neg	normal	neg	neg

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TABLE 9-2

Monkey

Sex: Female	Day: 10 Relative to Start Date	Urinalysis - Individual Data					
		Urinalysis					
Group 4: 350/225/ 200 Units/kg	Nitrite	Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (µmol/L)	Bilirubin	Haemoglobin (ery/µL)
	28	pos	neg	normal	neg	neg	10
	29	pos	neg	normal	neg	neg	10
	30	neg	neg	normal	neg	neg	neg
	31	neg	neg	normal	neg	neg	neg
	32	neg	neg	normal	neg	neg	10

Allogenic APOSEC™

TABLE 9-2

Monkey

Sex: Female Day: 25 Relative to Start Date

Group 1: Control	Urinalysis					
	Nitrite	Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (µmol/L)	Bilirubin
9	neg	neg	normal	neg	normal	neg
10	pos	neg	normal	neg	normal	neg
						Haemoglobin (ery/µL) 50 neg

Allogenic APOSEC™

TABLE 9-2

Sex: Female			Day: 25 Relative to Start Date		Urinalysis - Individual Data				Monkey
			Urinalysis						
Group 4: 350/225/ 200 Units/kg	Nitrite		Protein (g/L)	Glucose (mmol/L)	Ketones	Urobili- nogen (μmol/L)	Bilirubin	Haemoglobin (ery/μL)	
	neg		neg	normal	neg	normal	neg	neg	
	neg		neg	normal	neg	normal	neg	neg	

Allogenic APOSEC™		
TABLE 10	Ophthalmological Examination	Monkey

Animal no.	Predose		Eye ^{#1} TD 11		TD 25	
	left	right	left	right	left	right

Male animals

Group 1: Control

(1)	MS	0	0	0	0	-	-
(2)	MS	0	0	0	0	-	-
(3)	MS	0	0	0	0	-	-
(4)	RP	0	0	0	0	0	0
(5)	RP	0	0	0	0	0	0

Group 2: 35 U/kg

(11)	MS	0	0	0	0	-	-
(12)	MS	0	0	0	0	-	-
(13)	MS	0	0	0	0	-	-

Group 3: 110 U/kg

(17)	MS	0	0	0	0	-	-
(18)	MS	0	0	0	0	-	-
(19)	MS	0	0	0	0	-	-

Group 4: 350/225/200 U/kg

(23)	MS	0	0	0	0	-	-
(24)	MS	0	0	0	0	-	-
(25)	MS	0	0	0	0	-	-
(26) ^{#2}	MS	0	0	-	-	-	-
(27) ^{#3}	MS	0	0	-	-	-	-
(33)	RP	0	0	0	0	0	0
(34)	RP	0	0	0	0	0	0

MS = main study

RP = recovery period

TD = test day

0 = no pathological findings

#1 = includes: adnexa oculi (i.e. lids, lacrimal apparatus), conjunctiva, cornea, anterior chamber, lens, vitreous body, fundus (retina, optic disc)

#2 = Male no. 26 had to be sacrificed prematurely on test day 1.

#3 = Male no. 27 had to be sacrificed prematurely on test day 1.

Allogenic APOSEC™		
TABLE 10	Ophthalmological Examination	Monkey

Animal no.	Eye [#]					
	Predose		TD 11		TD 25	
	left	right	left	right	left	right
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
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85						
86						
87						
88						

Female animals

Group 1: Control

(6)	MS	0	0	0	0	-	-
(7)	MS	0	0	0	0	-	-
(8)	MS	0	0	0	0	-	-
(9)	RP	0	0	0	0	0	0
(10)	RP	0	0	0	0	0	0

Group 2: 35 U/kg

(14)	MS	0	0	0	0	-	-
(15)	MS	0	0	0	0	-	-
(16)	MS	0	0	0	0	-	-

Group 3: 110 U/kg

(20)	MS	0	0	0	0	-	-
(21)	MS	0	0	0	0	-	-
(22)	MS	0	0	0	0	-	-

Group 4: 350/225/200 U/kg

(28)	MS	0	0	0	0	-	-
(29)	MS	0	0	0	0	-	-
(30)	MS	0	0	0	0	-	-
(31)	RP	0	0	0	0	0	0
(32)	RP	0	0	0	0	0	0

MS = main study

RP = recovery period

TD = test day

0 = no pathological findings

= includes: adnexa oculi (i.e. lids, lacrimal apparatus), conjunctiva, cornea, anterior chamber, lens, vitreous body, fundus (retina, optic disc)

TABLE 11		Allogenic APOSEC™ Auditory Examination			Monkey
Animal no.		Predose	Hearing TD 11	TD 25	
Male animals					
Group 1: Control					
(1)	MS	0	0	-	
(2)	MS	0	0	-	
(3)	MS	0	0	-	
(4)	RP	0	0	0	
(5)	RP	0	0	0	
Group 2: 35 U/kg					
(11)	MS	0	0	-	
(12)	MS	0	0	-	
(13)	MS	0	0	-	
Group 3: 110 U/kg					
(17)	MS	0	0	-	
(18)	MS	0	0	-	
(19)	MS	0	0	-	
Group 4: 350/225/200 U/kg					
(23)	MS	0	0	-	
(24)	MS	0	0	-	
(25)	MS	0	0	-	
(26) ^{#1}	MS	0	-	-	
(27) ^{#2}	MS	0	-	-	
(33)	RP	0	0	0	
(34)	RP	0	0	0	

MS = main study

RP = recovery period

TD = test day

0 = no pathological findings

#1 = Male no. 26 had to be sacrificed prematurely on test day 1.

#2 = Male no. 27 had to be sacrificed prematurely on test day 1.

Allogenic APOSEC™

TABLE 12

Macroscopic Post Mortem Findings

Monkey

Animal No.	Sacrifice / Dead	Affected Organs	Findings
------------	------------------	-----------------	----------

Males

Group 1: Control

Terminal sacrifice

(1)	TS / TD 12	Infusion site (last):	haemorrhagic (subcutaneous)
(2)	TS / TD 12	Infusion site (last):	haemorrhagic (subcutaneous)
(3)	TS / TD 12	—	no pathological findings

Recovery sacrifice

(4)	RS / TD 26	—	no pathological findings
(5)	RS / TD 26	—	no pathological findings

TD test day
TS terminal sacrifice
RS recovery sacrifice

TABLE 12		Allogenic APOSEC™ Macroscopic Post Mortem Findings		Monkey
Animal No.	Sacrifice / Dead	Affected Organs	Findings	

Males

Group 2: 35 U/kg

Terminal sacrifice

(11)	TS / TD 12	Infusion site (last):	haemorrhagic (subcutaneous)
		Thyroid (left):	pale, reduced in size, soft consistency
(12)	TS / TD 12	—	no pathological findings
(13)	TS / TD 12	Infusion site (last):	haemorrhagic (subcutaneous)
		Lymph node (axillary):	enlarged

Group 3: 110 U/kg

Terminal sacrifice

(17)	TS / TD 12	Infusion site (last):	haemorrhagic (subcutaneous)
(18)	TS / TD 12	Infusion site (last):	haemorrhagic (subcutaneous)
(19)	TS / TD 12	Infusion site (last):	haemorrhagic (subcutaneous)

TD test day
TS terminal sacrifice

	Allogenic APOSEC™	
TABLE 12	Macroscopic Post Mortem Findings	Monkey

Animal No.	Sacrifice / Dead	Affected Organs	Findings
------------	------------------	-----------------	----------

Males

Group 4: 350/225/200 U/kg

Terminal sacrifice

(23)	TS / TD 12	Infusion site (last):	haemorrhagic (subcutaneous)
		Spleen:	enlarged
(24)	TS / TD 12	Infusion site (last):	haemorrhagic (subcutaneous)
(25)	TS / TD 12	Infusion site (last):	haemorrhagic (subcutaneous)
		Spleen:	enlarged
		Lymph node (axillary):	enlarged
(26)	PS / TD 1	Lymph nodes (axillary):	enlarged
		Lungs:	emphysematous
(27)	PS / TD 1	Lymph nodes (axillary):	enlarged
		Lymph nodes (cervical):	enlarged
		Adrenal glands:	enlarged
		Thighs (bilateral):	subcutaneous tissue: oedematous, haemorrhagic
		Lower legs (bilateral):	subcutaneous tissue: oedematous, haemorrhagic

PS premature sacrifice
TD test day
TS terminal sacrifice

Allogenic APOSEC™

TABLE 12

Macroscopic Post Mortem Findings

Monkey

Animal No.	Sacrifice / Dead	Affected Organs	Findings
------------	------------------	-----------------	----------

Males

Group 4: 350/225/200 U/kg

Recovery sacrifice

(33)	RS / TD 26	—	no pathological findings
(34)	RS / TD 26	—	no pathological findings

TD test day
RS recovery sacrifice

Allogenic APOSEC™

TABLE 12

Macroscopic Post Mortem Findings

Monkey

Animal No.	Sacrifice / Dead	Affected Organs	Findings
------------	------------------	-----------------	----------

Females

Group 1: Control

Terminal sacrifice

(6)	TS / TD 12	—	no pathological findings
(7)	TS / TD 12	Infusion site (last):	haemorrhagic (subcutaneous)
		Ovary (left):	cystic
(8)	TS / TD 12	Infusion site (last):	haemorrhagic (subcutaneous)

Recovery sacrifice

(9)	RS / TD 26	—	no pathological findings
(10)	RS / TD 26	—	no pathological findings

TD test day
TS terminal sacrifice
RS recovery sacrifice

TABLE 12		Allogenic APOSEC™ Macroscopic Post Mortem Findings		Monkey
Animal No.	Sacrifice / Dead	Affected Organs	Findings	

Females

Group 2: 35 U/kg

Terminal sacrifice

(14)	TS / TD 12	—	no pathological findings
(15)	TS / TD 12	Infusion site (last):	haemorrhagic (subcutaneous)
(16)	TS / TD 12	Infusion site (last):	haemorrhagic (subcutaneous)

Group 3: 110 U/kg

Terminal sacrifice

(20)	TS / TD 12	Infusion site (last):	haemorrhagic (subcutaneous)
		Ovary (left):	cystic
(21)	TS / TD 12	Infusion site (last):	haemorrhagic (subcutaneous)
(22)	TS / TD 12	Infusion site (last):	haemorrhagic (subcutaneous)

TD test day
TS terminal sacrifice

Allogenic APOSEC™

TABLE 12

Macroscopic Post Mortem Findings

Monkey

Animal No.	Sacrifice / Dead	Affected Organs	Findings
------------	------------------	-----------------	----------

Females

Group 4: 350/225/200 U/kg

Terminal sacrifice

(28)	TS / TD 12	—	no pathological findings
(29)	TS / TD 12	Infusion site (last):	haemorrhagic (subcutaneous)
(30)	TS / TD 12	Thymus:	reduced in size

Recovery sacrifice

(31)	RS / TD 26	—	no pathological findings
(32)	RS / TD 26	—	no pathological findings

TD test day

TS terminal sacrifice

RS recovery sacrifice

Allogenic APOSEC™

TABLE 13-1 Relative Organ Weights - Summary Monkey

Day: 12 Relative to Start Date		Relative Organ Weights							
Sex: Male		Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Epididymis (left) (g/kg b.w.)	Epididymis (right) (g/kg b.w.)	Testis (left) (g/kg b.w.)	Testis (right) (g/kg b.w.)	
Group 1: Control	Mean	[a]	[a]	[a]	[a]	[a]	[a]	[a]	
	SD	0.112	0.104	29.87	0.127	0.127	0.26	0.27	
	N	0.026	0.011	4.39	0.025	0.032	0.05	0.06	
		3	3	3	3	3	3	3	
Group 2: 35 Units/kg	Mean	-	-	-	-	-	-	-	
	SD	0.103	0.084	30.32	0.142	0.126	0.20	0.17	
	N	0.007	0.010	2.87	0.039	0.016	0.03	0.05	
	%Diff	3	3	3	3	3	3	3	
Group 3: 110 Units/kg	Mean	-8.2	-19.3	1.5	11.6	-0.9	-20.1	-35.2	
	SD	0.120	0.096	29.49	0.133	0.138	0.17	0.20	
	N	0.014	0.023	0.25	0.048	0.031	0.04	0.03	
	%Diff	3	3	3	3	3	3	3	
Group 4: 350/225/ 200 Units/kg	Mean	7.5	-8.4	-1.3	4.7	8.3	-31.8	-24.7	
	SD	0.132	0.117	31.09	0.106	0.093	0.13**	0.13*	
	N	0.021	0.011	1.87	0.017	0.009	0.01	0.04	
	%Diff	3	3	3	3	3	3	3	
	Mean	17.6	12.2	4.1	-17.1	-27.1	-48.8	-51.8	
	SD								
	N								
	%Diff								

[a] - Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$

Allogenic APOSEC™

TABLE 13-1 Relative Organ Weights - Summary Monkey

Day: 12 Relative to Start Date		Relative Organ Weights						
Sex: Male		Heart (g/kg b.w.)	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Lungs (g/kg b.w.)	Lymph node (axillar) (g/kg b.w.)	Lymph node (cerv.) (g/kg b.w.)
Group 1: Control	Mean	[a]	[a]	[a]	[a]	[a1]	[a]	[a]
	SD	4.38	2.40	2.28	23.45	6.42	0.0410	0.0163
	N	0.31	0.15	0.09	0.79	0.96	0.0164	0.0067
		3	3	3	3	3	3	3
Group 2: 35 Units/kg	Mean	-	-	-	-	-	-	-
	SD	4.53	2.31	2.34	23.59	5.51	0.0910	0.0175
	N	0.20	0.16	0.12	1.56	0.07	0.0450	0.0103
	%Diff	3	3	3	3	3	3	3
Group 3: 110 Units/kg	Mean	3.3	-3.8	2.3	0.6	-14.1	122.0	7.8
	SD	4.26	2.48	2.43	23.97	5.80	0.0491	0.0126
	N	0.53	0.16	0.23	1.64	0.37	0.0230	0.0106
	%Diff	3	3	3	3	3	3	3
Group 4: 350/225/ 200 Units/kg	Mean	-2.8	3.4	6.7	2.2	-9.6	19.8	-22.5
	SD	3.96	2.27	2.36	21.60	5.45	0.0741	0.0231
	N	0.32	0.06	0.09	1.50	0.13	0.0389	0.0048
	%Diff	3	3	3	3	3	3	3
	Mean	-9.7	-5.1	3.4	-7.9	-15.0	80.7	42.2
	SD							
	N							
	%Diff							

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Rank)

Allogenic APOSEC™

TABLE 13-1 Relative Organ Weights - Summary Monkey

Day: 12 Relative to Start Date		Relative Organ Weights				
Sex: Male		Pituitary (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Thyroid/Par. (left) (g/kg b.w.)	Thyroid/Par. (right) (g/kg b.w.)
		[a]	[a]	[a]	[a]	[a]
Group 1: Control	Mean	0.0221	1.76	1.822	0.075	0.078
	SD	0.0096	0.71	0.488	0.018	0.020
	N	3	3	3	3	3
Group 2: 35 Units/kg	Mean	-	-	-	-	-
	SD	0.0192	1.38	1.379	0.066	0.065
	N	0.0034	0.07	0.373	0.036	0.018
	%Diff	3	3	3	3	3
Group 3: 110 Units/kg	Mean	-13.1	-21.9	-24.3	-11.7	-16.7
	SD	0.0187	1.57	1.649	0.059	0.059
	N	0.0053	0.38	0.512	0.005	0.007
	%Diff	3	3	3	3	3
Group 4: 350/225/ 200 Units/kg	Mean	-15.6	-11.3	-9.5	-21.0	-23.8
	SD	0.0164	1.85	0.862	0.048	0.051
	N	0.0028	0.58	0.188	0.013	0.011
	%Diff	3	3	3	3	3
		-25.7	4.7	-52.7	-35.9	-34.5

[a] - Anova & Dunnett

Allogenic APOSEC™

Day: 26 Relative to Start Date		TABLE 13-1 Relative Organ Weights - Summary				Monkey			
Sex: Male		Relative Organ Weights							
		Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Epididymis (left) (g/kg b.w.)	Epididymis (right) (g/kg b.w.)	Testis (left) (g/kg b.w.)	Testis (right) (g/kg b.w.)	
Group 1: Control	Mean	0.120n	0.087n	29.06n	0.144n	0.144n	0.20n	0.16n	
	SD	-	-	-	-	-	-	-	
	N	2	2	2	2	2	2	2	
Group 4: 350/225/ 200 Units/kg	Mean	0.105n	0.088n	28.49n	0.127n	0.117n	0.17n	0.19n	
	SD	-	-	-	-	-	-	-	
	N	2	2	2	2	2	2	2	
	%Diff	-12.6	1.3	-2.0	-11.3	-19.1	-14.3	23.2	

[a] - Anova & Dunnett: n - Inappropriate for statistics

Allogenic APOSEC™

Day: 26 Relative to Start Date		TABLE 13-1 Relative Organ Weights - Summary					Monkey	
Sex: Male		Relative Organ Weights						
		Heart (g/kg b.w.)	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Lungs (g/kg b.w.)	Lymph node (axillar) (g/kg b.w.)	Lymph node (cerv.) (g/kg b.w.)
Group 1: Control	Mean	[a] 4.18n	[a] 2.13n	[a] 2.36n	[a] 25.87n	[a] 5.62n	[a] 0.0412n	[a] 0.0204n
	SD	-	-	-	-	-	-	-
	N	2	2	2	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	4.39n	1.94n	2.05n	22.74n	5.41n	0.0549n	0.0260n
	SD	-	-	-	-	-	-	-
	N	2	2	2	2	2	2	2
	%Diff	4.9	-9.2	-13.1	-12.1	-3.8	33.2	27.6

[a] - Anova & Dunnett: n - Inappropriate for statistics

Allogenic APOSEC™

TABLE 13-1 Relative Organ Weights - Summary Monkey

Day: 26 Relative to Start Date		Relative Organ Weights				
Sex: Male		Pituitary (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Thyroid/Par. (left) (g/kg b.w.)	Thyroid/Par. (right) (g/kg b.w.)
		[a]	[a]	[a]	[a]	[a]
Group 1: Control	Mean	0.0187n	1.07n	1.423n	0.049n	0.042n
	SD	-	-	-	-	-
	N	2	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	0.0155n	2.07n	1.593n	0.057n	0.060n
	SD	-	-	-	-	-
	N	2	2	2	2	2
	%Diff	-17.2	93.6	11.9	17.2	40.7

[a] - Anova & Dunnett: n - Inappropriate for statistics

Allogenic APOSEC™

TABLE 13-1 Relative Organ Weights - Summary

Monkey

Day: 12 Relative to Start Date		Relative Organ Weights					
Sex: Female		Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Ovary (left) (g/kg b.w.)	Ovary (right) (g/kg b.w.)	Heart (g/kg b.w.)
		[a]	[a]	[a]	[a1]	[a]	[a]
Group 1: Control	Mean	0.144	0.104	31.14	0.148	0.036	4.11
	SD	0.027	0.029	1.77	0.198	0.013	0.10
	N	3	3	3	3	3	3
		-	-	-	-	-	-
Group 2: 35 Units/kg	Mean	0.133	0.116	30.76	0.038	0.035	4.06
	SD	0.016	0.022	2.30	0.021	0.018	0.19
	N	3	3	3	3	3	3
	%Diff	-7.6	11.4	-1.2	-74.5	-3.9	-1.1
Group 3: 110 Units/kg	Mean	0.130	0.104	30.05	0.114	0.043	4.04
	SD	0.016	0.016	0.50	0.131	0.005	0.20
	N	3	3	3	3	3	3
	%Diff	-9.7	-0.5	-3.5	-23.3	19.3	-1.7
Group 4: 350/225/ 200 Units/kg	Mean	0.118	0.104	31.35	0.044	0.039	4.12
	SD	0.028	0.040	3.10	0.016	0.011	0.79
	N	3	3	3	3	3	3
	%Diff	-17.7	-0.1	0.7	-70.5	7.7	0.3

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Log)

Allogenic APOSEC™

TABLE 13-1 Relative Organ Weights - Summary Monkey

Day: 12 Relative to Start Date		Relative Organ Weights					
Sex: Female		Relative Organ Weights					
		Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Lungs (g/kg b.w.)	Lymph node (axillar) (g/kg b.w.)	Lymph node (cerv.) (g/kg b.w.)
		[a]	[a]	[a1]	[a]	[a]	[a]
Group 1: Control	Mean	2.29	2.41	22.81	5.65	0.0589	0.0169
	SD	0.21	0.18	2.62	0.31	0.0182	0.0020
	N	3	3	3	3	3	3
Group 2: 35 Units/kg	Mean	2.34	2.50	23.54	5.71	0.0604	0.0295
	SD	0.37	0.32	2.49	0.26	0.0212	0.0136
	N	3	3	3	3	3	3
	%Diff	2.3	3.6	3.2	1.1	2.4	74.5
Group 3: 110 Units/kg	Mean	2.36	2.30	23.18	5.43	0.0660	0.0258
	SD	0.59	0.53	0.48	0.55	0.0156	0.0096
	N	3	3	3	3	3	3
	%Diff	3.4	-4.4	1.6	-3.9	11.9	52.8
Group 4: 350/225/ 200 Units/kg	Mean	2.20	2.28	24.41	5.48	0.0308	0.0269
	SD	0.38	0.45	7.07	0.87	0.0193	0.0094
	N	3	3	3	3	3	3
	%Diff	-3.9	-5.4	7.0	-2.9	-47.7	59.4

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Log)

Allogenic APOSEC™

TABLE 13-1 Relative Organ Weights - Summary Monkey

Day: 12 Relative to Start Date		Relative Organ Weights					
Sex: Female		Pituitary (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Thyroid/Par. (left) (g/kg b.w.)	Thyroid/Par. (right) (g/kg b.w.)	Uterus (g/kg b.w.)
		[a]	[a]	[a]	[a1]	[a]	[a1]
Group 1: Control	Mean	0.0148	1.43	1.377	0.072	0.068	0.199
	SD	0.0066	0.30	0.200	0.011	0.011	0.137
	N	3	3	3	3	3	3
Group 2: 35 Units/kg	Mean	-	-	-	-	-	-
	SD	0.0193	1.13	1.953	0.076	0.084	0.236
	N	0.0026	0.20	0.738	0.028	0.019	0.157
	%Diff	30.1	-21.3	41.8	6.2	23.3	18.7
Group 3: 110 Units/kg	Mean	0.0174	1.46	1.379	0.060	0.049	0.234
	SD	0.0018	0.40	0.322	0.010	0.007	0.084
	N	3	3	3	3	3	3
	%Diff	17.2	2.0	0.1	-16.1	-27.7	17.8
Group 4: 350/225/ 200 Units/kg	Mean	0.0108	1.27	0.792	0.071	0.063	0.200
	SD	0.0015	0.07	0.357	0.001	0.013	0.005
	N	3	3	3	3	3	3
	%Diff	-26.8	-11.1	-42.5	-1.0	-8.1	0.5

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Rank)

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TABLE 13-1 Relative Organ Weights - Summary Monkey

Day: 26 Relative to Start Date		Relative Organ Weights					
Sex: Female		Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Ovary (left) (g/kg b.w.)	Ovary (right) (g/kg b.w.)	Heart (g/kg b.w.)
Group 1: Control	Mean	0.109n	[a]	[a]	[a]	[a]	[a]
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	0.115n	0.093n	29.36n	0.043n	0.045n	4.16n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
%Diff		5.6	-5.3	-3.9	5.5	4.1	-1.0

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 13-1 Relative Organ Weights - Summary

Monkey

Day: 26 Relative to Start Date		Relative Organ Weights					
Sex: Female		Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Lungs (g/kg b.w.)	Lymph node (axillar) (g/kg b.w.)	Lymph node (cerv.) (g/kg b.w.)
Group 1: Control	Mean	[a] 2.07n	[a] 2.09n	[a] 26.77n	[a] 5.68n	[a] 0.0564n	[a] 0.0230n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
Group 4: 350/225/200 Units/kg	Mean	2.34n	2.29n	29.01n	6.60n	0.0516n	0.0213n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
%Diff		13.1	9.6	8.4	16.1	-8.4	-7.4

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 13-1 Relative Organ Weights - Summary Monkey

Day: 26 Relative to Start Date		Relative Organ Weights					
Sex: Female		Pituitary (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Thyroid/Par. (left) (g/kg b.w.)	Thyroid/Par. (right) (g/kg b.w.)	Uterus (g/kg b.w.)
		[a]	[a]	[a]	[a]	[a]	[a]
Group 1: Control	Mean	0.0175n	1.48n	1.984n	0.055n	0.068n	0.382n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	0.0237n	1.42n	1.572n	0.067n	0.072n	0.489n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
%Diff		35.5	-3.9	-20.8	22.8	5.2	28.0

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 13-1 Relative Organ Weights - Summary Monkey

Comments and Markers

Page	Day	Group	Sex	Measurement	Marker	Comment
				Testis (left)	**	Anova & Dunnett: ** = $p \leq 0.01$
	12	4	Male	Testis (right)	*	Anova & Dunnett: * = $p \leq 0.05$
	12	4	Male	Adren. Gland (left)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Adren. Gland (right)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Brain	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Epididymis (left)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Epididymis (right)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Testis (left)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Testis (right)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Adren. Gland (left)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Adren. Gland (right)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Brain	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Epididymis (left)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Epididymis (right)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Testis (left)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Testis (right)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Heart	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Kidney (left)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Kidney (right)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Liver	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Lungs	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Lymph node (axillar)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Lymph node (cerv.)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Heart	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Kidney (left)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Kidney (right)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Liver	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Lungs	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Lymph node (axillar)	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Lymph node (cerv.)	n	Anova & Dunnett: n - Inappropriate for statistics

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TABLE 13-1 Relative Organ Weights - Summary Monkey

Comments and Markers					
Page	Day	Group	Sex	Measurement	
					Marker
					Comment
	26	1	Male	Pituitary	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Spleen	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Thymus	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Thyroid/Par. (left)	Anova & Dunnett: n - Inappropriate for statistics
	26	1	Male	Thyroid/Par. (right)	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Pituitary	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Spleen	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Thymus	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Thyroid/Par. (left)	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Male	Thyroid/Par. (right)	Anova & Dunnett: n - Inappropriate for statistics

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TABLE 13-1 Relative Organ Weights - Summary Monkey

Comments and Markers

<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker</u>	<u>Comment</u>
26	26	1	Female	Adren. Gland (left)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Adren. Gland (right)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Brain	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Ovary (left)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Ovary (right)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Heart	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Adren. Gland (left)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Adren. Gland (right)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Brain	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Ovary (left)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Ovary (right)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Heart	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Kidney (left)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Kidney (right)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Liver	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Lungs	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Lymph node (axillar)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Lymph node (cerv.)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Kidney (left)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Kidney (right)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Liver	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Lungs	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Lymph node (axillar)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Female	Lymph node (cerv.)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Pituitary	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Spleen	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Thymus	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Thyroid/Par. (left)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Thyroid/Par. (right)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Female	Uterus	n	Anova & Dunnett: n - Inappropriate for statistics

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TABLE 13-1 Relative Organ Weights - Summary Monkey

Comments and Markers					
Page	Day	Group	Sex	Measurement	
					<u>Marker</u>
					<u>Comment</u>
	26	4	Female	Pituitary	n Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Spleen	n Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Thymus	n Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Thyroid/Par. (left)	n Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Thyroid/Par. (right)	n Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Uterus	n Anova & Dunnett: n - Inappropriate for statistics

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TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Male		Day: 1 Relative to Start Date	Relative Organ Weights					
Group 4: 350/225/ 200 Units/kg	Adren. Gland (left) (g/kg b.w.)		Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Epididymis (left) (g/kg b.w.)	Epididymis (right) (g/kg b.w.)	Testis (left) (g/kg b.w.)	Testis (right) (g/kg b.w.)
	26	0.08	0.07	26.7	0.11	0.11	0.1	0.1
	27	0.11	0.09	30.7	0.08	0.09	0.1	0.1
	Mean	0.095	0.080	28.67	0.093	0.100	0.10	0.10
	SD	-	-	-	-	-	-	-
	N	2	2	2	2	2	2	2

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TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Male Day: 1 Relative to Start Date								
Group 4: 350/225/ 200 Units/kg		Relative Organ Weights						
		Heart (g/kg b.w.)	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Lungs (g/kg b.w.)	Lymph node (axillar) (g/kg b.w.)	Lymph node (cerv.) (g/kg b.w.)
26	3.9	2.1	2.1	23.1	7.4	0.044	0.010	
27	3.5	2.5	2.4	22.8	7.0	0.049	0.026	
Mean	3.68	2.28	2.26	22.97	7.20	0.0466	0.0176	
SD	-	-	-	-	-	-	-	
N	2	2	2	2	2	2	2	

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TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Male	Day: 1 Relative to Start Date	Relative Organ Weights			
		Pituitary (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Thyroid/Par. (left) (g/kg b.w.)
Group 4: 350/225/ 200 Units/kg	26	0.011	1.5	1.89	Thyroid/Par. (right) (g/kg b.w.)
	27	0.012	1.3	1.88	0.06 0.05
Mean		0.0117	1.39	1.887	0.056
SD		-	-	-	-
N		2	2	2	2

TABLE 13-2
Relative Organ Weights - Individual Data
Monkey

Sex: Male Day: 12 Relative to Start Date							
Group 1: Control	Relative Organ Weights						
	Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Epididymis (left) (g/kg b.w.)	Epididymis (right) (g/kg b.w.)	Testis (left) (g/kg b.w.)	Testis (right) (g/kg b.w.)
1	0.09	0.10	26.5	0.16	0.16	0.2	0.2
2	0.11	0.10	34.8	0.12	0.11	0.3	0.3
3	0.14	0.12	28.3	0.11	0.10	0.3	0.3
Mean	0.112	0.104	29.87	0.127	0.127	0.26	0.27
SD	0.026	0.011	4.39	0.025	0.032	0.05	0.06
N	3	3	3	3	3	3	3

TABLE 13-2
Relative Organ Weights - Individual Data
Monkey

Sex: Male Day: 12 Relative to Start Date							
Group 2: 35 Units/kg	Relative Organ Weights						
	Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Epididymis (left) (g/kg b.w.)	Epididymis (right) (g/kg b.w.)	Testis (left) (g/kg b.w.)	Testis (right) (g/kg b.w.)
11	0.11	0.08	32.1	0.19	0.14	0.2	0.2
12	0.10	0.08	27.0	0.12	0.12	0.2	0.1
13	0.10	0.10	31.9	0.12	0.11	0.2	0.2
Mean	0.103	0.084	30.32	0.142	0.126	0.20	0.17
SD	0.007	0.010	2.87	0.039	0.016	0.03	0.05
N	3	3	3	3	3	3	3

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TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Male		Day: 12 Relative to Start Date		Relative Organ Weights				
Group 3: 110 Units/kg	Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Epididymis (left) (g/kg b.w.)	Epididymis (right) (g/kg b.w.)	Testis (left) (g/kg b.w.)	Testis (right) (g/kg b.w.)	
	17	0.13	0.09	29.3	0.18	0.17	0.2	
	18	0.10	0.08	29.4	0.14	0.14	0.2	
	19	0.13	0.12	29.8	0.08	0.10	0.1	
Mean	0.120	0.096	29.49	0.133	0.138	0.17	0.20	
SD	0.014	0.023	0.25	0.048	0.031	0.04	0.03	
N	3	3	3	3	3	3	3	

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TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Relative Organ Weights						
		Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Epididymis (left) (g/kg b.w.)	Epididymis (right) (g/kg b.w.)	Testis (left) (g/kg b.w.)	Testis (right) (g/kg b.w.)
Group 4: 350/225/ 200 Units/kg	23	0.11	0.11	31.7	0.09	0.08	0.1	0.1
	24	0.14	0.11	29.0	0.11	0.10	0.1	0.1
	25	0.15	0.13	32.6	0.12	0.10	0.1	0.2
	Mean	0.132	0.117	31.09	0.106	0.093	0.13	0.13
	SD	0.021	0.011	1.87	0.017	0.009	0.01	0.04
	N	3	3	3	3	3	3	3

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TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Male		Day: 12 Relative to Start Date		Relative Organ Weights				
Group 1: Control		Heart (g/kg b.w.)	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Lungs (g/kg b.w.)	Lymph node (axillar) (g/kg b.w.)	Lymph node (cerv.) (g/kg b.w.)
	1	4.2	2.3	2.2	22.8	6.2	0.055	0.024
	2	4.2	2.6	2.4	23.2	5.6	0.045	0.010
	3	4.7	2.3	2.2	24.3	7.5	0.023	0.015
	Mean	4.38	2.40	2.28	23.45	6.42	0.0410	0.0163
	SD	0.31	0.15	0.09	0.79	0.96	0.0164	0.0067
	N	3	3	3	3	3	3	3

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TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Male		Day: 12 Relative to Start Date		Relative Organ Weights							
Group 2: 35 Units/kg		Heart (g/kg b.w.)	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Lungs (g/kg b.w.)	Lymph node (axillar) (g/kg b.w.)	Lymph node (cerv.) (g/kg b.w.)			
11		4.5	2.1	2.2	22.0	5.5	0.114	0.006			
12		4.3	2.3	2.3	25.1	5.5	0.039	0.023			
13		4.7	2.5	2.5	23.6	5.6	0.120	0.024			
Mean		4.53	2.31	2.34	23.59	5.51	0.0910	0.0175			
SD		0.20	0.16	0.12	1.56	0.07	0.0450	0.0103			
N		3	3	3	3	3	3	3			

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TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Relative Organ Weights						
		Heart (g/kg b.w.)	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Lungs (g/kg b.w.)	Lymph node (axillar) (g/kg b.w.)	Lymph node (cerv.) (g/kg b.w.)
Group 3: 110 Units/kg	17	4.0	2.3	2.3	22.2	6.2	0.023	0.004
	18	4.9	2.7	2.7	24.3	5.8	0.063	0.010
	19	3.9	2.4	2.3	25.4	5.4	0.061	0.024
	Mean	4.26	2.48	2.43	23.97	5.80	0.0491	0.0126
	SD	0.53	0.16	0.23	1.64	0.37	0.0230	0.0106
	N	3	3	3	3	3	3	3

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Relative Organ Weights						
		Heart (g/kg b.w.)	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Lungs (g/kg b.w.)	Lymph node (axillar) (g/kg b.w.)	Lymph node (cerv.) (g/kg b.w.)
Group 4: 350/225/ 200 Units/kg	23	3.6	2.2	2.3	22.6	5.4	0.064	0.028
	24	4.2	2.3	2.3	22.4	5.6	0.041	0.019
	25	4.0	2.3	2.5	19.9	5.3	0.117	0.023
	Mean	3.96	2.27	2.36	21.60	5.45	0.0741	0.0231
	SD	0.32	0.06	0.09	1.50	0.13	0.0389	0.0048
	N	3	3	3	3	3	3	3

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TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Male		Day: 12 Relative to Start Date		Relative Organ Weights - Individual Data				Monkey
Group 1: Control		Pituitary	Spleen	Thymus	Thyroid/Par. (left)	Thyroid/Par. (right)		
		(g/kg b.w.)	(g/kg b.w.)	(g/kg b.w.)	(g/kg b.w.)	(g/kg b.w.)		
	1	0.021	1.1	2.38	0.06	0.06		
	2	0.032	1.7	1.47	0.08	0.07		
	3	0.013	2.5	1.61	0.09	0.10		
	Mean	0.0221	1.76	1.822	0.075	0.078		
	SD	0.0096	0.71	0.488	0.018	0.020		
	N	3	3	3	3	3		

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TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Male Day: 12 Relative to Start Date

Group 2: 35 Units/kg	Pituitary (g/kg b.w.)	Spleen (g/kg b.w.)	Relative Organ Weights			
			Thymus (g/kg b.w.)	Thyroid/Par. (left) (g/kg b.w.)	Thyroid/Par. (right) (g/kg b.w.)	
11	0.023	1.3	1.79	0.03	0.05	
12	0.019	1.3	1.30	0.10	0.08	
13	0.016	1.5	1.05	0.08	0.06	
Mean	0.0192	1.38	1.379	0.066	0.065	
SD	0.0034	0.07	0.373	0.036	0.018	
N	3	3	3	3	3	

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TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Group 3: 110 Units/kg	Relative Organ Weights				
	Pituitary (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Thyroid/Par. (left) (g/kg b.w.)	Thyroid/Par. (right) (g/kg b.w.)
17	0.017	1.3	1.45	0.06	0.05
18	0.025	2.0	2.23	0.06	0.06
19	0.015	1.3	1.27	0.07	0.07
Mean	0.0187	1.57	1.649	0.059	0.059
SD	0.0053	0.38	0.512	0.005	0.007
N	3	3	3	3	3

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Relative Organ Weights				
		Pituitary (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Thyroid/Par. (left) (g/kg b.w.)	Thyroid/Par. (right) (g/kg b.w.)
Group 4: 350/225/ 200 Units/kg	23	0.017	2.4	0.78	0.05	0.05
	24	0.014	1.3	1.08	0.06	0.06
	25	0.019	1.8	0.73	0.03	0.04
	Mean	0.0164	1.85	0.862	0.048	0.051
	SD	0.0028	0.58	0.188	0.013	0.011
	N	3	3	3	3	3

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Female		Day: 12 Relative to Start Date		Relative Organ Weights						
Group 1: Control		Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Ovary (left) (g/kg b.w.)	Ovary (right) (g/kg b.w.)	Heart (g/kg b.w.)			
	6	0.15	0.08	29.1	0.04	0.03	4.0			
	7	0.17	0.14	31.8	0.38	0.05	4.2			
	8	0.12	0.10	32.5	0.03	0.03	4.2			
	Mean	0.144	0.104	31.14	0.148	0.036	4.11			
	SD	0.027	0.029	1.77	0.198	0.013	0.10			
	N	3	3	3	3	3	3			

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Female		Day: 12 Relative to Start Date		Relative Organ Weights					
Group 2: 35 Units/kg	Adren. Gland (left) (g/kg b.w.)		Adren. Gland (right) (g/kg b.w.)		Brain (g/kg b.w.)	Ovary (left) (g/kg b.w.)	Ovary (right) (g/kg b.w.)	Heart (g/kg b.w.)	
	14		0.14		0.09		28.2	0.01	4.0
	15		0.14		0.13		32.6	0.05	4.3
	16		0.11		0.13		31.5	0.05	4.0
	Mean		0.133		0.116		30.76	0.038	4.06
SD		0.016		0.022		2.30	0.021	0.19	
N		3		3		3	3	3	

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Female		Day: 12 Relative to Start Date		Relative Organ Weights								
Group 3: 110 Units/kg	Adren. Gland (left) (g/kg b.w.)		Adren. Gland (right) (g/kg b.w.)		Brain (g/kg b.w.)		Ovary (left) (g/kg b.w.)		Ovary (right) (g/kg b.w.)		Heart (g/kg b.w.)	
	20	0.12	0.09	30.3	0.27	0.04	4.3					
	21	0.12	0.10	30.3	0.05	0.05	3.9					
	22	0.15	0.12	29.5	0.03	0.04	4.0					
	Mean	0.130	0.104	30.05	0.114	0.043	4.04					
	SD	0.016	0.016	0.50	0.131	0.005	0.20					
	N	3	3	3	3	3	3					

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TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Female		Day: 12 Relative to Start Date		Relative Organ Weights					
Group 4: 350/225/ 200 Units/kg	Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Ovary (left) (g/kg b.w.)	Ovary (right) (g/kg b.w.)	Heart (g/kg b.w.)			
	28	0.11	0.08	30.2	0.04	4.4			
	29	0.15	0.15	34.9	0.06	4.8			
	30	0.10	0.08	29.0	0.03	3.2			
	Mean	0.118	0.104	31.35	0.044	0.039	4.12		
SD	0.028	0.040	3.10	0.016	0.011	0.79			
N	3	3	3	3	3	3			

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Female	Day: 12 Relative to Start Date	Relative Organ Weights - Individual Data					
		Relative Organ Weights					
Group 1: Control		Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Lungs (g/kg b.w.)	Lymph node (axillar) (g/kg b.w.)	Lymph node (cerv.) (g/kg b.w.)
		6	2.0	21.9	5.3	0.060	0.018
		7	2.4	25.8	6.0	0.076	0.015
		8	2.4	20.8	5.7	0.040	0.018
		Mean	2.29	22.81	5.65	0.0589	0.0169
	SD	0.21	0.18	2.62	0.31	0.0182	0.0020
	N	3	3	3	3	3	3

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Female		Day: 12 Relative to Start Date		Relative Organ Weights					
Group 2: 35 Units/kg		Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Lungs (g/kg b.w.)	Lymph node (axillar) (g/kg b.w.)	Lymph node (cerv.) (g/kg b.w.)		
		14	2.7	2.8	25.2	5.5	0.036	0.014	
		15	2.4	2.6	24.8	6.0	0.068	0.034	
		16	2.0	2.1	20.7	5.6	0.077	0.040	
		Mean	2.34	2.50	23.54	5.71	0.0604	0.0295	
	SD	0.37	0.32	2.49	0.26	0.0212	0.0136		
	N	3	3	3	3	3	3		

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Female		Day: 12 Relative to Start Date		Relative Organ Weights					
Group 3: 110 Units/kg		Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Lungs (g/kg b.w.)	Lymph node (axillar) (g/kg b.w.)	Lymph node (cerv.) (g/kg b.w.)		
		20	3.0	2.9	23.5	5.6	0.082	0.017	
		21	2.0	2.0	23.4	5.9	0.065	0.024	
		22	2.0	2.0	22.6	4.8	0.051	0.036	
		Mean	2.36	2.30	23.18	5.43	0.0660	0.0258	
SD	0.59	0.53	0.48	0.55	0.0156	0.0096			
N	3	3	3	3	3	3	3		

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Female Day: 12 Relative to Start Date		Relative Organ Weights						
		Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Lungs (g/kg b.w.)	Lymph node (axillar) (g/kg b.w.)	Lymph node (cerv.) (g/kg b.w.)	
Group 4: 350/225/ 200 Units/kg								
	28	2.4	2.5	31.8	5.6	0.041	0.017	
	29	2.4	2.6	23.8	6.3	0.043	0.035	
	30	1.8	1.8	17.7	4.6	0.009	0.029	
Mean SD N								
		2.20	2.28	24.41	5.48	0.0308	0.0269	
		0.38	0.45	7.07	0.87	0.0193	0.0094	
	3	3	3	3	3	3	3	

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Female	Day: 12 Relative to Start Date	Relative Organ Weights - Individual Data					Monkey
		Pituitary (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Thyroid/Par. (left) (g/kg b.w.)	Thyroid/Par. (right) (g/kg b.w.)	
Group 1: Control							Uterus (g/kg b.w.)
	6	0.013	1.1	1.21	0.08	0.08	0.35
	7	0.009	1.4	1.32	0.06	0.06	0.15
	8	0.022	1.8	1.60	0.08	0.06	0.09
Mean SD N		0.0148	1.43	1.377	0.072	0.068	0.199
		0.0066	0.30	0.200	0.011	0.011	0.137
		3	3	3	3	3	3

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Female		Day: 12 Relative to Start Date		Relative Organ Weights					
Group 2: 35 Units/kg	Pituitary (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Thyroid/Par. (left) (g/kg b.w.)	Thyroid/Par. (right) (g/kg b.w.)	Uterus (g/kg b.w.)			
	14	0.016	0.9	1.18	0.10	0.10			
	15	0.021	1.3	2.65	0.05	0.07			
	16	0.020	1.2	2.02	0.08	0.08			
Mean	0.0193	1.13	1.953	0.076	0.084	0.236			
SD	0.0026	0.20	0.738	0.028	0.019	0.157			
N	3	3	3	3	3	3			

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Female	Day: 12 Relative to Start Date	Relative Organ Weights - Individual Data					Monkey
		Pituitary (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Thyroid/Par. (left) (g/kg b.w.)	Thyroid/Par. (right) (g/kg b.w.)	
Group 3: 110 Units/kg							Uterus (g/kg b.w.)
	20	0.018	1.9	1.67	0.06	0.05	0.17
	21	0.019	1.3	1.03	0.05	0.04	0.33
	22	0.015	1.1	1.43	0.07	0.06	0.20
Mean SD N		0.0174	1.46	1.379	0.060	0.049	0.234
		0.0018	0.40	0.322	0.010	0.007	0.084
		3	3	3	3	3	3

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Female	Day: 12 Relative to Start Date	Relative Organ Weights - Individual Data					Monkey
		Pituitary (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Thyroid/Par. (left) (g/kg b.w.)	Thyroid/Par. (right) (g/kg b.w.)	
Group 4: 350/225/ 200 Units/kg							
	28	0.010	1.3	1.19	0.07	0.08	0.20
	29	0.013	1.3	0.69	0.07	0.05	0.20
	30	0.010	1.2	0.50	0.07	0.06	0.20
Mean SD N		0.0108	1.27	0.792	0.071	0.063	0.200
		0.0015	0.07	0.357	0.001	0.013	0.005
		3	3	3	3	3	3

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Male		Day: 26 Relative to Start Date		Relative Organ Weights				Monkey			
Group 1: Control		Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Relative Organ Weights		Epididymis (left) (g/kg b.w.)	Epididymis (right) (g/kg b.w.)	Testis (left) (g/kg b.w.)	Testis (right) (g/kg b.w.)	
4		0.13	0.09	27.4			0.18	0.16	0.3	0.2	
5		0.11	0.08	30.7			0.10	0.13	0.1	0.1	
Mean		0.120	0.087	29.06			0.144	0.144	0.20	0.16	
SD		-	-	-			-	-	-	-	
N		2	2	2			2	2	2	2	

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TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Male		Day: 26 Relative to Start Date		Relative Organ Weights					
Group 4: 350/225/ 200 Units/kg		Adren. Gland (left) (g/kg b.w.)	Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Epididymis (left) (g/kg b.w.)	Epididymis (right) (g/kg b.w.)	Testis (left) (g/kg b.w.)	Testis (right) (g/kg b.w.)	
33		0.08	0.07	27.5	0.14	0.14	0.2	0.2	
34		0.13	0.11	29.4	0.11	0.10	0.2	0.2	
Mean		0.105	0.088	28.49	0.127	0.117	0.17	0.19	
SD		-	-	-	-	-	-	-	
N		2	2	2	2	2	2	2	

TABLE 13-2
Relative Organ Weights - Individual Data
Monkey

Sex: Male Day: 26 Relative to Start Date							
Group 1: Control	Relative Organ Weights						
	Heart (g/kg b.w.)	Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Lungs (g/kg b.w.)	Lymph node (axillar) (g/kg b.w.)	Lymph node (cerv.) (g/kg b.w.)
4	4.0	2.1	2.3	28.7	5.7	0.058	0.023
5	4.4	2.2	2.4	23.0	5.6	0.024	0.017
Mean	4.18	2.13	2.36	25.87	5.62	0.0412	0.0204
SD	-	-	-	-	-	-	-
N	2	2	2	2	2	2	2

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TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Male		Day: 26 Relative to Start Date	Relative Organ Weights					
Group 4: 350/225/ 200 Units/kg	Heart (g/kg b.w.)		Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Lungs (g/kg b.w.)	Lymph node (axillar) (g/kg b.w.)	Lymph node (cerv.) (g/kg b.w.)
33	4.3		1.8	1.8	23.0	5.3	0.056	0.024
34	4.5		2.0	2.3	22.4	5.5	0.053	0.028
Mean	4.39		1.94	2.05	22.74	5.41	0.0549	0.0260
SD	-		-	-	-	-	-	-
N	2		2	2	2	2	2	2

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TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Male		Day: 26 Relative to Start Date		Relative Organ Weights - Individual Data			Monkey
Group 1: Control		Pituitary (g/kg b.w.)	Spleen (g/kg b.w.)	Relative Organ Weights			
				Thymus (g/kg b.w.)	Thyroid/Par. (left) (g/kg b.w.)	Thyroid/Par. (right) (g/kg b.w.)	
4	0.016	1.0	1.08	0.05	0.04		
5	0.021	1.1	1.76	0.05	0.05		
Mean	0.0187	1.07	1.423	0.049	0.042		
SD	-	-	-	-	-		
N	2	2	2	2	2	2	

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Male	Day: 26 Relative to Start Date	Relative Organ Weights				
		Pituitary (g/kg b.w.)	Spleen (g/kg b.w.)	Thymus (g/kg b.w.)	Thyroid/Par. (left) (g/kg b.w.)	Thyroid/Par. (right) (g/kg b.w.)
Group 4: 350/225/ 200 Units/kg	33	0.017	1.9	1.24	0.06	0.06
	34	0.014	2.3	1.95	0.05	0.06
Mean		0.0155	2.07	1.593	0.057	0.060
SD		-	-	-	-	-
N		2	2	2	2	2

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Female		Day: 26 Relative to Start Date		Relative Organ Weights					
Group 1: Control	Adren. Gland (left) (g/kg b.w.)		Adren. Gland (right) (g/kg b.w.)		Brain (g/kg b.w.)		Ovary (left) (g/kg b.w.)	Ovary (right) (g/kg b.w.)	Heart (g/kg b.w.)
	9		0.07		0.09		29.2		0.05
	10		0.15		0.11		31.9		0.03
Mean		0.109		0.098		30.55		0.041	0.043
SD		-		-		-		-	-
N		2		2		2		2	2

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Female		Day: 26 Relative to Start Date		Relative Organ Weights				
Group 4: 350/225/ 200 Units/kg	Adren. Gland (left) (g/kg b.w.)		Adren. Gland (right) (g/kg b.w.)	Brain (g/kg b.w.)	Ovary (left) (g/kg b.w.)	Ovary (right) (g/kg b.w.)	Heart (g/kg b.w.)	
31	0.11		0.08	29.0	0.06	0.05	4.0	
32	0.12		0.10	29.7	0.03	0.04	4.4	
Mean	0.115		0.093	29.36	0.043	0.045	4.16	
SD	-		-	-	-	-	-	
N	2		2	2	2	2	2	

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TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Female		Day: 26 Relative to Start Date	Relative Organ Weights - Individual Data				Monkey
Group 1: Control			Relative Organ Weights				
			Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Lungs (g/kg b.w.)	
	9		2.0	2.0	27.0	4.9	Lymph node (axillar) (g/kg b.w.)
	10		2.2	2.2	26.5	6.5	Lymph node (cerv.) (g/kg b.w.)
Mean SD N	2.07		2.09	26.77	5.68	0.027 0.019 0.0230	
	-		-	-	-	-	
	2		2	2	2	2	2

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Female	Day: 26 Relative to Start Date	Relative Organ Weights					
		Kidney (left) (g/kg b.w.)	Kidney (right) (g/kg b.w.)	Liver (g/kg b.w.)	Lungs (g/kg b.w.)	Lymph node (axillar) (g/kg b.w.)	Lymph node (cerv.) (g/kg b.w.)
Group 4: 350/225/ 200 Units/kg	31	2.4	2.3	27.2	6.2	0.059	0.030
	32	2.3	2.3	30.8	7.0	0.044	0.013
	Mean	2.34	2.29	29.01	6.60	0.0516	0.0213
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Female		Day: 26 Relative to Start Date	Relative Organ Weights - Individual Data				Monkey
Group 1: Control		Pituitary (g/kg b.w.)	Spleen (g/kg b.w.)	Relative Organ Weights			Uterus (g/kg b.w.)
				Thymus (g/kg b.w.)	Thyroid/Par. (left) (g/kg b.w.)	Thyroid/Par. (right) (g/kg b.w.)	
9	0.019	1.4	1.63	0.06	0.09	0.36	
10	0.016	1.6	2.34	0.05	0.05	0.40	
Mean	0.0175	1.48	1.984	0.055	0.068	0.382	
SD	-	-	-	-	-	-	-
N	2	2	2	2	2	2	2

Allogenic APOSEC™

TABLE 13-2 Relative Organ Weights - Individual Data Monkey

Sex: Female		Day: 26 Relative to Start Date	Relative Organ Weights - Individual Data				Monkey
Group 4: 350/225/ 200 Units/kg		Pituitary (g/kg b.w.)	Spleen (g/kg b.w.)	Relative Organ Weights			Uterus (g/kg b.w.)
				Thymus (g/kg b.w.)	Thyroid/Par. (left) (g/kg b.w.)	Thyroid/Par. (right) (g/kg b.w.)	
31	0.023	1.4	2.15	0.07	0.08	0.59	
32	0.025	1.5	0.99	0.06	0.06	0.39	
Mean	0.0237	1.42	1.572	0.067	0.072	0.489	
SD	-	-	-	-	-	-	-
N	2	2	2	2	2	2	2

Allogenic APOSEC™

TABLE 14-1 Absolute Organ Weights - Summary Monkey

Day: 12 Relative to Start Date		Absolute Organ Weights							
Sex: Male		Absolute Organ Weights							
		Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Epididymis (left) (g)	Epididymis (right) (g)	Testis (left) (g)	Testis (right) (g)	
Group 1: Control	Mean	[a] 0.263	[a] 0.247	[a] 70.47	[a] 0.303	[a] 0.303	[a] 0.60	[a] 0.63	
	SD	0.051	0.021	8.36	0.076	0.093	0.10	0.12	
	N	3	3	3	3	3	3	3	
		-	-	-	-	-	-	-	
Group 2: 35 Units/kg	Mean	0.237	0.193	69.57	0.327	0.290	0.47	0.40*	
	SD	0.023	0.015	4.52	0.090	0.040	0.06	0.10	
	N	3	3	3	3	3	3	3	
	%Diff	-10.1	-21.6	-1.3	7.7	-4.4	-22.2	-36.8	
Group 3: 110 Units/kg	Mean	0.277	0.220	67.83	0.307	0.317	0.40*	0.47	
	SD	0.032	0.053	0.59	0.111	0.071	0.10	0.06	
	N	3	3	3	3	3	3	3	
	%Diff	5.1	-10.8	-3.7	1.1	4.4	-33.3	-26.3	
Group 4: 350/225/ 200 Units/kg	Mean	0.303	0.270	71.63	0.243	0.213	0.30**	0.30**	
	SD	0.055	0.035	7.28	0.045	0.025	0.00	0.10	
	N	3	3	3	3	3	3	3	
	%Diff	15.2	9.5	1.7	-19.8	-29.7	-50.0	-52.6	

[a] - Anova & Dunnett: * = $p \leq 0.05$; ** = $p \leq 0.01$

Allogenic APOSEC™

TABLE 14-1 Absolute Organ Weights - Summary Monkey

Day: 12 Relative to Start Date		Absolute Organ Weights						
Sex: Male		Heart (g)	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Lungs (g)	Lymph node (axillar) (g)	Lymph node (cerv.) (g)
Group 1: Control		[a]	[a]	[a]	[a]	[a]	[a]	[a]
	Mean	10.37	5.67	5.40	55.47	15.17	0.0980	0.0390
	SD	0.68	0.32	0.26	1.96	2.16	0.0427	0.0180
	N	3	3	3	3	3	3	3
Group 2: 35 Units/kg		-	-	-	-	-	-	-
	Mean	10.40	5.30	5.37	54.30	12.67	0.2067	0.0403
	SD	0.00	0.36	0.25	5.24	0.40	0.0976	0.0238
	N	3	3	3	3	3	3	3
Group 3: 110 Units/kg		0.3	-6.5	-0.6	-2.1	-16.5	110.9	3.4
	%Diff							
	Mean	9.80	5.70	5.60	55.13	13.33	0.1130	0.0290
	SD	1.23	0.36	0.53	3.78	0.85	0.0529	0.0243
Group 4: 350/225/ 200 Units/kg		3	3	3	3	3	3	3
	%Diff	-5.5	0.6	3.7	-0.6	-12.1	15.3	-25.6
	Mean	9.10	5.23	5.43	49.60	12.53	0.1730	0.0533
	SD	0.72	0.32	0.45	2.13	0.25	0.0976	0.0120
	N	3	3	3	3	3	3	3
	%Diff	-12.2	-7.6	0.6	-10.6	-17.4	76.5	36.8

[a] - Anova & Dunnett

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TABLE 14-1 Absolute Organ Weights - Summary Monkey

Day: 12 Relative to Start Date		Absolute Organ Weights				
Sex: Male		Pituitary	Spleen	Thymus	Thyroid/Par. (left)	Thyroid/Par. (right)
		(g)	(g)	(g)	(g)	(g)
		[a]	[a1]	[a]	[a]	[a]
Group 1: Control	Mean	0.0523	4.13	4.350	0.177	0.183
	SD	0.0220	1.53	1.395	0.035	0.042
	N	3	3	3	3	3
Group 2: 35 Units/kg	Mean	0.0443	3.17	3.180	0.153	0.150
	SD	0.0086	0.06	0.897	0.086	0.046
	N	3	3	3	3	3
Group 3: 110 Units/kg	%Diff	-15.3	-23.4	-26.9	-13.2	-18.2
	Mean	0.0430	3.60	3.793	0.137	0.137
	SD	0.0123	0.87	1.177	0.012	0.015
Group 4: 350/225/ 200 Units/kg	N	3	3	3	3	3
	%Diff	-17.8	-12.9	-12.8	-22.6	-25.5
	Mean	0.0380	4.27	1.970	0.110	0.117
	SD	0.0080	1.40	0.347	0.026	0.021
	N	3	3	3	3	3
	%Diff	-27.4	3.2	-54.7	-37.7	-36.4

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Rank)

Allogenic APOSEC™

TABLE 14-1 Absolute Organ Weights - Summary Monkey

Day: 26 Relative to Start Date		Absolute Organ Weights							
Sex: Male		Absolute Organ Weights							
		Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Epididymis (left) (g)	Epididymis (right) (g)	Testis (left) (g)	Testis (right) (g)	
		[a]	[a]	[a]	[a]	[a]	[a]	[a]	
Group 1: Control	Mean	0.270n	0.195n	65.30n	0.325n	0.325n	0.45n	0.35n	
	SD	-	-	-	-	-	-	-	
	N	2	2	2	2	2	2	2	
Group 4: 350/225/ 200 Units/kg	Mean	0.245n	0.205n	66.90n	0.300n	0.275n	0.40n	0.45n	
	SD	-	-	-	-	-	-	-	
	N	2	2	2	2	2	2	2	
%Diff		-9.3	5.1	2.5	-7.7	-15.4	-11.1	28.6	

[a] - Anova & Dunnett: n - Inappropriate for statistics

Allogenic APOSEC™

TABLE 14-1 Absolute Organ Weights - Summary Monkey

Day: 26 Relative to Start Date		Absolute Organ Weights						
Sex: Male		Heart (g)	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Lungs (g)	Lymph node (axillar) (g)	Lymph node (cerv.) (g)
Group 1: Control	Mean	9.40n	[a]	[a]	[a]	[a]	[a]	[a]
	SD	-	4.80n	5.30n	58.35n	12.65n	0.0935n	0.0460n
	N	2	2	2	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	10.30n	4.55n	4.80n	53.45n	12.70n	0.1290n	0.0610n
	SD	-	-	-	-	-	-	-
	N	2	2	2	2	2	2	2
%Diff		9.6	-5.2	-9.4	-8.4	0.4	38.0	32.6

[a] - Anova & Dunnett: n - Inappropriate for statistics

Allogenic APOSEC™

TABLE 14-1 Absolute Organ Weights - Summary Monkey

Day: 26 Relative to Start Date		Absolute Organ Weights				
Sex: Male		Pituitary (g)	Spleen (g)	Thymus (g)	Thyroid/Par. (left) (g)	Thyroid/Par. (right) (g)
		[a]	[a]	[a]	[a]	[a]
Group 1: Control	Mean	0.0420n	2.40n	3.185n	0.110n	0.095n
	SD	-	-	-	-	-
	N	2	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	0.0365n	4.85n	3.725n	0.135n	0.140n
	SD	-	-	-	-	-
	N	2	2	2	2	2
%Diff		-13.1	102.1	17.0	22.7	47.4

[a] - Anova & Dunnett: n - Inappropriate for statistics

Allogenic APOSEC™

TABLE 14-1 Absolute Organ Weights - Summary Monkey

Day: 12 Relative to Start Date		Absolute Organ Weights					
Sex: Female		Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Ovary (left) (g)	Ovary (right) (g)	Heart (g)
		[a]	[a]	[a]	[a1]	[a]	[a]
Group 1: Control	Mean	0.303	0.220	65.37	0.323	0.077	8.63
	SD	0.070	0.070	4.36	0.439	0.031	0.49
	N	3	3	3	3	3	3
		-	-	-	-	-	-
Group 2: 35 Units/kg	Mean	0.283	0.247	65.53	0.080	0.073	8.67
	SD	0.038	0.040	3.29	0.044	0.038	0.35
	N	3	3	3	3	3	3
	%Diff	-6.6	12.1	0.3	-75.3	-4.3	0.4
Group 3: 110 Units/kg	Mean	0.280	0.223	65.13	0.257	0.093	8.77
	SD	0.026	0.025	4.14	0.307	0.012	0.91
	N	3	3	3	3	3	3
	%Diff	-7.7	1.5	-0.4	-20.6	21.7	1.5
Group 4: 350/225/ 200 Units/kg	Mean	0.243	0.213	64.67	0.090	0.080	8.50
	SD	0.051	0.075	4.56	0.030	0.020	1.48
	N	3	3	3	3	3	3
	%Diff	-19.8	-3.0	-1.1	-72.2	4.3	-1.5

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Log)

Allogenic APOSEC™							
TABLE 14-1			Absolute Organ Weights - Summary		Monkey		
Day: 12 Relative to Start Date							
Sex: Female		Absolute Organ Weights					
		Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Lungs (g)	Lymph node (axillar) (g)	Lymph node (cerv.) (g)
Group 1: Control		[a]	[a]	[a]	[a]	[a]	[a]
	Mean	4.80	5.07	48.07	11.87	0.1250	0.0353
	SD	0.50	0.55	7.78	1.07	0.0440	0.0031
	N	3	3	3	3	3	3
Group 2: 35 Units/kg		-	-	-	-	-	-
	Mean	5.00	5.33	50.27	12.17	0.1280	0.0623
	SD	0.90	0.80	6.18	0.40	0.0425	0.0278
	N	3	3	3	3	3	3
	%Diff	4.2	5.3	4.6	2.5	2.4	76.4
Group 3: 110 Units/kg		5.17	5.03	50.23	11.77	0.1440	0.0553
	Mean	1.59	1.44	3.37	1.47	0.0416	0.0186
	SD	3	3	3	3	3	3
	N	7.6	-0.7	4.5	-0.8	15.2	56.6
	%Diff						
Group 4: 350/225/200 Units/kg		4.53	4.70	50.47	11.30	0.0633	0.0553
	Mean	0.74	0.87	15.01	1.54	0.0393	0.0182
	SD	3	3	3	3	3	3
	N	-5.6	-7.2	5.0	-4.8	-49.3	56.6
	%Diff						

[a] - Anova & Dunnett

Allogenic APOSEC™

TABLE 14-1 Absolute Organ Weights - Summary Monkey

Day: 12 Relative to Start Date							
Sex: Female		Absolute Organ Weights					
		Pituitary	Spleen	Thymus	Thyroid/Par. (left)	Thyroid/Par. (right)	Uterus
		(g)	(g)	(g)	(g)	(g)	(g)
		[a]	[a]	[a]	[a1]	[a]	[a2]
Group 1: Control	Mean	0.0307	3.00	2.883	0.150	0.143	0.420
	SD	0.0122	0.56	0.325	0.020	0.025	0.288
	N	3	3	3	3	3	3
		-	-	-	-	-	-
Group 2: 35 Units/kg	Mean	0.0410	2.40	4.140	0.163	0.180	0.500
	SD	0.0046	0.36	1.488	0.065	0.046	0.325
	N	3	3	3	3	3	3
	%Diff	33.7	-20.0	43.6	8.9	25.6	19.0
Group 3: 110 Units/kg	Mean	0.0377	3.20	3.007	0.130	0.107	0.503
	SD	0.0051	1.06	0.835	0.020	0.015	0.163
	N	3	3	3	3	3	3
	%Diff	22.8	6.7	4.3	-13.3	-25.6	19.8
Group 4: 350/225/200 Units/kg	Mean	0.0223	2.63	1.640	0.147	0.130	0.413
	SD	0.0025	0.15	0.762	0.006	0.030	0.015
	N	3	3	3	3	3	3
	%Diff	-27.2	-12.2	-43.1	-2.2	-9.3	-1.6

[a] - Anova & Dunnett
[a1] - Anova & Dunnett(Log)
[a2] - Anova & Dunnett(Rank)

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TABLE 14-1 Absolute Organ Weights - Summary Monkey

Day: 26 Relative to Start Date							
Sex: Female		Absolute Organ Weights					
		Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Ovary (left) (g)	Ovary (right) (g)	Heart (g)
Group 1: Control	Mean	0.240n	0.215n	67.20n	0.090n	0.095n	9.25n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	0.260n	0.210n	66.10n	0.095n	0.100n	9.40n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
	%Diff	8.3	-2.3	-1.6	5.6	5.3	1.6

[a] - Anova & Dunnett: n - Inappropriate for statistics

Allogenic APOSEC™							
TABLE 14-1			Absolute Organ Weights - Summary		Monkey		
Day: 26 Relative to Start Date							
Sex: Female			Absolute Organ Weights				
			Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Lungs (g)	Lymph node (axillar) (g)
Group 1: Control	Mean	[a]	[a]	[a]	[a]	[a]	[a]
	SD	4.55n	4.60n	58.90n	12.50n	0.1240n	0.0505n
	N	-	-	-	-	-	-
Group 4: 350/225/200 Units/kg		2	2	2	2	2	2
	Mean	5.25n	5.15n	65.55n	14.90n	0.1150n	0.0465n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
	%Diff	15.4	12.0	11.3	19.2	-7.3	-7.9

[a] - Anova & Dunnett: n - Inappropriate for statistics

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TABLE 14-1 Absolute Organ Weights - Summary Monkey

Day: 26 Relative to Start Date		Absolute Organ Weights					
Sex: Female		Pituitary (g)	Spleen (g)	Thymus (g)	Thyroid/Par. (left) (g)	Thyroid/Par. (right) (g)	Uterus (g)
		[a]	[a]	[a]	[a]	[a]	[a]
Group 1: Control	Mean	0.0385n	3.25n	4.365n	0.120n	0.150n	0.840n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
Group 4: 350/225/ 200 Units/kg	Mean	0.0535n	3.20n	3.450n	0.150n	0.160n	1.085n
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2
%Diff		39.0	-1.5	-21.0	25.0	6.7	29.2

[a] - Anova & Dunnett: n - Inappropriate for statistics

Allogenic APOSEC™

TABLE 14-1 Absolute Organ Weights - Summary Monkey

Comments and Markers

Page	Day	Group	Sex	Measurement	Marker	Comment
12	12	2	Male	Testis - Right	*	Anova & Dunnett: * = $p \leq 0.05$
12	12	3	Male	Testis - Left	*	Anova & Dunnett: * = $p \leq 0.05$
12	12	4	Male	Testis - Left	**	Anova & Dunnett: ** = $p \leq 0.01$
12	12	4	Male	Testis - Right	**	Anova & Dunnett: ** = $p \leq 0.01$
26	26	1	Male	Adrenal Wt left	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Adrenal Wt right	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Brain Weight	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Epididymis - Left	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Epididymis - Right	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Testis - Left	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Testis - Right	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Adrenal Wt left	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Adrenal Wt right	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Brain Weight	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Epididymis - Left	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Epididymis - Right	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Testis - Left	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Testis - Right	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Heart Weight	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Kidney Wt left	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Kidney Wt right	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Liver	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Lungs Weight	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Lymph node (axillar)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Lymph node (cerv.)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Heart Weight	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Kidney Wt left	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Kidney Wt right	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Liver	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Lungs Weight	n	Anova & Dunnett: n - Inappropriate for statistics

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TABLE 14-1 Absolute Organ Weights - Summary Monkey

Comments and Markers

<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker</u>	<u>Comment</u>
26	26	4	Male	Lymph node (axillar)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Lymph node (cerv.)	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Pituitary	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Spleen Weight	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Thymus Weight	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Thyroid/Par. Left	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	1	Male	Thyroid/Par. Right	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Pituitary	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Spleen Weight	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Thymus Weight	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Thyroid/Par. Left	n	Anova & Dunnett: n - Inappropriate for statistics
26	26	4	Male	Thyroid/Par. Right	n	Anova & Dunnett: n - Inappropriate for statistics

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TABLE 14-1 Absolute Organ Weights - Summary Monkey

Comments and Markers

<u>Page</u>	<u>Day</u>	<u>Group</u>	<u>Sex</u>	<u>Measurement</u>	<u>Marker</u>	<u>Comment</u>
26		1	Female	Adrenal Wt left	n	Anova & Dunnett: n - Inappropriate for statistics
26		1	Female	Adrenal Wt right	n	Anova & Dunnett: n - Inappropriate for statistics
26		1	Female	Brain Weight	n	Anova & Dunnett: n - Inappropriate for statistics
26		1	Female	Ovary Weight - Left	n	Anova & Dunnett: n - Inappropriate for statistics
26		1	Female	Ovary Weight - Right	n	Anova & Dunnett: n - Inappropriate for statistics
26		1	Female	Heart Weight	n	Anova & Dunnett: n - Inappropriate for statistics
26		4	Female	Adrenal Wt left	n	Anova & Dunnett: n - Inappropriate for statistics
26		4	Female	Adrenal Wt right	n	Anova & Dunnett: n - Inappropriate for statistics
26		4	Female	Brain Weight	n	Anova & Dunnett: n - Inappropriate for statistics
26		4	Female	Ovary Weight - Left	n	Anova & Dunnett: n - Inappropriate for statistics
26		4	Female	Ovary Weight - Right	n	Anova & Dunnett: n - Inappropriate for statistics
26		4	Female	Heart Weight	n	Anova & Dunnett: n - Inappropriate for statistics
26		1	Female	Kidney Wt left	n	Anova & Dunnett: n - Inappropriate for statistics
26		1	Female	Kidney Wt right	n	Anova & Dunnett: n - Inappropriate for statistics
26		1	Female	Liver	n	Anova & Dunnett: n - Inappropriate for statistics
26		1	Female	Lungs Weight	n	Anova & Dunnett: n - Inappropriate for statistics
26		1	Female	Lymph node (axillar)	n	Anova & Dunnett: n - Inappropriate for statistics
26		1	Female	Lymph node (cerv.)	n	Anova & Dunnett: n - Inappropriate for statistics
26		4	Female	Kidney Wt left	n	Anova & Dunnett: n - Inappropriate for statistics
26		4	Female	Kidney Wt right	n	Anova & Dunnett: n - Inappropriate for statistics
26		4	Female	Liver	n	Anova & Dunnett: n - Inappropriate for statistics
26		4	Female	Lungs Weight	n	Anova & Dunnett: n - Inappropriate for statistics
26		4	Female	Lymph node (axillar)	n	Anova & Dunnett: n - Inappropriate for statistics
26		4	Female	Lymph node (cerv.)	n	Anova & Dunnett: n - Inappropriate for statistics
26		1	Female	Pituitary	n	Anova & Dunnett: n - Inappropriate for statistics
26		1	Female	Spleen Weight	n	Anova & Dunnett: n - Inappropriate for statistics
26		1	Female	Thymus Weight	n	Anova & Dunnett: n - Inappropriate for statistics
26		1	Female	Thyroid/Par. Left	n	Anova & Dunnett: n - Inappropriate for statistics
26		1	Female	Thyroid/Par. Right	n	Anova & Dunnett: n - Inappropriate for statistics
26		1	Female	Uterus	n	Anova & Dunnett: n - Inappropriate for statistics

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TABLE 14-1 Absolute Organ Weights - Summary Monkey

Comments and Markers

Page	Day	Group	Sex	Measurement	Marker	Comment
	26	4	Female	Pituitary	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Spleen Weight	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Thymus Weight	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Thyroid/Par. Left	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Thyroid/Par. Right	n	Anova & Dunnett: n - Inappropriate for statistics
	26	4	Female	Uterus	n	Anova & Dunnett: n - Inappropriate for statistics

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Sex: Male		Day: 1 Relative to Start Date		TABLE 14-2		Absolute Organ Weights - Individual Data		Monkey	
Group 4: 350/225/ 200 Units/kg		Absolute Organ Weights							
		Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Epididymis (left) (g)	Epididymis (right) (g)	Testis (left) (g)	Testis (right) (g)	
26	0.19	0.17		66.7	0.27	0.27	0.3	0.3	
27	0.26	0.21		70.5	0.18	0.21	0.2	0.2	
Mean	0.225	0.190		68.60	0.225	0.240	0.25	0.25	
SD	-	-		-	-	-	-	-	
N	2	2		2	2	2	2	2	

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Male	Day: 1 Relative to Start Date	Absolute Organ Weights						
		Heart (g)	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Lungs (g)	Lymph node (axillar) (g)	Lymph node (cerv.) (g)
Group 4: 350/225/ 200 Units/kg	26	9.7	5.2	5.2	57.8	18.5	0.110	0.024
	27	8.0	5.7	5.6	52.5	16.1	0.113	0.059
	Mean	8.85	5.45	5.40	55.15	17.30	0.1115	0.0415
	SD	-	-	-	-	-	-	-
	N	2	2	2	2	2	2	2

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Male Day: 1 Relative to Start Date		Absolute Organ Weights				
Group 4: 350/225/ 200 Units/kg		Pituitary	Spleen	Thymus	Thyroid/Par. (left) (g)	Thyroid/Par. (right) (g)
		(g)	(g)	(g)		
26		0.028	3.7	4.73	0.15	0.15
27		0.028	3.0	4.33	0.12	0.12
Mean		0.0280	3.35	4.530	0.135	0.135
SD		-	-	-	-	-
N		2	2	2	2	2

TABLE 14-2 Absolute Organ Weights - Individual Data

Sex: Male Day: 12 Relative to Start Date							
Group 1: Control	Absolute Organ Weights						
	Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Epididymis (left) (g)	Epididymis (right) (g)	Testis (left) (g)	Testis (right) (g)
1	0.22	0.24	66.2	0.39	0.41	0.5	0.5
2	0.25	0.23	80.1	0.27	0.26	0.6	0.7
3	0.32	0.27	65.1	0.25	0.24	0.7	0.7
Mean	0.263	0.247	70.47	0.303	0.303	0.60	0.63
SD	0.051	0.021	8.36	0.076	0.093	0.10	0.12
N	3	3	3	3	3	3	3

Allogenic APOSEC™

TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Absolute Organ Weights							
		Absolute Organ Weights							
Group 2: 35 Units/kg	Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Epididymis (left) (g)	Epididymis (right) (g)	Testis (left) (g)	Testis (right) (g)		
	11	0.25	0.19	73.8	0.43	0.33	0.5	0.5	0.5
	12	0.25	0.18	64.8	0.28	0.29	0.4	0.3	0.3
	13	0.21	0.21	70.1	0.27	0.25	0.5	0.4	0.4
	Mean	0.237	0.193	69.57	0.327	0.290	0.47	0.40	0.40
	SD	0.023	0.015	4.52	0.090	0.040	0.06	0.10	0.10
	N	3	3	3	3	3	3	3	3

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TABLE 14-2 Absolute Organ Weights - Individual Data

Sex: Male Day: 12 Relative to Start Date							
Group 3: 110 Units/kg	Absolute Organ Weights						
	Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Epididymis (left) (g)	Epididymis (right) (g)	Testis (left) (g)	Testis (right) (g)
17	0.29	0.20	67.4	0.41	0.38	0.5	0.5
18	0.24	0.18	67.6	0.32	0.33	0.4	0.5
19	0.30	0.28	68.5	0.19	0.24	0.3	0.4
Mean	0.277	0.220	67.83	0.307	0.317	0.40	0.47
SD	0.032	0.053	0.59	0.111	0.071	0.10	0.06
N	3	3	3	3	3	3	3

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Absolute Organ Weights							
		Absolute Organ Weights							
Group 4: 350/225/ 200 Units/kg	Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Epididymis (left) (g)	Epididymis (right) (g)	Testis (left) (g)	Testis (right) (g)		
	23	0.25	0.25	72.9	0.20	0.19	0.3	0.2	
	24	0.30	0.25	63.8	0.24	0.21	0.3	0.3	
	25	0.36	0.31	78.2	0.29	0.24	0.3	0.4	
	Mean	0.303	0.270	71.63	0.243	0.213	0.30	0.30	
	SD	0.055	0.035	7.28	0.045	0.025	0.00	0.10	
	N	3	3	3	3	3	3	3	

Monkey

Sex: Male		Day: 12 Relative to Start Date		Absolute Organ Weights						
Group 1: Control		Heart (g)	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Lungs (g)	Lymph node (axillar) (g)	Lymph node (cerv.) (g)		
1		10.6	5.8	5.6	57.1	15.4	0.138	0.059		
2		9.6	5.9	5.5	53.3	12.9	0.103	0.024		
3		10.9	5.3	5.1	56.0	17.2	0.053	0.034		
Mean		10.37	5.67	5.40	55.47	15.17	0.0980	0.0390		
SD		0.68	0.32	0.26	1.96	2.16	0.0427	0.0180		
N		3	3	3	3	3	3	3		

Monkey

Sex: Male		Day: 12 Relative to Start Date		Absolute Organ Weights						
Group 2: 35 Units/kg	Heart	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Lungs (g)	Lymph node (axillar) (g)	Lymph node (cerv.) (g)			
11	10.4	4.9	5.1	50.6	12.6	0.262	0.013			
12	10.4	5.6	5.6	60.3	13.1	0.094	0.056			
13	10.4	5.4	5.4	52.0	12.3	0.264	0.052			
Mean	10.40	5.30	5.37	54.30	12.67	0.2067	0.0403			
SD	0.00	0.36	0.25	5.24	0.40	0.0976	0.0238			
N	3	3	3	3	3	3	3			

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Sex: Male			Day: 12 Relative to Start Date		TABLE 14-2			Absolute Organ Weights - Individual Data			Monkey		
Group 3: 110 Units/kg					Absolute Organ Weights								
	Heart (g)	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Lungs (g)	Lymph node (axillar) (g)	Lymph node (cerv.) (g)						
	17	9.3	5.4	5.4	51.0	14.2	0.052	0.009					
	18	11.2	6.1	6.2	56.0	13.3	0.146	0.022					
	19	8.9	5.6	5.2	58.4	12.5	0.141	0.056					
Mean	9.80	5.70	5.60	55.13	13.33	0.1130	0.0290						
SD	1.23	0.36	0.53	3.78	0.85	0.0529	0.0243						
N	3	3	3	3	3	3	3	3					

Allogenic APOSEC™

Sex: Male		Day: 12 Relative to Start Date		TABLE 14-2			Absolute Organ Weights - Individual Data			Monkey		
Group 4: 350/225/ 200 Units/kg		Heart (g)	Kidney (left) (g)	Kidney (right) (g)	Absolute Organ Weights			Lungs (g)	Lymph node (axillar) (g)	Lymph node (cerv.) (g)		
23		8.3	5.1	5.4	51.9		12.5	0.147		0.065		
24		9.3	5.0	5.0	49.2		12.3	0.091		0.041		
25		9.7	5.6	5.9	47.7		12.8	0.281		0.054		
Mean		9.10	5.23	5.43	49.60		12.53	0.1730		0.0533		
SD		0.72	0.32	0.45	2.13		0.25	0.0976		0.0120		
N		3	3	3	3		3	3		3		

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Absolute Organ Weights					
		Pituitary (g)	Spleen (g)	Thymus (g)	Thyroid/Par. (left) (g)	Thyroid/Par. (right) (g)	
Group 1: Control	1	0.053	2.8	5.95	0.14	0.15	
	2	0.074	3.8	3.39	0.18	0.17	
	3	0.030	5.8	3.71	0.21	0.23	
Mean SD N		0.0523 0.0220 3	4.13 1.53 3	4.350 1.395 3	0.177 0.035 3	0.183 0.042 3	

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Absolute Organ Weights				
		Pituitary (g)	Spleen (g)	Thymus (g)	Thyroid/Par. (left) (g)	Thyroid/Par. (right) (g)
Group 2: 35 Units/kg	11	0.052	3.1	4.11	0.06	0.11
	12	0.046	3.2	3.11	0.23	0.20
	13	0.035	3.2	2.32	0.17	0.14
	Mean	0.0443	3.17	3.180	0.153	0.150
	SD	0.0086	0.06	0.897	0.086	0.046
	N	3	3	3	3	3

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Absolute Organ Weights				
		Pituitary (g)	Spleen (g)	Thymus (g)	Thyroid/Par. (left) (g)	Thyroid/Par. (right) (g)
Group 3: 110 Units/kg	17	0.038	3.1	3.34	0.13	0.12
	18	0.057	4.6	5.13	0.13	0.14
	19	0.034	3.1	2.91	0.15	0.15
	Mean	0.0430	3.60	3.793	0.137	0.137
	SD	0.0123	0.87	1.177	0.012	0.015
	N	3	3	3	3	3

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Male	Day: 12 Relative to Start Date	Absolute Organ Weights				
		Pituitary (g)	Spleen (g)	Thymus (g)	Thyroid/Par. (left) (g)	Thyroid/Par. (right) (g)
Group 4: 350/225/ 200 Units/kg	23	0.038	5.6	1.79	0.12	0.11
	24	0.030	2.8	2.37	0.13	0.14
	25	0.046	4.4	1.75	0.08	0.10
	Mean	0.0380	4.27	1.970	0.110	0.117
	SD	0.0080	1.40	0.347	0.026	0.021
	N	3	3	3	3	3

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Female		Day: 12 Relative to Start Date		Absolute Organ Weights						
Group 1: Control		Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Ovary (left) (g)	Ovary (right) (g)	Heart (g)			
	6	0.31	0.17	61.2	0.09	0.07	8.4			
	7	0.37	0.30	69.9	0.83	0.11	9.2			
	8	0.23	0.19	65.0	0.05	0.05	8.3			
	Mean	0.303	0.220	65.37	0.323	0.077	8.63			
SD	0.070	0.070	4.36	0.439	0.031	0.49				
N	3	3	3	3	3	3	3			

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Female	Day: 12 Relative to Start Date	Absolute Organ Weights					Monkey
		Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Ovary (left) (g)	Ovary (right) (g)	
Group 2: 35 Units/kg							
	14	0.31	0.20	62.0	0.03	0.03	8.7
	15	0.30	0.27	68.5	0.10	0.10	9.0
	16	0.24	0.27	66.1	0.11	0.09	8.3
Mean SD N		0.283	0.247	65.53	0.080	0.073	8.67
		0.038	0.040	3.29	0.044	0.038	0.35
		3	3	3	3	3	3

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Female	Day: 12 Relative to Start Date	Absolute Organ Weights					
		Absolute Organ Weights					
Group 3: 110 Units/kg	Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Ovary (left) (g)	Ovary (right) (g)	Heart (g)	
	20	0.27	0.20	69.8	0.61	0.10	9.8
	21	0.26	0.22	63.7	0.10	0.10	8.1
	22	0.31	0.25	61.9	0.06	0.08	8.4
	Mean	0.280	0.223	65.13	0.257	0.093	8.77
	SD	0.026	0.025	4.14	0.307	0.012	0.91
	N	3	3	3	3	3	3

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Female		Day: 12 Relative to Start Date		Absolute Organ Weights				
Group 4: 350/225/ 200 Units/kg	Adren. Gland (left) (g)		Adren. Gland (right) (g)	Brain (g)	Ovary (left) (g)	Ovary (right) (g)	Heart (g)	
	28		0.23	0.17	63.5	0.09	0.08	9.2
	29		0.30	0.30	69.7	0.12	0.10	9.5
	30		0.20	0.17	60.8	0.06	0.06	6.8
	Mean		0.243	0.213	64.67	0.090	0.080	8.50
SD		0.051	0.075	4.56	0.030	0.020	1.48	
N		3	3	3	3	3	3	

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Female	Day: 12 Relative to Start Date	Absolute Organ Weights					
		Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Lungs (g)	Lymph node (axillar) (g)	Lymph node (cerv.) (g)
Group 1: Control	6	4.3	4.7	45.9	11.2	0.127	0.038
	7	5.3	5.7	56.7	13.1	0.168	0.032
	8	4.8	4.8	41.6	11.3	0.080	0.036
	Mean	4.80	5.07	48.07	11.87	0.1250	0.0353
	SD	0.50	0.55	7.78	1.07	0.0440	0.0031
	N	3	3	3	3	3	3

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Female	Day: 12 Relative to Start Date	Absolute Organ Weights					
		Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Lungs (g)	Lymph node (axillar) (g)	Lymph node (cerv.) (g)
Group 2: 35 Units/kg	14	5.9	6.1	55.4	12.1	0.080	0.031
	15	5.0	5.4	52.0	12.6	0.143	0.072
	16	4.1	4.5	43.4	11.8	0.161	0.084
	Mean	5.00	5.33	50.27	12.17	0.1280	0.0623
	SD	0.90	0.80	6.18	0.40	0.0425	0.0278
	N	3	3	3	3	3	3

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Female	Day: 12 Relative to Start Date	Absolute Organ Weights					
		Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Lungs (g)	Lymph node (axillar) (g)	Lymph node (cerv.) (g)
Group 3: 110 Units/kg	20	7.0	6.7	54.0	12.9	0.189	0.040
	21	4.3	4.2	49.2	12.3	0.136	0.050
	22	4.2	4.2	47.5	10.1	0.107	0.076
	Mean	5.17	5.03	50.23	11.77	0.1440	0.0553
	SD	1.59	1.44	3.37	1.47	0.0416	0.0186
	N	3	3	3	3	3	3

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Female	Day: 12 Relative to Start Date	Absolute Organ Weights					
		Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Lungs (g)	Lymph node (axillar) (g)	Lymph node (cerv.) (g)
Group 4: 350/225/ 200 Units/kg	28	5.1	5.3	66.7	11.7	0.086	0.035
	29	4.8	5.1	47.6	12.6	0.086	0.070
	30	3.7	3.7	37.1	9.6	0.018	0.061
	Mean	4.53	4.70	50.47	11.30	0.0633	0.0553
	SD	0.74	0.87	15.01	1.54	0.0393	0.0182
	N	3	3	3	3	3	3

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Female	Day: 12 Relative to Start Date	Absolute Organ Weights					
		Pituitary (g)	Spleen (g)	Thymus (g)	Thyroid/Par. (left) (g)	Thyroid/Par. (right) (g)	Uterus (g)
Group 1: Control	6	0.028	2.4	2.55	0.17	0.17	0.74
	7	0.020	3.1	2.90	0.13	0.14	0.34
	8	0.044	3.5	3.20	0.15	0.12	0.18
	Mean	0.0307	3.00	2.883	0.150	0.143	0.420
	SD	0.0122	0.56	0.325	0.020	0.025	0.288
	N	3	3	3	3	3	3

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Female	Day: 12 Relative to Start Date	Absolute Organ Weights					
		Pituitary (g)	Spleen (g)	Thymus (g)	Thyroid/Par. (left) (g)	Thyroid/Par. (right) (g)	Uterus (g)
Group 2: 35 Units/kg	14	0.036	2.0	2.60	0.23	0.23	0.26
	15	0.045	2.7	5.57	0.10	0.14	0.87
	16	0.042	2.5	4.25	0.16	0.17	0.37
	Mean	0.0410	2.40	4.140	0.163	0.180	0.500
	SD	0.0046	0.36	1.488	0.065	0.046	0.325
	N	3	3	3	3	3	3

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Female	Day: 12 Relative to Start Date	Absolute Organ Weights					Monkey
		Pituitary (g)	Spleen (g)	Thymus (g)	Thyroid/Par. (left) (g)	Thyroid/Par. (right) (g)	
Group 3: 110 Units/kg							Uterus (g)
	20	0.042	4.4	3.84	0.13	0.11	0.39
	21	0.039	2.8	2.17	0.11	0.09	0.69
	22	0.032	2.4	3.01	0.15	0.12	0.43
Mean SD N		0.0377	3.20	3.007	0.130	0.107	0.503
		0.0051	1.06	0.835	0.020	0.015	0.163
		3	3	3	3	3	3

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Female	Day: 12 Relative to Start Date	Absolute Organ Weights					
		Pituitary (g)	Spleen (g)	Thymus (g)	Thyroid/Par. (left) (g)	Thyroid/Par. (right) (g)	Uterus (g)
Group 4: 350/225/ 200 Units/kg	28	0.020	2.8	2.50	0.15	0.16	0.43
	29	0.025	2.6	1.37	0.14	0.10	0.40
	30	0.022	2.5	1.05	0.15	0.13	0.41
	Mean	0.0223	2.63	1.640	0.147	0.130	0.413
	SD	0.0025	0.15	0.762	0.006	0.030	0.015
	N	3	3	3	3	3	3

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Sex: Male			Day: 26 Relative to Start Date		TABLE 14-2		Absolute Organ Weights - Individual Data		Monkey	
Group 1: Control			Absolute Organ Weights							
			Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Epididymis (left) (g)	Epididymis (right) (g)	Testis (left) (g)	Testis (right) (g)	
4			0.29	0.21	63.0	0.42	0.36	0.6	0.4	
5			0.25	0.18	67.6	0.23	0.29	0.3	0.3	
Mean			0.270	0.195	65.30	0.325	0.325	0.45	0.35	
SD			-	-	-	-	-	-	-	
N			2	2	2	2	2	2	2	

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Male	Day: 26 Relative to Start Date	Absolute Organ Weights						
		Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Epididymis (left) (g)	Epididymis (right) (g)	Testis (left) (g)	Testis (right) (g)
Group 4: 350/225/ 200 Units/kg	33	0.20	0.16	66.1	0.34	0.33	0.4	0.5
	34	0.29	0.25	67.7	0.26	0.22	0.4	0.4
Mean		0.245	0.205	66.90	0.300	0.275	0.40	0.45
SD		-	-	-	-	-	-	-
N		2	2	2	2	2	2	2

Monkey

Sex: Male Day: 26 Relative to Start Date							
Group 1: Control	Absolute Organ Weights						
	Heart (g)	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Lungs (g)	Lymph node (axillar) (g)	Lymph node (cerv.) (g)
4	9.1	4.8	5.3	66.0	13.0	0.134	0.054
5	9.7	4.8	5.3	50.7	12.3	0.053	0.038
Mean	9.40	4.80	5.30	58.35	12.65	0.0935	0.0460
SD	-	-	-	-	-	-	-
N	2	2	2	2	2	2	2

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Male		Day: 26 Relative to Start Date		Absolute Organ Weights				
Group 4: 350/225/ 200 Units/kg	Heart (g)	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Lungs (g)	Lymph node (axillar) (g)	Lymph node (cerv.) (g)	
33	10.2	4.4	4.4	55.3	12.8	0.135	0.058	
34	10.4	4.7	5.2	51.6	12.6	0.123	0.064	
Mean	10.30	4.55	4.80	53.45	12.70	0.1290	0.0610	
SD	-	-	-	-	-	-	-	
N	2	2	2	2	2	2	2	

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Male		Day: 26 Relative to Start Date		Absolute Organ Weights				
Group 1: Control		Pituitary	Spleen	Thymus	Thyroid/Par. (left) (g)	Thyroid/Par. (right) (g)		
		(g)	(g)	(g)				
4		0.037	2.3	2.49	0.11	0.09		
5		0.047	2.5	3.88	0.11	0.10		
Mean		0.0420	2.40	3.185	0.110	0.095		
SD		-	-	-	-	-		
N		2	2	2	2	2		

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Male	Day: 26 Relative to Start Date	Absolute Organ Weights				
		Pituitary (g)	Spleen (g)	Thymus (g)	Thyroid/Par. (left) (g)	Thyroid/Par. (right) (g)
Group 4: 350/225/ 200 Units/kg	33	0.040	4.5	2.97	0.15	0.15
	34	0.033	5.2	4.48	0.12	0.13
Mean		0.0365	4.85	3.725	0.135	0.140
SD		-	-	-	-	-
N		2	2	2	2	2

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TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Female		Day: 26 Relative to Start Date		Absolute Organ Weights						
Group 1: Control		Adren. Gland (left) (g)	Adren. Gland (right) (g)	Brain (g)	Ovary (left) (g)	Ovary (right) (g)	Heart (g)			
9		0.16	0.19	64.3	0.11	0.12	8.8			
10		0.32	0.24	70.1	0.07	0.07	9.7			
Mean		0.240	0.215	67.20	0.090	0.095	9.25			
SD		-	-	-	-	-	-			
N		2	2	2	2	2	2			

Allogenic APOSEC™

TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Female		Day: 26 Relative to Start Date	Absolute Organ Weights				Monkey
Group 4: 350/225/ 200 Units/kg	Adren. Gland		Adren. Gland (right) (g)	Brain (g)	Ovary (left) (g)	Ovary (right) (g)	Heart (g)
	(left) (g)						
31	0.23		0.17	61.0	0.12	0.11	8.3
32	0.29		0.25	71.2	0.07	0.09	10.5
Mean	0.260		0.210	66.10	0.095	0.100	9.40
SD	-		-	-	-	-	-
N	2		2	2	2	2	2

TABLE 14-2 Absolute Organ Weights - Individual Data

Sex: Female		Day: 26 Relative to Start Date				
Group 1: Control	Absolute Organ Weights					
	Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Lungs (g)	Lymph node (axillar) (g)	Lymph node (cerv.) (g)
9	4.3	4.4	59.4	10.8	0.158	0.059
10	4.8	4.8	58.4	14.2	0.090	0.042
Mean	4.55	4.60	58.90	12.50	0.1240	0.0505
SD	-	-	-	-	-	-
N	2	2	2	2	2	2

Allogenic APOSEC™

TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Female	Day: 26 Relative to Start Date	Absolute Organ Weights					
		Kidney (left) (g)	Kidney (right) (g)	Liver (g)	Lungs (g)	Lymph node (axillar) (g)	Lymph node (cerv.) (g)
Group 4: 350/225/ 200 Units/kg	31	5.1	4.9	57.2	13.1	0.124	0.063
	32	5.4	5.4	73.9	16.7	0.106	0.030
	Mean	5.25	5.15	65.55	14.90	0.1150	0.0465
	SD	-	-	-	-	-	-
	N	2	2	2	2	2	2

Allogenic APOSEC™

TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Female		Day: 26 Relative to Start Date		Absolute Organ Weights					
Group 1: Control		Pituitary	Spleen	Thymus	Thyroid/Par. (left)	Thyroid/Par. (right)	Uterus		
		(g)	(g)	(g)	(g)	(g)	(g)		
9		0.042	3.0	3.59	0.14	0.19	0.80		
10		0.035	3.5	5.14	0.10	0.11	0.88		
Mean		0.0385	3.25	4.365	0.120	0.150	0.840		
SD		-	-	-	-	-	-		
N		2	2	2	2	2	2		

Allogenic APOSEC™

TABLE 14-2 Absolute Organ Weights - Individual Data Monkey

Sex: Female	Day: 26 Relative to Start Date	Absolute Organ Weights					Monkey
		Pituitary (g)	Spleen (g)	Thymus (g)	Thyroid/Par. (left) (g)	Thyroid/Par. (right) (g)	
Group 4: 350/225/ 200 Units/kg	31	0.048	2.9	4.52	0.15	0.17	1.23
	32	0.059	3.5	2.38	0.15	0.15	0.94
Mean		0.0535	3.20	3.450	0.150	0.160	1.085
SD		-	-	-	-	-	-
N		2	2	2	2	2	2

TABLE 15-1	Allogenic APOSEC™ Bone Marrow - Summary				Monkey
	Myeloids (in %)	Erythroids (in %)	Myeloid/Erythroid ratio	Chi ² -Test (p-value)	
	Males				
	Terminal sacrifice (test day 12)				
	Group 1: Control				
Mean:	69.33	30.67	2.343 : 1		
SD:	6.03	6.03	-	-	
Group 2: 35 U/kg					
Mean:	65.00	35.00	1.897 : 1		
SD:	5.22	5.22	-	ns	
Group 3: 110 U/kg					
Mean:	65.83	34.17	1.930 : 1		
SD:	0.76	0.76	-	ns	
Group 4: 350/225/200 U/kg					
Mean:	64.50	35.50	1.843 : 1		
SD:	4.09	4.09	-	ns	

** : ($p \leq 0.01$), Chi²-test
ns: not statistically significant

TABLE 15-1	Allogenic APOSEC™ Bone Marrow - Summary			Monkey
	Myeloids (in %)	Erythroids (in %)	Myeloid/Erythroid ratio	Chi ² -Test (p-value)
	Males			
	Recovery sacrifice (test day 26)			
	Group 1: Control			
Mean:	61.25	38.75	1.595 : 1	
SD:	3.89	3.89	-	-
Group 4: 350/225/200 U/kg				
Mean:	61.75	38.25	1.645 : 1	
SD:	6.01	6.01	-	ns

** : ($p \leq 0.01$), Chi²-test
ns: not statistically significant

TABLE 15-1	Allogenic APOSEC™ Bone Marrow - Summary			Monkey
	Myeloids (in %)	Erythroids (in %)	Myeloid/Erythroid ratio	Chi ² -Test (p-value)
	Females			
	Terminal sacrifice (test day 12)			
	Group 1: Control			
Mean:	63.00	37.00	1.777 : 1	
SD:	7.00	7.00	-	-
Group 2: 35 U/kg				
Mean:	60.67	39.33	1.515 : 1	
SD:	3.21	3.21	-	ns
Group 3: 110 U/kg				
Mean:	68.83	31.17	2.227 : 1	
SD:	2.75	2.75	-	ns
Group 4: 350/225/200 U/kg				
Mean:	65.33	34.67	1.943 : 1	
SD:	5.80	5.80	-	ns

** : ($p \leq 0.01$), Chi²-test
ns: not statistically significant

TABLE 15-1	Allogenic APOSEC™ Bone Marrow - Summary			Monkey
	Myeloids (in %)	Erythroids (in %)	Myeloid/Erythroid ratio	Chi ² -Test (p-value)
	Females			
	Recovery sacrifice (test day 26)			
	Group 1: Control			
Mean:	63.00	37.00	1.705 : 1	
SD:	0.71	0.71	-	-
Group 4: 350/225/200 U/kg				
Mean:	61.75	38.25	1.615 : 1	ns
SD:	1.06	1.06	-	

** : ($p \leq 0.01$), Chi²-test
ns: not statistically significant

TABLE 15-2	Allogenic APOSEC™ Bone Marrow - Individual Data			Monkey
	Myeloids (in %)	Erythroids (in %)	Myeloid/Erythroid ratio	
	Chi ² -Test (p-value)			

Males				
Premature sacrifice (test day 1)				
Group 4: 350/225/200 U/kg				
(26)	60.0	40.0	1.50 : 1	
(27)	67.0	33.0	2.03 : 1	
Mean:	63.50	36.50	1.765 : 1	
SD:	4.95	4.95	-	-

TABLE 15-2		Allogenic APOSEC™ Bone Marrow - Individual Data			Monkey
	Myeloids (in %)	Erythroids (in %)	Myeloid/Erythroid ratio	Chi ² -Test (p-value)	
Males					
Terminal sacrifice (test day 12)					
Group 1: Control					
(1)	70.0	30.0	2.33 : 1		
(2)	75.0	25.0	3.00 : 1		
(3)	63.0	37.0	1.70 : 1		
Mean:	69.33	30.67	2.343 : 1		
SD:	6.03	6.03	-		
			-		
Group 2: 35 U/kg					
(11)	68.5	31.5	2.17 : 1	0.457	
(12)	59.0	41.0	1.44 : 1		
(13)	67.5	32.5	2.08 : 1		
Mean:	65.00	35.00	1.897 : 1		
SD:	5.22	5.22	-		
			-		
Group 3: 110 U/kg					
(17)	66.5	33.5	1.99 : 1	0.594	
(18)	66.0	34.0	1.94 : 1		
(19)	65.0	35.0	1.86 : 1		
Mean:	65.83	34.17	1.930 : 1		
SD:	0.76	0.76	-		
			-		
Group 4: 350/225/200 U/kg					
(23)	60.0	40.0	1.50 : 1	0.396	
(24)	68.0	32.0	2.13 : 1		
(25)	65.5	34.5	1.90 : 1		
Mean:	64.50	35.50	1.843 : 1		
SD:	4.09	4.09	-		
			-		

** : ($p \leq 0.01$), Chi²-test

TABLE 15-2	Allogenic APOSEC™ Bone Marrow - Individual Data			Monkey
	Myeloids (in %)	Erythroids (in %)	Myeloid/Erythroid ratio	Chi ² -Test (p-value)
	Males			
	Recovery sacrifice (test day 26)			
	Group 1: Control			
(4)	58.5	41.5	1.41 : 1	
(5)	64.0	36.0	1.78 : 1	
Mean:	61.25	38.75	1.595 : 1	
SD:	3.89	3.89	-	-
Group 4: 350/225/200 U/kg				
(33)	57.5	42.5	1.35 : 1	
(34)	66.0	34.0	1.94 : 1	
Mean:	61.75	38.25	1.645 : 1	
SD:	6.01	6.01	-	0.92

**: ($p \leq 0.01$), Chi²-test

TABLE 15-2		Allogenic APOSEC™ Bone Marrow - Individual Data			Monkey
	Myeloids (in %)	Erythroids (in %)	Myeloid/Erythroid ratio	Chi ² -Test (p-value)	
Females					
Terminal sacrifice (test day 12)					
Group 1: Control					
(6)	71.0	29.0	2.45 : 1		
(7)	60.0	40.0	1.50 : 1		
(8)	58.0	42.0	1.38 : 1		
Mean:	63.00	37.00	1.777 : 1		
SD:	7.00	7.00	-		-
Group 2: 35 U/kg					
(14)	57.0	43.0	1.33 : 1		
(15)	62.0	38.0			
(16)	63.0	37.0	1.70 : 1		
Mean:	60.67	39.33	1.515 : 1		
SD:	3.21	3.21	-		0.757
Group 3: 110 U/kg					
(20)	67.5	32.5	2.08 : 1		
(21)	67.0	33.0	2.03 : 1		
(22)	72.0	28.0	2.57 : 1		
Mean:	68.83	31.17	2.227 : 1		
SD:	2.75	2.75	-		0.246
Group 4: 350/225/200 U/kg					
(28)	64.5	35.5	1.82 : 1		
(29)	60.0	40.0	1.50 : 1		
(30)	71.5	28.5	2.51 : 1		
Mean:	65.33	34.67	1.943 : 1		
SD:	5.80	5.80	-		0.755

** : (p ≤ 0.01), Chi²-test

TABLE 15-2	Allogenic APOSEC™ Bone Marrow - Individual Data			Monkey
	Myeloids (in %)	Erythroids (in %)	Myeloid/Erythroid ratio	Chi ² -Test (p-value)
	Females			
	Recovery sacrifice (test day 26)			
	Group 1: Control			
(9)	63.5	36.5	1.74 : 1	
(10)	62.5	37.5	1.67 : 1	
Mean:	63.00	37.00	1.705 : 1	
SD:	0.71	0.71	-	-
Group 4: 350/225/200 U/kg				
(31)	62.5	37.5	1.67 : 1	
(32)	61.0	39.0	1.56 : 1	
Mean:	61.75	38.25	1.615 : 1	
SD:	1.06	1.06	-	0.918

**: ($p \leq 0.01$), Chi²-test

6. APPENDICES

A P P E N D I X 1

Certificates of Analysis



ÖSTERREICHISCHES ROTES KREUZ

OBERÖSTERREICH

Aus Liebe zum Menschen.

CERTIFICATE OF ANALYSIS

Manufacturer: Österreichisches Rotes Kreuz, Landesverband Oberösterreich, Blutzentrale Linz
Krankenhausstraße 7, 4010 Linz, Austria
Name: APOSEC™
Filling size: 100 mL glass bottle with 20 mL lyophilised APOSEC™
Batch-No: A000918399109
Man. Date: 02.10.2018
Valid for: Non-clinical trials

TEST	SPECIFICATION	RESULTS
Endotoxine	< 0,25 EU/mL	< 0,25 EU/mL
Mycoplasma	negative	negative
IDENTITY PROTEIN ASSAY		
EGF	Report value	76 pg/mL
TGF-β	Report value	2.822 pg/mL
IL-8	Report value	4.211 pg/mL
POTENCY PROTEIN ASSAY		
AP-1	Report value	95 % (rel. potency)
HSP27	Report value	95 % (rel. potency)
STERILITY		
Drug product	sterile	sterile

The above lot was manufactured according to Austrian Medicinal Product Act (AMG) and GMP regulations. All donations were tested negative for HIV, HCV, HBV, HAV, HEV, Parvo B19 and syphilis. Additionally, the intermediate was tested negative for HSV 1/2.

This human investigational medicinal product is only intended for toxicological studies and not for human use. During this developmental phase the formal approval of the Qualified Person is not mandatory.

05.02.2019 

Date / Signature (Head of quality control)



ÖSTERREICHISCHES ROTES KREUZ

OBERÖSTERREICH

Aus Liebe zum Menschen.

CERTIFICATE OF ANALYSIS

Manufacturer: Österreichisches Rotes Kreuz, Landesverband Oberösterreich, Blutzentrale Linz
Krankenhausstraße 7, 4010 Linz, Austria
Name: APOSEC™
Filling size: 100 mL glass bottle with 20 mL lyophilised APOSEC™
Batch-No: A000918399110
Man. Date: 02.10.2018
Valid for: Non-clinical trials

TEST	SPECIFICATION	RESULTS
Endotoxine	< 0,25 EU/mL	< 0,25 EU/mL
Mycoplasma	negative	negative
IDENTITY PROTEIN ASSAY		
EGF	Report value	103 pg/mL
TGF-β	Report value	3.907 pg/mL
IL-8	Report value	6.548 pg/mL
POTENCY PROTEIN ASSAY		
AP-1	Report value	106 % (rel. potency)
HSP27	Report value	115 % (rel. potency)
STERILITY		
Drug product	sterile	sterile

The above lot was manufactured according to Austrian Medicinal Product Act (AMG) and GMP regulations. All donations were tested negative for HIV, HCV, HBV, HAV, HEV, Parvo B19 and syphilis. Additionally, the intermediate was tested negative for HSV 1/2.

This human investigational medicinal product is only intended for toxicological studies and not for human use. During this developmental phase the formal approval of the Qualified Person is not mandatory.

05 FEB 2019 

Date / Signature (Head of quality control)



ÖSTERREICHISCHES ROTES KREUZ

OBERÖSTERREICH

Aus Liebe zum Menschen.

CERTIFICATE OF ANALYSIS

Manufacturer: Österreichisches Rotes Kreuz, Landesverband Oberösterreich, Blutzentrale Linz
Krankenhausstraße 7, 4010 Linz, Austria
Name: APOSEC™
Filling size: 100 mL glass bottle with 20 mL lyophilised APOSEC™
Batch-No: A000918399111
Man. Date: 15.10.2018
Valid for: Non-clinical trials

TEST	SPECIFICATION	RESULTS
Endotoxine	< 0,25 EU/mL	< 0,25 EU/mL
Mycoplasma	negative	negative
IDENTITY PROTEIN ASSAY		
EGF	Report value	85 pg/mL
TGF-β	Report value	2.656 pg/mL
IL-8	Report value	2.954 pg/mL
POTENCY PROTEIN ASSAY		
AP-1	Report value	99 % (rel. potency)
HSP27	Report value	104 % (rel. potency)
STERILITY		
Drug product	sterile	sterile

The above lot was manufactured according to Austrian Medicinal Product Act (AMG) and GMP regulations. All donations were tested negative for HIV, HCV, HBV, HAV, HEV, Parvo B19 and syphilis. Additionally, the intermediate was tested negative for HSV 1/2.

This human investigational medicinal product is only intended for toxicological studies and not for human use. During this developmental phase the formal approval of the Qualified Person is not mandatory.

05 FEB 2019 
Date / Signature (Head of quality control)



ÖSTERREICHISCHES ROTES KREUZ

OBERÖSTERREICH

Aus Liebe zum Menschen.

CERTIFICATE OF ANALYSIS

Manufacturer: Österreichisches Rotes Kreuz, Landesverband Oberösterreich, Blutzentrale Linz
Krankenhausstraße 7, 4010 Linz, Austria
Name: APOSEC™
Filling size: 100 mL glass bottle with 20 mL lyophilised APOSEC™
Batch-No: A000918399112
Man. Date: 15.10.2018
Valid for: Non-clinical trials

TEST	SPECIFICATION	RESULTS
Endotoxine	< 0,25 EU/mL	< 0,25 EU/mL
Mycoplasma	negative	negative
IDENTITY PROTEIN ASSAY		
EGF	Report value	80 pg/mL
TGF-β	Report value	2.245 pg/mL
IL-8	Report value	2.883 pg/mL
POTENCY PROTEIN ASSAY		
AP-1	Report value	72 % (rel. potency)
HSP27	Report value	64 % (rel. potency)
STERILITY		
Drug product	sterile	sterile

The above lot was manufactured according to Austrian Medicinal Product Act (AMG) and GMP regulations. All donations were tested negative for HIV, HCV, HBV, HAV, HEV, Parvo B19 and syphilis. Additionally, the intermediate was tested negative for HSV 1/2.

This human investigational medicinal product is only intended for toxicological studies and not for human use. During this developmental phase the formal approval of the Qualified Person is not mandatory.

06 FEB 2019

Date / Signature (Head of quality control)



ÖSTERREICHISCHES ROTES KREUZ

OBERÖSTERREICH

Aus Liebe zum Menschen.

CERTIFICATE OF ANALYSIS

Manufacturer: Österreichisches Rotes Kreuz, Landesverband Oberösterreich, Blutzentrale Linz
Krankenhausstraße 7, 4010 Linz, Austria
Name: APOSEC™
Filling size: 100 mL glass bottle with 20 mL lyophilised APOSEC™
Batch-No: A000918399113
Man. Date: 15.10.2018
Valid for: Non-clinical trials

TEST	SPECIFICATION	RESULTS
Endotoxine	< 0,25 EU/mL	< 0,25 EU/mL
Mycoplasma	negative	negative
IDENTITY PROTEIN ASSAY		
EGF	Report value	127 pg/mL
TGF-β	Report value	4.724 pg/mL
IL-8	Report value	6.082 pg/mL
POTENCY PROTEIN ASSAY		
AP-1	Report value	108 % (rel. potency)
HSP27	Report value	126 % (rel. potency)
STERILITY		
Drug product	sterile	sterile

The above lot was manufactured according to Austrian Medicinal Product Act (AMG) and GMP regulations. All donations were tested negative for HIV, HCV, HBV, HAV, HEV, Parvo B19 and syphilis. Additionally, the intermediate was tested negative for HSV 1/2.

This human investigational medicinal product is only intended for toxicological studies and not for human use. During this developmental phase the formal approval of the Qualified Person is not mandatory.

06 FEB 2019

Date / Signature (Head of quality control)



ÖSTERREICHISCHES ROTES KREUZ

OBERÖSTERREICH

Aus Liebe zum Menschen.

CERTIFICATE OF ANALYSIS

Manufacturer: Österreichisches Rotes Kreuz, Landesverband Oberösterreich, Blutzentrale Linz
Krankenhausstraße 7, 4010 Linz, Austria
Name: APOSEC™
Filling size: 100 mL glass bottle with 20 mL lyophilised APOSEC™
Batch-No: A000918399115
Man. Date: 15.10.2018
Valid for: Non-clinical trials

TEST	SPECIFICATION	RESULTS
Endotoxine	< 0,25 EU/mL	< 0,25 EU/mL
Mycoplasma	negative	negative
IDENTITY PROTEIN ASSAY		
EGF	Report value	91 pg/mL
TGF-β	Report value	3.716 pg/mL
IL-8	Report value	7.244 pg/mL
POTENCY PROTEIN ASSAY		
AP-1	Report value	101 % (rel. potency)
HSP27	Report value	144 % (rel. potency)
STERILITY		
Drug product	sterile	sterile

The above lot was manufactured according to Austrian Medicinal Product Act (AMG) and GMP regulations. All donations were tested negative for HIV, HCV, HBV, HAV, HEV, Parvo B19 and syphilis. Additionally, the intermediate was tested negative for HSV 1/2.

This human investigational medicinal product is only intended for toxicological studies and not for human use. During this developmental phase the formal approval of the Qualified Person is not mandatory.

06 FEB 2019 
Date / Signature (Head of quality control)



ÖSTERREICHISCHES ROTES KREUZ

OBERÖSTERREICH

Aus Liebe zum Menschen.

CERTIFICATE OF ANALYSIS

Manufacturer: Österreichisches Rotes Kreuz, Landesverband Oberösterreich, Blutzentrale Linz
Krankenhausstraße 7, 4010 Linz, Austria
Name: APOSEC™
Filling size: 100 mL glass bottle with 20 mL lyophilised APOSEC™
Batch-No: A000918399116
Man. Date: 15.10.2018
Valid for: Non-clinical trials

TEST	SPECIFICATION	RESULTS
Endotoxine	< 0,25 EU/mL	< 0,25 EU/mL
Mycoplasma	negative	negative
IDENTITY PROTEIN ASSAY		
EGF	Report value	89 pg/mL
TGF-β	Report value	2.918 pg/mL
IL-8	Report value	3.012 pg/mL
POTENCY PROTEIN ASSAY		
AP-1	Report value	102 % (rel. potency)
HSP27	Report value	101 % (rel. potency)
STERILITY		
Drug product	sterile	sterile

The above lot was manufactured according to Austrian Medicinal Product Act (AMG) and GMP regulations. All donations were tested negative for HIV, HCV, HBV, HAV, HEV, Parvo B19 and syphilis. Additionally, the intermediate was tested negative for HSV 1/2.

This human investigational medicinal product is only intended for toxicological studies and not for human use. During this developmental phase the formal approval of the Qualified Person is not mandatory.

06 FEB 2019 
Date / Signature (Head of quality control)



ÖSTERREICHISCHES ROTES KREUZ

OBERÖSTERREICH

Aus Liebe zum Menschen.

CERTIFICATE OF ANALYSIS

Manufacturer: Österreichisches Rotes Kreuz, Landesverband Oberösterreich, Blutzentrale Linz
Krankenhausstraße 7, 4010 Linz, Austria
Name: APOSEC™
Filling size: 100 mL glass bottle with 20 mL lyophilised APOSEC™
Batch-No: A000918399117
Man. Date: 15.10.2018
Valid for: Non-clinical trials

TEST	SPECIFICATION	RESULTS
Endotoxine	< 0,25 EU/mL	< 0,25 EU/mL
Mycoplasma	negative	negative
IDENTITY PROTEIN ASSAY		
EGF	Report value	108 pg/mL
TGF-β	Report value	3.743 pg/mL
IL-8	Report value	4.756 pg/mL
POTENCY PROTEIN ASSAY		
AP-1	Report value	109 % (rel. potency)
HSP27	Report value	114 % (rel. potency)
STERILITY		
Drug product	sterile	sterile

The above lot was manufactured according to Austrian Medicinal Product Act (AMG) and GMP regulations. All donations were tested negative for HIV, HCV, HBV, HAV, HEV, Parvo B19 and syphilis. Additionally, the intermediate was tested negative for HSV 1/2.

This human investigational medicinal product is only intended for toxicological studies and not for human use. During this developmental phase the formal approval of the Qualified Person is not mandatory.

06 FEB 2019 
Date / Signature (Head of quality control)



ÖSTERREICHISCHES ROTES KREUZ

OBERÖSTERREICH

Aus Liebe zum Menschen.

CERTIFICATE OF ANALYSIS

Manufacturer: Österreichisches Rotes Kreuz, Landesverband Oberösterreich, Blutzentrale Linz
Krankenhausstraße 7, 4010 Linz, Austria
Name: APOSEC™
Filling size: 100 mL glass bottle with 20 mL lyophilised APOSEC™
Batch-No: A000918399118
Man. Date: 06.11.2018
Valid for: Non-clinical trials

TEST	SPECIFICATION	RESULTS
Endotoxine	< 0,25 EU/mL	< 0,25 EU/mL
Mycoplasma	negative	negative
IDENTITY PROTEIN ASSAY		
EGF	Report value	87 pg/mL
TGF-β	Report value	4.038 pg/mL
IL-8	Report value	2.285 pg/mL
POTENCY PROTEIN ASSAY		
AP-1	Report value	83 % (rel. potency)
HSP27	Report value	75 % (rel. potency)
STERILITY		
Drug product	sterile	sterile

The above lot was manufactured according to Austrian Medicinal Product Act (AMG) and GMP regulations. All donations were tested negative for HIV, HCV, HBV, HAV, HEV, Parvo B19 and syphilis. Additionally, the intermediate was tested negative for HSV 1/2.

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06 FEB 2019 
Date / Signature (Head of quality control)

A P P E N D I X 2

Composition of the Diet, Limitation for Contaminants in the Diet and Drinking Water

Composition of the diet

Standard Diet for Monkeys
ssniff® Pri vegetarisch V3994
(ssniff Spezialdiäten GmbH, 59494 Soest, Germany)

Ingredients

(average % content in the diet)

dry substance	90.1
crude protein	22.0
crude fat	5.0
crude fibres	3.5
crude ash	7.3
N-free extracts	52.3
starch	38.7
sugar	4.2

Metabolizable Energy

(MJ/kg)

Gross energy	17.1
Metabolizable energy	14.3

Amino Acids

(average % content in the diet)

lysine	1.24
methionine	0.45
methionine/cysteine	0.84
glycine	0.96
leucine	2.31
isoleucine	1.00
arginine	1.19
phenylalanine	1.18
tryptophan	0.23
histidine	0.51
phenylalanine/tyrosine	2.11
aspartic acid	2.09
glutamic acid	3.83
valine	1.15
threonine	0.87
proline	1.47
alanine	1.30
serine	1.12

Minerals

(average % content in the diet)

calcium	1.10
phosphorus	0.80
sodium	0.25
magnesium	0.26
potassium	0.57

Trace Elements

(average content in mg per 1 000 g of diet)

manganese	47
copper	12
zinc	73
iodine	2.0
iron	167
selenium	0.3
cobalt	2.0

Vitamins

(additive per 1 000 g of diet)

vitamin A	15000	IU
vitamin D ₃	2000	IU
vitamin E	125	mg
vitamin B ₁	18	mg
vitamin B ₂	22	mg
vitamin B ₆	19	mg
vitamin B ₁₂	100	µg
biotin	440	µg
pantothenic acid	35	mg
choline chloride	2060	mg
folic acid	7	mg
nicotinic acid	85	mg
vitamin K	5	mg
inositol	100	mg
vitamin C	2500	mg

Fatty acids

(average % content in the diet)

C 8:0	-
C 10:0	-
C 12:0	-
C 14:0	0.01
C 16:0	0.60
C 16:1	0.03
C 18:0	0.11
C 18:1	1.26
C 18:2	2.10
C 18:3	0.13
C 20:0	0.01
C 20:1	-
C 20:5	-
C 22:6	-

Limitation for contaminants in the diet [ppb]

	min.	max.
Aflatoxin (B ₁ , B ₂ , G ₁ , G ₂) total		5.0
Lindane		100.0
Heptachlor		10.0
Malathion		1000.0
DDT (Total)		50.0
Dieldrin		10.0
Cadmium		400.0
Arsenic		1000.0
Lead		1500.0
Mercury		100.0
Selenium	100.0	600.0
PCB		50.0

Limitation for contaminants in the drinking water [mg/L]

	max.
Iron	0.200
Manganese	0.050
Ammonium	0.50
Chloride	250
Arsenic	0.010
Lead	0.010
Cadmium	0.0030
Chromium	0.050
Cyanide	0.050
Fluoride	1.5
Nickel	0.020
Nitrite	0.50
Nitrate	50
Mercury	0.0010
Vinylchloride	0.00050
Acrylamide	0.00010
Benzene	0.001
Boron	1.0
Bromate	0.010
Selenium	0.010
Antimony	0.0050
Copper	2.0
Aluminium	0.200
Sodium	200
Sulphate	250
Uranium	0.010

Polycyclic aromatic hydrocarbons

- Benzo-(b)-fluoranthene	
- Benzo-(k)-fluoranthene	
- Benzo-(ghi)-perylene	
- Indeno-(1,2,3-cd)-pyrene	total 0.00010
- Benzo-(a)-pyrene	0.000010

Chlorinated organic compounds

Trihalogenemethane	
including Trichloromethane,	
Bromodichloromethane,	
Dibromochloromethane and	
Tribromomethane	total 0.050
- 1,2-Dichloroethane	0.0030
- Tetrachloroethene and Trichloroethene	0.010
- Epichlorohydrine	0.00010

Organic chemical compounds used as
pesticides and biocides including
their toxic metabolites
except for

maximum of 0.00010/substance

- Aldrin	0.000030
- Dieldrin	0.000030
- Heptachlor	0.000030
- Heptachloroepoxide	0.000030

maximum total of 0.00050

Tritium [Bq/L]	100
----------------	-----

pH between 6.5 and 9.5

A P P E N D I X 3

Phase Report on Histopathology

(Phase Number 528)

(issued by Global Pathology Support B.V.)



Global Pathology Support B.V.

TOXICOLOGIC PATHOLOGY

FINAL

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FINAL PATHOLOGIST'S REPORT

2-Week Toxicity Study of Allogenic APOSEC™ by Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys Followed by a 2-Week Treatment-Free Period

- Multi-Site Study -

- PATHOLOGY ASSESSMENT -

Test Site Reference no. 528

LPT Study no. 35015

Issue date report: 29 October, 2019

Author: R.J.M.M. Thoolen



Test Site Reference no. 528 / LPT Study no. 35015

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Test Site Reference no. 528 / LPT Study no. 35015

1. STUDY INFORMATION SHEET

Test Facility:

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Test Site Reference no. 528 / LPT Study no. 35015

Test Site study identification:

528

Histopathological assessment period:

10 April, 2019 – 27 September, 2019.

Guidelines:

This study phase was performed in compliance with the OECD Principles of Good Laboratory Practice (as revised in 1997), OECD Environmental Health and Safety Publications, ENV/MC/CHEM(98)17, Paris 1998 and subsequent consensus documents.

The OECD Principles of Good Laboratory Practice are accepted by Regulatory Authorities throughout the European Community, United States of America (FDA and EPA) and Japan (MHLW, MAFF and METI).



Test Site Reference no. 528 / LPT Study no. 35015

1.1 GLP COMPLIANCE

GLP Compliance Statement

With respect to the following study phase, which is a part of LPT study 35015:

Test Site Reference number: 528

**2-Week Toxicity Study of Allogenic APOSEC™
by Repeated Twice Weekly Intravenous Infusion
to Cynomolgus Monkeys Followed by
a 2-Week Treatment-Free Period**

- Multi-Site Study -

- PATHOLOGY ASSESSMENT -

as conducted by and performed at Global Pathology Support B.V., The Hague, The Netherlands.

I the undersigned, declare this phase report constitutes a true and faithful account of the procedures adopted and the histopathology results obtained in this delegated part of the study.

This delegated part of the study described in this phase report was conducted in compliance with the OECD Principles of Good Laboratory Practice (as revised in 1997), OECD Environmental Health and Safety Publications, ENV/MC/CHEM(98)17, Paris 1998 and subsequent consensus documents.

The OECD Principles of Good Laboratory Practice are accepted by Regulatory Authorities throughout the European Community, United States of America (FDA and EPA) and Japan (MHLW, MAFF and METI).

Macroscopic observations and histological preparation were performed under the responsibility of LPT.

I, the undersigned consider the presented data to be valid.

Signature:

Date:

R.J.M.M. Thoolen

Principal Investigator Pathology /
Managing Director Global Pathology Support B.V.



Test Site Reference no. 528 / LPT Study no. 35015

1.2 QUALITY ASSURANCE

This Quality Assurance Statement concerns Global Pathology Support B.V. study phase:

Test Site Reference number: 528

**2-Week Toxicity Study of Allogenic APOSEC™
by Repeated Twice Weekly Intravenous Infusion
to Cynomolgus Monkeys Followed by
a 2-Week Treatment-Free Period**

- Multi-Site Study -

- PATHOLOGY ASSESSMENT -

which is a part of LPT study 35015.

In compliance with the OECD Principles of Good Laboratory Practices the performance of this part of the study was monitored by the Global Pathology Support B.V. Unit by means of study-based auditing of pre-defined critical phases.

All observations were reported in writing to the Principal Investigator, Test Site Management and to the Study Director, Leading QA and Test Facility Management. The specifications of the inspections performed are presented below:

Type of audit	Phase(s) of the study inspected	Date(s) of audit	Date(s) reported to Principal Investigator / Test Site Management	Date(s) reported to Study Director, Leading QA and Test Facility Management
Study plan	Pre-study phase	19-Sept-2019	20-Sept-2019	20-Sept-2019
Data Input	Histopathology phase	19-Sept-2019	20-Sept-2019	20-Sept-2019
Raw data & Draft Report	Reporting phase	17 and 18-Oct-2019	25-Oct-2019	25-Oct-2019

This part of the report was audited by the Quality Assurance Unit of Global Pathology Support B.V.. It represents an accurate description of the performance of the study phase. The data reported are an accurate reflection of the raw data produced during the performance of this part of the study.

Signature:

Date:

N. Tirtodikromo
Quality Assurance Manager
Global Pathology Support B.V.



Test Site Reference no. 528 / LPT Study no. 35015

2. ANIMAL ALLOCATION AND ANIMAL TREATMENT SCHEME

Group	Dose levels [Units/kg b.w.]	No. and sex of animals MS + RP	Animal study numbers MS	Animal study numbers RP
1	0 (negative control)	3 + 2 m 3 + 2 f	1 – 3 6 – 8	4, 5 9, 10
2	35	3 m 3 f	11 – 13 14 – 16	None
3	110	3 m 3 f	17 – 19 20 – 22	None
4	350/225 ¹ /200 ²	5 + 2 m 3 + 2 f	23 – 25, 26, 27 28 – 30	33, 34 31, 32

¹ Group 4: dose reduction as of February 18, 2019.

² Group 4: dose reduction as of February 21, 2019.

b.w.: body weight
m: male
f: female
MS: Main study
RP: Recovery period

3. METHODS

3.1 Necropsy

Necropsy was performed by LPT.

On test day 12 (approximately 24 hours after the last dosing) the main study animals were dissected following a randomisation scheme. Necropsy of animals allocated to the recovery period started on test day 26.

The animals were sacrificed (150 mg Pentobarbital/kg b.w., i.v.) and exsanguinated by carotid dissection, weighed, dissected and inspected macroscopically under the direction of a pathologist.



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Tissue samples or the whole organ from all animals (including prematurely sacrificed animals) were preserved in neutral buffered 10% formalin. The eyes and lacrimal glands were preserved in Davidson's solution and the testicles including epididymides in modified Davidson's solution for optimum fixation.

Table 1: **Tissues collected at necropsy**

Adrenal gland (2)	Muscle (<i>skeletal, leg</i>)
Aorta abdominalis	Nerve (<i>sciatic</i>)
Bone (<i>os femoris with joint</i>)	Esophagus
Bone marrow (<i>os femoris</i>)	Ovary (2)
Brain (<i>cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts</i>)	Pancreas
Caecum	Pituitary
Epididymis (2)	Prostate
Eye with optic nerve (2)	Salivary glands (<i>mandibular, parotid, sublingual</i>)
Gall bladder	Seminal vesicle
Gross lesions	Skin (<i>left flank</i>)
Heart (<i>left/right ventricle, septum</i>)	Spinal cord (<i>3 sections</i>)
Infusion site(s); last dosing	Spleen
Intestine, large (<i>colon, rectum</i>)	Sternum
Intestine, small including Peyer's patches (<i>duodenum, jejunum, ileum</i>)	Stomach
Kidney and ureter (2)	Testicle (2)
Lacrimal gland (2)	Thymus
Liver (<i>3 sections: left (medial), right (medial) and caudal lobe</i>)	Thyroid (2) (<i>incl. parathyroids</i>)
Lungs (<i>with mainstem bronchi and bronchioles; 3 sections: one through each of three different lobes</i>)	Tissue masses or tumours (<i>including regional lymph nodes</i>)
Lymph node (1, <i>axillary</i>)	Tongue (<i>incl. base</i>)
Lymph node (1, <i>cervical</i>)	Trachea (<i>incl. larynx</i>)
Mammary gland	Urinary bladder
	Uterus (<i>incl. cervix and oviducts</i>)
	Vagina

3.2 Macroscopic post-mortem examination

For all animals, a complete macroscopic post-mortem examination, weighing of organs and statistical analysis of organ weights were performed by LPT.

Full details of the test protocol are available in LPT Study Plan 35015 and Study Plan Amendment(s). In-life and laboratory results are available in LPT Report 35015.



Test Site Reference no. 528 / LPT Study no. 35015

3.3 Histotechnology

The afore-listed organs of all surviving animals and any prematurely sacrificed animals were examined histopathologically after preparation of paraffin sections and haematoxylin-eosin (HE) staining.

In addition, frozen sections of the heart, liver and one kidney were made, stained with Oil Red O and examined microscopically.

During dissection of all animals (main study and recovery animals) fresh bone marrow was obtained from a suitable rib e.g. the 7th rib (3 air-dried smears/animal) and stained according to PAPPENHEIM.

3.4 Histopathology

The methods followed by the pathologist for evaluation and reporting were according to the test site Standard Operating Procedures. The computerized system used for pathology is Provantis 10.1. The nomenclature used is an in-house nomenclature with consideration and/or reference to WHO/IARC/STP/RITA nomenclatures for non-proliferative and proliferative lesions.

4. LOCATION OF STUDY RECORDS

The following data and materials will be sent to LPT to archive: one signed final pathology report, all slides, dispatch list(s) and a copy of the electronic records made by the pathologist as captured by the appropriate software after completion of the histopathology phase of the study.

All raw data and relevant documentation and a copy of the signed final pathology report will be maintained in the document retrieval system at the test site and according to the test site Standard Operating Procedures archived under the Test Site reference no. 528 by Global Pathology Support B.V.. Duration of archiving at the test site (Global Pathology Support B.V. archive room) will be for 3 years. Thereafter, the data will be transferred to LPT.

5. DEVIATIONS FROM PROTOCOL

There were no deviations from protocol during the study for histopathology.



Test Site Reference no. 528 / LPT Study no. 35015

6. RESULTS

6.1 Mortality

All animals survived until the scheduled necropsy, except for two males of group 4 (animal nos. 26 and 27) that were prematurely sacrificed on test day 1 and were initially dosed with 350 Units/kg. Two additional males were added to group 4 to replace the prematurely sacrificed animals 26 and 27. Dose reduction of group 4 to 200 Units/kg was due to poor health condition of the males.

6.2 Macroscopic observations

Main groups

Haemorrhagic subcutaneous tissue at the infusion site(s) was observed in all group males and females (group 1: 2/3 males and females, group 2: 2/3 males and females, group 3: 3/3 males and females, group 4: 3/5 males and 1/3 females). These animals were given repeated twice weekly intravenous infusion with Allogenic APOSEC™ up to 350/225¹/200² Units/kg (¹⁺² dose reduction) and most of the macroscopic haemorrhagic subcutaneous tissue could be confirmed by microscopy. These macroscopic observations did not show a dose-relationship and were not considered to be test item-related, but rather due to the application procedure (intravenous infusion).

In group 4 males, spleens were enlarged in animal nos. 23 and 25 (schedule sacrifice), for which a microscopic correlate (follicular hyperplasia) was made for animal no. 23 only. Enlarged axillary lymph nodes were observed for males no. 25 (group 4) and no. 13 (group 2) (schedule sacrifice), 26 and 27 (group 4: premature sacrifice), for which microscopic correlates were seen in animal nos. 13 and 25 only (medullary hyperplasia). Oedematous lungs were observed for male no. 26 that could not be associated with microscopy. This was also the case for enlarged cervical lymph node and adrenal glands in animal no. 27, also sacrificed on test day 1 of the study. However, haemorrhagic and oedematous subcutaneous tissue in the thighs and lower legs of animal no. 27 were associated with slight diffuse phlegmonous inflammation, consisting of acute inflammation with interstitial oedema and minimal haemorrhage as observed at microscopy. These macroscopic changes were related to the test item.

In female group 4, the thymus of animal no. 30 was associated with marked atrophy, which is considered to fall within the normal background change for females and not considered to be related to the test item.

Recovery groups

There were no macroscopic changes observed in the recovery group animals.



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6.3 Microscopic observations

Main groups

The infusion site(s) of all groups (groups 1 to 4) showed microscopic changes (e.g. subcutis; acute inflammatory cell infiltrate, fibrosis, granulation tissue, haemorrhage, necrosis, (peri-)vasculitis, pigment deposition, vessel; intimal thickening) to different degree. In most cases the subcutaneous haemorrhage observed at the infusion site(s) at autopsy, could be associated with microscopy (subcutaneous haemorrhage). These changes were not statistically different from the control groups.

In group 4 males that were sacrificed on schedule (nos. 23-25) test item-related changes were observed in spleen of animals 23 (follicular cell hyperplasia) which was associated with splenic enlargement at autopsy. Lymphoid hyperplasia of the medulla in the axillary lymph node was observed for animal no. 25 with enlarged axillary lymph node at macroscopy. This was also observed for 1/3 group 2 males (no. 13) for which the draining axillary lymph node was also enlarged at macroscopy.

For group 4 males that were sacrificed prematurely (nos. 26 and 27), histopathology revealed diffuse phlegmonous inflammation in the thighs and lower legs of animal no. 27, consisting of acute inflammation with interstitial oedema and minimal haemorrhage which was related to macroscopy (haemorrhagic and oedematous subcutaneous tissue). This was related to the test item.

Recovery groups

After cessation of treatment, no toxicologically relevant changes were observed at the infusion site(s) and/or other organs.

All microscopic changes in all animals were either coincidental, related to macroscopic incidental findings, mode of application (intravenous infusion) and/or of spontaneous background origin.



Test Site Reference no. 528 / LPT Study no. 35015

7. DISCUSSION & CONCLUSIONS ABOUT AUTOPSY & HISTOPATHOLOGY FINDINGS

All animals survived until scheduled necropsy, except for two group 4 males that were prematurely sacrificed on test day 1 and were initially dosed with 350 Units/kg. Subsequently the two group 4 males were replaced and finally the dose was lowered to 200 Units/kg for group 4 animals.

At the infusion site(s), macroscopic haemorrhagic subcutaneous tissue was observed in all groups to a different degree, however not in a dose-related manner and microscopic evaluation of these lesions did not reveal any statistically significant and/or toxicologically relevant difference with regard to the test item (Allogenic APOSEC™). The microscopic changes observed at the infusion site(s) for main groups animals (e.g. subcutis; acute inflammatory cell infiltrate, fibrosis, granulation tissue, haemorrhage, necrosis, pigment deposition, (peri-)vasculitis, vessel; intimal thickening) were attributed to the mode of application (intravenous infusion) and was not associated with the administration of the test item.

Two males that were sacrificed prematurely on test day 1 (dosed 350 Units/kg), had macroscopic and/or microscopic test item-related lesions. In the other three males where finally, the dose was lowered to 200 Units/kg for group 4 animals, follicular cell hyperplasia was observed in one animal which was associated with splenic enlargement at autopsy. Lymphoid hyperplasia of the medulla in the axillary lymph node was observed for 1/5 group 4 males and 1/3 group 2 males, with enlarged axillary lymph nodes at macroscopy. This draining lymph node was affected in these 2 animals and represent a local effect of the test item following intravenous infusion. This was not observed in group 3 males and or group 3 females.

For the recovery animals, no toxicologically relevant changes were observed at the infusion site(s) and/or other organs.

All macroscopic and/or microscopic observations were considered to be of no toxicological relevance, except for males in which for spleen and regional lymph nodes, test item-related effects were observed in group 4 males and 1/3 group 2 males (axillary lymph node). Evaluation of all organs did not reveal any test item-relationship when Allogenic APOSEC™ was applied twice weekly by intravenous infusion to Cynomolgus monkeys for 2 weeks for up to 350/225¹/200² Units/kg (¹⁺² dose reduction) in females with a 2-week recovery period. Recovery animals of both sexes did not reveal any test item effects. Other findings were considered to be spontaneous in nature and fall within the normal (post-mortem) background pathology commonly seen in Cynomolgus monkeys.



8. GROSS PATHOLOGY (MAIN GROUPS)



Provantis

Test Site Reference number: 528 / Study no. 35015

GROSS PATHOLOGY SUMMARY - MAIN GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
 Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
 Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group: Number of Animals: Number of Completed Animals:	Male				Female			
	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
	3	3	3	5	3	3	3	3
	3	3	3	5	3	3	3	3
adrenal gland (2)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	4	3	3	3	3
enlarged	0	0	0	1	0	0	0	0
aorta abdominalis								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
bone (os femoris with joint)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
bone marrow (os femoris)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
caecum								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
colon								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
duodenum								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
epididymis (2)								
Submitted	3	3	3	5	.	.	.	.
No abnormalities detected	3	3	3	5	.	.	.	.
esophagus								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
eye with optic nerve (2)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3



Provantis

Test Site Reference number: 528 / Study no. 35015

GROSS PATHOLOGY SUMMARY - MAIN GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
 Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
 Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group: Number of Animals: Number of Completed Animals:	Male				Female			
	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
	3	3	3	5	3	3	3	3
	3	3	3	5	3	3	3	3
gall bladder								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
heart (left/right ventricle, septum)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
ileum								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
infusion site(s) - last dosing								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	1	1	0	2	1	1	0	2
haemorrhagic (subcutaneous)	2	2	3	3	2	2	3	1
jejunum								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
kidney (2)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
lacrimal gland (2)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
liver (3 sections - left (medial), right (medial) and caudal lobe)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
lower legs								
Submitted	0	0	0	1	.	.	.	.
subcutaneous tissue; haemorrhagic	.	.	.	1	.	.	.	.
subcutaneous tissue; oedematous	.	.	.	1	.	.	.	.
lungs (with mainstem bronchi and bronchioles - 3 sections)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	4	3	3	3	3



Provantis

Test Site Reference number: 528 / Study no. 35015

GROSS PATHOLOGY SUMMARY - MAIN GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by

Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys

Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group:	Male				Female			
	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
Number of Animals:	3	3	3	5	3	3	3	3
Number of Completed Animals:	3	3	3	5	3	3	3	3
lungs (with mainstem bronchi and bronchioles - 3 sections)								
(Continued...)								
emphysematous	0	0	0	1	0	0	0	0
lymph node (1, axillary)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	2	3	2	3	3	3	3
enlarged	0	1	0	3	0	0	0	0
lymph node (1, cervical)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	4	3	3	3	3
enlarged	0	0	0	1	0	0	0	0
mammary gland								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
muscle (skeletal, leg)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
nerve (sciatic)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
ovary (2)								
Submitted	.	.	.	.	3	3	3	3
No abnormalities detected	.	.	.	.	2	3	2	3
left; cystic	.	.	.	.	1	0	1	0
pancreas								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
peyer's patches								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
pituitary								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3



Provantis

Test Site Reference number: 528 / Study no. 35015

GROSS PATHOLOGY SUMMARY - MAIN GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by

Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys

Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group:	Male				Female			
	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
Number of Animals:	3	3	3	5	3	3	3	3
Number of Completed Animals:	3	3	3	5	3	3	3	3
prostate								
Submitted	3	3	3	5	.	.	.	.
No abnormalities detected	3	3	3	5	.	.	.	.
rectum								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
salivary glands (mandibular, parotid, sublingual)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
seminal vesicle								
Submitted	3	3	3	5	.	.	.	.
No abnormalities detected	3	3	3	5	.	.	.	.
skin (left flank)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
spinal cord (3 sections)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
spleen								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	3	3	3	3	3
enlarged	0	0	0	2	0	0	0	0
sternum								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
stomach								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
testicle (2)								
Submitted	3	3	3	5	.	.	.	.
No abnormalities detected	3	3	3	5	.	.	.	.
thymus								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	2



Provantis

Test Site Reference number: 528 / Study no. 35015

GROSS PATHOLOGY SUMMARY - MAIN GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
 Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
 Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group:	Male				Female			
	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
Number of Animals:	3	3	3	5	3	3	3	3
Number of Completed Animals:	3	3	3	5	3	3	3	3
thymus (Continued...)								
reduced in size	0	0	0	0	0	0	0	1
thyroid (2) (incl. parathyroids)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	2	3	5	3	3	3	3
left; pale	0	1	0	0	0	0	0	0
left; reduced in size	0	1	0	0	0	0	0	0
left; soft consistency	0	1	0	0	0	0	0	0
thighs								
Submitted	0	0	0	1	.	.	.	.
subcutaneous tissue; haemorrhagic	.	.	.	1	.	.	.	.
subcutaneous tissue; oedematous	.	.	.	1	.	.	.	.
tissue masses or tumours (including regional lymph nodes)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
tongue (incl. base)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
trachea (incl. larynx)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
ureter (2)								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
urinary bladder								
Submitted	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
uterus (incl. cervix and oviducts)								
Submitted	.	.	.	.	3	3	3	3
No abnormalities detected	.	.	.	.	3	3	3	3
vagina								
Submitted	.	.	.	.	3	3	3	3
No abnormalities detected	.	.	.	.	3	3	3	3



9. GROSS PATHOLOGY (RECOVERY GROUPS)



Provantis

Test Site Reference number: 528 / Study no. 35015

GROSS PATHOLOGY SUMMARY - RECOVERY GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by

Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys

Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Number of Animals	2	2	2	2
Number of Completed Animals	2	2	2	2
adrenal gland (2)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
aorta abdominalis				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
bone (os femoris with joint)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
bone marrow (os femoris)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
caecum				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
colon				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
duodenum				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
epididymis (2)				
Submitted	2	2	.	.
No abnormalities detected	2	2	.	.
esophagus				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
eye with optic nerve (2)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2



Provantis

Test Site Reference number: 528 / Study no. 35015

GROSS PATHOLOGY SUMMARY - RECOVERY GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by

Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys

Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Number of Animals	2	2	2	2
Number of Completed Animals	2	2	2	2
gall bladder				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
heart (left/right ventricle, septum)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
ileum				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
infusion site(s) - last dosing				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
jejunum				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
kidney (2)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
lacrimal gland (2)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
liver (3 sections - left (medial), right (medial) and caudal lobe)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
lungs (with mainstem bronchi and bronchioles - 3 sections)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
lymph node (1, axillary)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
lymph node (1, cervical)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2



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Test Site Reference number: 528 / Study no. 35015

GROSS PATHOLOGY SUMMARY - RECOVERY GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by

Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys

Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Number of Animals	2	2	2	2
Number of Completed Animals	2	2	2	2
mammary gland				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
muscle (skeletal, leg)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
nerve (sciatic)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
ovary (2)				
Submitted	.	.	2	2
No abnormalities detected	.	.	2	2
pancreas				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
peyer's patches				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
pituitary				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
prostate				
Submitted	2	2	.	.
No abnormalities detected	2	2	.	.
rectum				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
salivary glands (mandibular, parotid, sublingual)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
seminal vesicle				
Submitted	2	2	.	.
No abnormalities detected	2	2	.	.



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Test Site Reference number: 528 / Study no. 35015

GROSS PATHOLOGY SUMMARY - RECOVERY GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by

Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys

Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Number of Animals	2	2	2	2
Number of Completed Animals	2	2	2	2
skin (left flank)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
spinal cord (3 sections)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
spleen				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
sternum				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
stomach				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
testicle (2)				
Submitted	2	2	.	.
No abnormalities detected	2	2	.	.
thymus				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
thyroid (2) (incl. parathyroids)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
tissue masses or tumours (including regional lymph nodes)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
tongue (incl. base)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
trachea (incl. larynx)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2



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Test Site Reference number: 528 / Study no. 35015

GROSS PATHOLOGY SUMMARY - RECOVERY GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by

Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys

Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Number of Animals	2	2	2	2
Number of Completed Animals	2	2	2	2
ureter (2)				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
urinary bladder				
Submitted	2	2	2	2
No abnormalities detected	2	2	2	2
uterus (incl. cervix and oviducts)				
Submitted	.	.	2	2
No abnormalities detected	.	.	2	2
vagina				
Submitted	.	.	2	2
No abnormalities detected	.	.	2	2



10. HISTOPATHOLOGY (MAIN GROUPS)



Provantis

Test Site Reference number: 528 / Study no. 35015

HISTOPATHOLOGY SUMMARY - MAIN GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group: Number of Animals: Number of Completed Animals:	Male				Female			
	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
	3	3	3	5	3	3	3	3
	3	3	3	5	3	3	3	3
adrenal gland (2)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	2	3	3	1
accessory (adrenal) cortical nodule(s); unilateral	0	0	0	0	1	0	0	2
.... one	0	0	0	0	1	0	0	2
aorta abdominalis								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
bone (os femoris with joint)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
bone marrow (os femoris)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
caecum								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
colon								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
duodenum								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	2	3	3	3
mucosa; pigment deposition; multifocal	0	0	0	0	1	0	0	0
.... slight	0	0	0	0	1	0	0	0
epididymis (2)								
Examined	3	3	3	5	.	.	.	.
No abnormalities detected	0	0	1	1	.	.	.	.

Fisher's Exact

Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance



Provantis

Test Site Reference number: 528 / Study no. 35015

HISTOPATHOLOGY SUMMARY - MAIN GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
 Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
 Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group: Number of Animals: Number of Completed Animals:	Male				Female			
	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
	3	3	3	5	3	3	3	3
	3	3	3	5	3	3	3	3
epididymis (2) (Continued...)								
aspermia	3	3	2	4	.	.	.	.
duct(s); contain(s) mucus/debris; left	1	2	0	0	.	.	.	.
.... minimal	0	2	0	0	.	.	.	.
.... slight	1	0	0	0	.	.	.	.
esophagus								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
eye with optic nerve (2)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
gall bladder								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
heart (left/right ventricle, septum)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	0	0	0	1	0	0	1	0
ventricle; myocardium; infiltrate, inflammatory cell, mononuclear; focal	0	0	0	0	1	0	0	0
.... minimal	0	0	0	0	1	0	0	0
ventricle; myocardium; infiltrate, inflammatory cell, mononuclear; multifocal	0	0	0	0	0	0	1	0
.... minimal	0	0	0	0	0	0	1	0
oil red o staining	3	3	3	4	3	3	2	3
.... minimal	3	3	2	4	3	3	2	2
.... slight	0	0	1	0	0	0	0	1
ileum								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
infusion site(s) - last dosing								
Examined	3	3	3	5	3	3	3	3

Fisher's Exact

Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance



Provantis

Test Site Reference number: 528 / Study no. 35015

HISTOPATHOLOGY SUMMARY - MAIN GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group: Number of Animals: Number of Completed Animals:	Male				Female			
	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
	3	3	3	5	3	3	3	3
	3	3	3	5	3	3	3	3
infusion site(s) - last dosing (Continued...)								
No abnormalities detected	0	0	0	2	0	0	0	0
subcutis; infiltrate, inflammatory cell, acute	2	3	2	2	3	2	3	3
.... minimal	0	0	0	0	1	0	0	1
.... slight	1	1	1	0	0	2	1	2
.... moderate	1	2	1	2	1	0	0	0
.... marked	0	0	0	0	1	0	2	0
subcutis; fibrosis	1	2	2	3	2	0	0	1
.... minimal	0	0	1	0	0	0	0	0
.... slight	1	2	1	3	2	0	0	1
subcutis; granulation tissue	1	3	2	2	1	0	1	2
.... minimal	1	2	2	2	1	0	0	2
.... slight	0	1	0	0	0	0	1	0
subcutis; haemorrhage	3	3	3	3	2	3	3	3
.... minimal	1	0	0	0	0	2	0	1
.... slight	2	2	2	2	1	1	3	2
.... moderate	0	1	1	1	1	0	0	0
subcutis; necrosis	2	2	3	3	2	1	2	1
.... minimal	1	0	0	1	0	1	0	1
.... slight	0	1	3	2	2	0	2	0
.... moderate	1	1	0	0	0	0	0	0
subcutis; (peri-)vasculitis	1	2	3	2	2	0	3	2
.... minimal	0	0	1	1	0	0	1	2
.... slight	1	1	2	1	2	0	0	0
.... moderate	0	1	0	0	0	0	2	0
subcutis; pigment deposition	2	1	3	2	1	2	2	2
.... minimal	0	0	1	2	0	0	1	0
.... slight	2	1	2	0	1	2	1	2
subcutis; vessel, intimal thickening	2	0	0	0	3	0	2	0
.... minimal	1	0	0	0	2	0	1	0

Fisher's Exact

Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance



Provantis

Test Site Reference number: 528 / Study no. 35015

HISTOPATHOLOGY SUMMARY - MAIN GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by

Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys

Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group: Number of Animals: Number of Completed Animals:	Male				Female			
	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
	3	3	3	5	3	3	3	3
	3	3	3	5	3	3	3	3
infusion site(s) - last dosing								
(Continued...)								
.... slight	1	0	0	0	1	0	0	0
.... moderate	0	0	0	0	0	0	1	0
jejunum								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
kidney (2)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	0	0	2	3	2	1	3	1
interstitial nephritis; unilateral	0	2	0	1	0	1	0	0
.... minimal	0	1	0	1	0	1	0	0
.... slight	0	1	0	0	0	0	0	0
interstitial nephritis; bilateral	1	1	1	0	0	0	0	0
.... minimal	1	1	1	0	0	0	0	0
oil red o staining	2	1	0	1	1	1	0	2
.... minimal	1	0	0	1	1	1	0	1
.... slight	1	1	0	0	0	0	0	0
.... marked	0	0	0	0	0	0	0	1
lacrimal gland (2)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	0	2	2	4	2	3	3	2
infiltrate, inflammatory cell, mononuclear; left	1	0	0	1	0	0	0	0
.... minimal	0	0	0	1	0	0	0	0
.... slight	1	0	0	0	0	0	0	0
infiltrate, inflammatory cell, mononuclear; right	2	0	1	0	1	0	0	1
.... minimal	1	0	1	0	1	0	0	0
.... slight	1	0	0	0	0	0	0	1
infiltrate, inflammatory cell, mononuclear; bilateral	0	1	0	0	0	0	0	0
.... slight	0	1	0	0	0	0	0	0

Fisher's Exact

Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance



Provantis

Test Site Reference number: 528 / Study no. 35015

HISTOPATHOLOGY SUMMARY - MAIN GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group:	Male				Female			
	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
Number of Animals:	3	3	3	5	3	3	3	3
Number of Completed Animals:	3	3	3	5	3	3	3	3
liver (3 sections - left (medial), right (medial) and caudal lobe)								
Examined	3	3	3	5	3	3	3	3
infiltrate, inflammatory cell, mononuclear; multifocal	1	1	1	1	0	2	2	1
.... minimal	1	1	1	1	0	2	2	1
oil red o staining	3	3	3	5	3	3	3	3
.... slight	2	2	2	5	2	2	3	2
.... moderate	1	1	1	0	1	1	0	0
.... marked	0	0	0	0	0	0	0	1
lower legs								
Examined	0	0	0	1	.	.	.	.
haemorrhage	.	.	.	1n	.	.	.	.
.... minimal	.	.	.	1n	.	.	.	.
inflammation; phlegmonous, diffuse	.	.	.	1n	.	.	.	.
.... slight	.	.	.	1n	.	.	.	.
lungs (with mainstem bronchi and bronchioles - 3 sections)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	0	3	3	4	3	3	3	3
alveolar (pigmented) macrophage(s)	3	0	0	0	0	0	0	0
.... a few	1	0	0	0	0	0	0	0
.... several	2	0	0	0	0	0	0	0
congestion	0	0	0	1	0	0	0	0
.... slight	0	0	0	1	0	0	0	0
lymph node (1, axillary)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	1	0	1	0	0	0	0	0
erythrophagocytosis	1	3	2	4	3	3	3	1
.... minimal	1	1	0	1	2	1	0	0
.... slight	0	1	1	3	0	1	0	0
.... moderate	0	1	1	0	1	0	3	1

Fisher's Exact: n - Inappropriate for statistics

Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance



Provantis

Test Site Reference number: 528 / Study no. 35015

HISTOPATHOLOGY SUMMARY - MAIN GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
 Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
 Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group:	Male				Female			
	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
Number of Animals:	3	3	3	5	3	3	3	3
Number of Completed Animals:	3	3	3	5	3	3	3	3
lymph node (1, axillary)								
(Continued...)								
.... marked	0	0	0	0	0	1	0	0
medulla; lymphoid hyperplasia	0	1	0	1	0	0	0	0
.... moderate	0	1	0	1	0	0	0	0
pigment deposition	2	1	0	3	1	2	3	0
.... minimal	1	0	0	1	0	1	0	0
.... slight	0	1	0	2	1	0	3	0
.... moderate	1	0	0	0	0	1	0	0
sinus histiocytosis	2	3	1	3	3	3	3	3
.... minimal	0	2	0	1	2	1	0	1
.... slight	2	1	0	2	1	1	0	0
.... moderate	0	0	1	0	0	0	3	2
.... marked	0	0	0	0	0	1	0	0
lymph node (1, cervical)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	2	3	2	2	1	1	0	2
erythrophagocytosis	1	0	0	0	1	1	1	0
.... minimal	1	0	0	0	1	1	1	0
pigment deposition	0	0	1	0	0	0	0	0
.... moderate	0	0	1	0	0	0	0	0
sinus histiocytosis	1	0	0	3	1	2	3	1
.... minimal	1	0	0	2	1	0	1	0
.... slight	0	0	0	1	0	1	2	1
.... moderate	0	0	0	0	0	1	0	0
mammary gland								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	0	0	0	0
mammary acinar development	0	0	0	0	3	3	3	3
.... minimal	0	0	0	0	3	2	3	3
.... slight	0	0	0	0	0	1	0	0
muscle (skeletal, leg)								
Examined	3	3	3	5	3	3	3	3

Fisher's Exact

Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance



Provantis

Test Site Reference number: 528 / Study no. 35015

HISTOPATHOLOGY SUMMARY - MAIN GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group: Number of Animals: Number of Completed Animals:	Male				Female			
	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
	3	3	3	5	3	3	3	3
	3	3	3	5	3	3	3	3
muscle (skeletal, leg) (Continued...)								
No abnormalities detected	3	3	2	5	3	3	3	2
infiltrate, inflammatory cell, acute; multifocal	0	0	1	0	0	0	0	0
.... moderate	0	0	1	0	0	0	0	0
infiltrate, inflammatory cell, mononuclear; multifocal	0	0	0	0	0	0	0	1
.... slight	0	0	0	0	0	0	0	1
nerve (sciatic)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	2	3	5	3	3	3	3
infiltrate, inflammatory cell, mononuclear; focal	0	1	0	0	0	0	0	0
.... slight	0	1	0	0	0	0	0	0
ovary (2)								
Examined	.	.	.	.	3	3	3	3
No abnormalities detected	.	.	.	.	2	3	2	3
cyst(s); unilateral	.	.	.	.	1	0	1	0
.... one	.	.	.	.	1	0	0	0
.... two	.	.	.	.	0	0	1	0
pancreas								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
peyer's patches								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
pituitary								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	4	3	3	3	3
pars distalis; cyst(s)	0	0	0	1	0	0	0	0
.... two	0	0	0	1	0	0	0	0
prostate								
Examined	3	3	3	5	.	.	.	.
No abnormalities detected	2	3	3	5	.	.	.	.

Fisher's Exact

Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance



Provantis

Test Site Reference number: 528 / Study no. 35015

HISTOPATHOLOGY SUMMARY - MAIN GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group:	Male				Female			
	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
Number of Animals:	3	3	3	5	3	3	3	3
Number of Completed Animals:	3	3	3	5	3	3	3	3
prostate (Continued...)								
stroma; infiltrate, inflammatory cell, mononuclear	1	0	0	0	.	.	.	.
.... slight	1	0	0	0	.	.	.	.
rectum								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
salivary glands (mandibular, parotid, sublingual)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
seminal vesicle								
Examined	3	3	3	5	.	.	.	.
No abnormalities detected	3	3	3	5	.	.	.	.
skin (left flank)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
spinal cord (3 sections)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
spleen								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	2	1	1	1	3	3	2	2
follicular cell hyperplasia	0	0	0	2	0	0	0	0
.... slight	0	0	0	2	0	0	0	0
pigment deposition	1	2	2	2	0	0	1	1
.... minimal	0	2	2	1	0	0	0	0
.... slight	1	0	0	1	0	0	1	1
sternum								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
stomach								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3

Fisher's Exact

Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance



Provantis

Test Site Reference number: 528 / Study no. 35015

HISTOPATHOLOGY SUMMARY - MAIN GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by

Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys

Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group:	Male				Female			
	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
Number of Animals:	3	3	3	5	3	3	3	3
Number of Completed Animals:	3	3	3	5	3	3	3	3
testicle (2)								
Examined	3	3	3	5	.	.	.	.
No abnormalities detected	0	0	1	1	.	.	.	.
immature	3	3	2	4	.	.	.	.
testicular fibrous hypoplasia; right	0	1	0	0	.	.	.	.
.... minimal	0	1	0	0	.	.	.	.
testicular fibrous hypoplasia; bilateral	0	1	0	0	.	.	.	.
.... marked	0	1	0	0	.	.	.	.
thymus								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	0	0	0	1	0	1	0	0
atrophy	3	3	3	4	3	2	3	3
.... slight	2	1	1	1	0	1	1	0
.... moderate	1	2	2	3	3	1	1	1
.... marked	0	0	0	0	0	0	1	2
cyst(s)	0	0	0	1	2	0	1	0
.... two	0	0	0	0	0	0	1	0
.... three	0	0	0	1	1	0	0	0
.... a few	0	0	0	0	1	0	0	0
thyroid (2) (incl. parathyroids)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	2	1	2	4	3	2	2	1
associated ectopic thymus; left	0	2	0	0	0	1	1	0
associated ectopic thymus; right	1	0	0	1	0	0	0	2
associated ectopic thymus; bilateral	0	0	1	0	0	0	0	0
thighs								
Examined	0	0	0	1	.	.	.	.
haemorrhage	.	.	.	1n	.	.	.	.
.... minimal	.	.	.	1n	.	.	.	.
inflammation; phlegmonous, diffuse	.	.	.	1n	.	.	.	.

Fisher's Exact: n - Inappropriate for statistics

Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance



Provantis

Test Site Reference number: 528 / Study no. 35015

HISTOPATHOLOGY SUMMARY - MAIN GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
 Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
 Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group: Number of Animals: Number of Completed Animals:	Male				Female			
	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 1	Gr. 2	Gr. 3	Gr. 4
	3	3	3	5	3	3	3	3
	3	3	3	5	3	3	3	3
thighs (Continued...)								
.... slight	.	.	.	1n	.	.	.	.
tissue masses or tumours (including regional lymph nodes)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
tongue (incl. base)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
trachea (incl. larynx)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	0	1	0	3	1	0	2	1
lamina propria; infiltrate, inflammatory cell, mononuclear	3	2	3	2	2	3	1	2
.... minimal	1	2	2	2	2	1	0	0
.... slight	2	0	1	0	0	2	1	2
ureter (2)								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
urinary bladder								
Examined	3	3	3	5	3	3	3	3
No abnormalities detected	3	3	3	5	3	3	3	3
uterus (incl. cervix and oviducts)								
Examined	.	.	.	.	3	3	3	3
endometrium; pigment deposition	.	.	.	.	0	0	1	0
.... moderate	.	.	.	.	0	0	1	0
immature/juvenile	.	.	.	.	2	2	3	3
follicular phase	.	.	.	.	1	1	0	0
vagina								
Examined	.	.	.	.	3	3	3	3
No abnormalities detected	.	.	.	.	3	3	3	3

Fisher's Exact: n - Inappropriate for statistics

Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance



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Test Site Reference number: 528 / Study no. 35015

HISTOPATHOLOGY SUMMARY - MAIN GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
 Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
 Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Comments and Markers

Sex	Group	Measurement	Marker
Male	4	lower legs : haemorrhage	n
<i>Comment:</i> Fisher's Exact: n - Inappropriate for statistics			
Male	4	lower legs : haemorrhage, minimal	n
<i>Comment:</i> Fisher's Exact: n - Inappropriate for statistics			
Male	4	lower legs : inflammation; phlegmonous, n diffuse	n
<i>Comment:</i> Fisher's Exact: n - Inappropriate for statistics			
Male	4	lower legs : inflammation; phlegmonous, n diffuse, slight	n
<i>Comment:</i> Fisher's Exact: n - Inappropriate for statistics			
Male	4	thighs : haemorrhage	n
<i>Comment:</i> Fisher's Exact: n - Inappropriate for statistics			
Male	4	thighs : haemorrhage, minimal	n
<i>Comment:</i> Fisher's Exact: n - Inappropriate for statistics			
Male	4	thighs : inflammation; phlegmonous, diffuse	n
<i>Comment:</i> Fisher's Exact: n - Inappropriate for statistics			
Male	4	thighs : inflammation; phlegmonous, diffuse, n slight	n
<i>Comment:</i> Fisher's Exact: n - Inappropriate for statistics			



11. HISTOPATHOLOGY (RECOVERY GROUPS)



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Test Site Reference number: 528 / Study no. 35015

HISTOPATHOLOGY SUMMARY - RECOVERY GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by

Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys

Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Number of Animals	2	2	2	2
Number of Completed Animals	2	2	2	2
adrenal gland (2)				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
aorta abdominalis				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
bone (os femoris with joint)				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
bone marrow (os femoris)				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts)				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
caecum				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
colon				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
duodenum				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
epididymis (2)				
Examined	2	2	.	.
aspermia	2	2	.	.
duct(s); contain(s) mucus/debris; left	0	1	.	.
.... minimal	0	1	.	.
esophagus				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2

Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance



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Test Site Reference number: 528 / Study no. 35015

HISTOPATHOLOGY SUMMARY - RECOVERY GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by

Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys

Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Number of Animals	2	2	2	2
Number of Completed Animals	2	2	2	2
eye with optic nerve (2)				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
gall bladder				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
heart (left/right ventricle, septum)				
Examined	2	2	2	2
No abnormalities detected	0	0	1	1
oil red o staining	2	2	1	1
.... minimal	2	1	1	1
.... slight	0	1	0	0
ileum				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
infusion site(s) - last dosing				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
jejunum				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
kidney (2)				
Examined	2	2	2	2
No abnormalities detected	0	0	1	0
interstitial nephritis; unilateral	1	0	0	0
.... minimal	1	0	0	0
oil red o staining	1	2	1	2
.... minimal	1	1	0	0
.... slight	0	1	0	1
.... moderate	0	0	1	0
.... marked	0	0	0	1
lacrimal gland (2)				
Examined	2	2	2	2

Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance



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Test Site Reference number: 528 / Study no. 35015

HISTOPATHOLOGY SUMMARY - RECOVERY GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by

Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys

Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Number of Animals	2	2	2	2
Number of Completed Animals	2	2	2	2
lacrimal gland (2) (Continued...)				
No abnormalities detected	1	1	1	2
infiltrate, inflammatory cell, mononuclear; left	1	0	0	0
.... slight	1	0	0	0
infiltrate, inflammatory cell, mononuclear; bilateral	0	1	1	0
.... minimal	0	1	0	0
.... slight	0	0	1	0
liver (3 sections - left (medial), right (medial) and caudal lobe)				
Examined	2	2	2	2
infiltrate, inflammatory cell, mononuclear; multifocal	0	1	0	1
.... slight	0	1	0	1
oil red o staining	2	2	2	2
.... slight	2	0	2	0
.... moderate	0	2	0	2
lungs (with mainstem bronchi and bronchioles - 3 sections)				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
lymph node (1, axillary)				
Examined	2	2	2	2
No abnormalities detected	0	0	0	2
erythrophagocytosis	1	0	2	0
.... minimal	1	0	2	0
pigment deposition	1	1	2	0
.... slight	1	1	1	0
.... moderate	0	0	1	0
sinus histiocytosis	2	2	2	0
.... minimal	1	0	0	0
.... slight	1	2	0	0
.... moderate	0	0	2	0
lymph node (1, cervical)				
Examined	2	2	2	2
No abnormalities detected	1	1	0	2
erythrophagocytosis	0	0	1	0

Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance



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Test Site Reference number: 528 / Study no. 35015

HISTOPATHOLOGY SUMMARY - RECOVERY GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by

Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys

Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Number of Animals	2	2	2	2
Number of Completed Animals	2	2	2	2
lymph node (1, cervical) (Continued...)				
.... minimal	0	0	1	0
sinus histiocytosis	1	1	2	0
.... minimal	0	0	1	0
.... slight	1	1	1	0
mammary gland				
Examined	2	2	2	2
No abnormalities detected	2	2	0	0
mammary acinar development	0	0	2	2
.... minimal	0	0	2	2
muscle (skeletal, leg)				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
nerve (sciatic)				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
ovary (2)				
Examined	.	.	2	2
No abnormalities detected	.	.	2	2
pancreas				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
peyer's patches				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
pituitary				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
prostate				
Examined	2	2	.	.
No abnormalities detected	2	2	.	.
rectum				
Examined	2	2	2	2

Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance



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Test Site Reference number: 528 / Study no. 35015

HISTOPATHOLOGY SUMMARY - RECOVERY GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
 Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
 Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Number of Animals	2	2	2	2
Number of Completed Animals	2	2	2	2
rectum (Continued...)				
No abnormalities detected	2	2	2	2
salivary glands (mandibular, parotid, sublingual)				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
seminal vesicle				
Examined	2	2	.	.
No abnormalities detected	2	2	.	.
skin (left flank)				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
spinal cord (3 sections)				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
spleen				
Examined	2	2	2	2
No abnormalities detected	1	0	0	2
pigment deposition	1	2	2	0
.... minimal	1	1	2	0
.... moderate	0	1	0	0
sternum				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
stomach				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
testicle (2)				
Examined	2	2	.	.
immature	2	2	.	.
testicular fibrous hypoplasia; bilateral	1	0	.	.
.... marked	1	0	.	.
thymus				
Examined	2	2	2	2

Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance



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Test Site Reference number: 528 / Study no. 35015

HISTOPATHOLOGY SUMMARY - RECOVERY GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by

Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys

Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Number of Animals	2	2	2	2
Number of Completed Animals	2	2	2	2
thymus (Continued...)				
atrophy	2	2	2	2
.... slight	0	1	0	0
.... moderate	2	1	2	2
cyst(s)	0	2	0	0
.... one	0	1	0	0
.... a few	0	1	0	0
thyroid (2) (incl. parathyroids)				
Examined	2	2	2	2
No abnormalities detected	1	1	2	2
associated ectopic thymus; left	0	1	0	0
associated ectopic thymus; right	1	0	0	0
tissue masses or tumours (including regional lymph nodes)				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
tongue (incl. base)				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
trachea (incl. larynx)				
Examined	2	2	2	2
No abnormalities detected	0	0	1	2
lamina propria; infiltrate, inflammatory cell, mononuclear	2	2	1	0
.... minimal	2	1	0	0
.... slight	0	1	1	0
ureter (2)				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
urinary bladder				
Examined	2	2	2	2
No abnormalities detected	2	2	2	2
uterus (incl. cervix and oviducts)				
Examined	.	.	2	2
follicular phase	.	.	2	2

Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance



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Test Site Reference number: 528 / Study no. 35015

HISTOPATHOLOGY SUMMARY - RECOVERY GROUPS

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
 Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
 Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Group	Male		Female	
	Gr. 1 Rec.	Gr. 4 Rec.	Gr. 1 Rec.	Gr. 4 Rec.
Number of Animals	2	2	2	2
Number of Completed Animals	2	2	2	2
vagina				
Examined	.	.	2	2
No abnormalities detected	.	.	2	2

Fisher's Two-Tailed Exact Test Performed: * = 5% Significance ** = 1% Significance



12. INDIVIDUAL ANIMAL PATHOLOGY



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Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	1	Group:	1	Sex:	Male
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	0 Units/kg		
Death Date:	22/02/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	22/02/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

infusion site(s) - last dosing : haemorrhagic (subcutaneous) (TGL) [infusion site(s) - last dosing : subcutis; haemorrhage; slight (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

epididymis (2) : aspermia

heart (left/right ventricle, septum) : oil red o staining; minimal

infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; slight

infusion site(s) - last dosing : subcutis; haemorrhage; slight [infusion site(s) - last dosing : haemorrhagic (subcutaneous) (G)]

infusion site(s) - last dosing : subcutis; necrosis; minimal

infusion site(s) - last dosing : subcutis; pigment deposition; slight

kidney (2) : oil red o staining; minimal

lacrimal gland (2) : infiltrate, inflammatory cell, mononuclear; right, minimal

liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; moderate

lungs (with mainstem bronchi and bronchioles - 3 sections) : alveolar (pigmented) macrophage(s); several : (comment) Green-brown pigment-laden macrophages.

lymph node (1, axillary) : erythrophagocytosis; minimal

lymph node (1, axillary) : pigment deposition; moderate

lymph node (1, axillary) : sinus histiocytosis; slight

lymph node (1, cervical) : erythrophagocytosis; minimal

lymph node (1, cervical) : sinus histiocytosis; minimal

testicle (2) : immature

thymus : atrophy; slight

thyroid (2) (incl. parathyroids) : (comment) Parathyroid(s); left one missing.

thyroid (2) (incl. parathyroids) : associated ectopic thymus; right

trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; slight



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	1 (Continued)	Group:	1	Sex:	Male
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Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; larynx; mammary gland; muscle (skeletal, leg); nerve (sciatic); pancreas; peyer's patches; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; sternum; stomach; tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	2	Group:	1	Sex:	Male
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	0 Units/kg		
Death Date:	22/02/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	22/02/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

infusion site(s) - last dosing : haemorrhagic (subcutaneous) (TGL) [infusion site(s) - last dosing : subcutis; haemorrhage; slight (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

epididymis (2) : aspermia
heart (left/right ventricle, septum) : oil red o staining; minimal
infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; moderate
infusion site(s) - last dosing : subcutis; fibrosis; slight
infusion site(s) - last dosing : subcutis; granulation tissue; minimal
infusion site(s) - last dosing : subcutis; haemorrhage; slight [infusion site(s) - last dosing : haemorrhagic (subcutaneous) (G)]
infusion site(s) - last dosing : subcutis; necrosis; moderate
infusion site(s) - last dosing : subcutis; (peri-)vasculitis; slight
infusion site(s) - last dosing : subcutis; vessel, intimal thickening; slight
kidney (2) : oil red o staining; slight
lacrimal gland (2) : infiltrate, inflammatory cell, mononuclear; right, slight
liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight
lungs (with mainstem bronchi and bronchioles - 3 sections) : alveolar (pigmented) macrophage(s); a few
lymph node (1, axillary) : pigment deposition; minimal
lymph node (1, axillary) : sinus histiocytosis; slight
prostate : (comment) Tissue incomplete; precludes further diagnosis.
testicle (2) : immature
thymus : atrophy; slight
thyroid (2) (incl. parathyroids) : (comment) Parathyroid(s); left one missing.
trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; slight



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	2 (Continued)	Group:	1	Sex:	Male
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Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; larynx; lymph node (1, cervical); mammary gland; muscle (skeletal, leg); nerve (sciatic); pancreas; peyer's patches; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	3	Group:	1	Sex:	Male
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	0 Units/kg		
Death Date:	22/02/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	22/02/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

epididymis (2) : aspermia
epididymis (2) : duct(s); contain(s) mucus/debris; left, slight
heart (left/right ventricle, septum) : oil red o staining; minimal
infusion site(s) - last dosing : subcutis; haemorrhage; minimal
infusion site(s) - last dosing : subcutis; pigment deposition; slight
infusion site(s) - last dosing : subcutis; vessel, intimal thickening; minimal
kidney (2) : interstitial nephritis; bilateral, minimal
lacrimal gland (2) : infiltrate, inflammatory cell, mononuclear; left, slight
liver (3 sections - left (medial), right (medial) and caudal lobe) : infiltrate, inflammatory cell, mononuclear; multifocal, minimal
liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight
lungs (with mainstem bronchi and bronchioles - 3 sections) : alveolar (pigmented) macrophage(s); several
prostate : stroma; infiltrate, inflammatory cell, mononuclear; slight
spleen : pigment deposition; slight
testicle (2) : immature
thymus : atrophy; moderate
thyroid (2) (incl. parathyroids) : (comment) Parathyroid(s); left one missing.
trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; minimal

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; larynx; lymph node (1, axillary); lymph node (1, cervical); mammary gland; muscle (skeletal, leg); nerve (sciatic); pancreas; peyer's patches; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	6	Group:	1	Sex:	Female
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	0 Units/kg		
Death Date:	01/03/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/03/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

adrenal gland (2) : accessory (adrenal) cortical nodule(s); unilateral, one
heart (left/right ventricle, septum) : oil red o staining; minimal
infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; minimal
infusion site(s) - last dosing : subcutis; vessel, intimal thickening; minimal
liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; moderate
lymph node (1, axillary) : erythrophagocytosis; minimal
lymph node (1, axillary) : sinus histiocytosis; minimal
lymph node (1, cervical) : erythrophagocytosis; minimal
mammary gland : mammary acinar development; minimal
thymus : atrophy; moderate
thymus : cyst(s); three
trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; minimal
uterus (incl. cervix and oviducts) : follicular phase

Histopathology - The following Tissues were Within Normal Limits:

aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; kidney (2); lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); muscle (skeletal, leg); nerve (sciatic); ovary (2); oviducts; pancreas; peyer's patches; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder; vagina



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	7	Group:	1	Sex:	Female
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	0 Units/kg		
Death Date:	01/03/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/03/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

infusion site(s) - last dosing : haemorrhagic (subcutaneous) (TGL) [infusion site(s) - last dosing : subcutis; haemorrhage; moderate (H)]

ovary (2) : left; cystic (TGL) [ovary (2) : cyst(s); unilateral, one : (comment) Large epithelial cyst. (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

heart (left/right ventricle, septum) : oil red o staining; minimal

infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; moderate

infusion site(s) - last dosing : subcutis; fibrosis; slight

infusion site(s) - last dosing : subcutis; haemorrhage; moderate [infusion site(s) - last dosing : haemorrhagic (subcutaneous) (G)]

infusion site(s) - last dosing : subcutis; necrosis; slight

infusion site(s) - last dosing : subcutis; (peri-)vasculitis; slight

infusion site(s) - last dosing : subcutis; pigment deposition; slight

infusion site(s) - last dosing : subcutis; vessel, intimal thickening; slight

liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight

lymph node (1, axillary) : erythrophagocytosis; moderate

lymph node (1, axillary) : sinus histiocytosis; slight

lymph node (1, cervical) : sinus histiocytosis; minimal

mammary gland : mammary acinar development; minimal

ovary (2) : (comment) One missing.

ovary (2) : cyst(s); unilateral, one : (comment) Large epithelial cyst. [ovary (2) : left; cystic (G)]

thymus : atrophy; moderate

thymus : cyst(s); a few

thyroid (2) (incl. parathyroids) : (comment) Parathyroid(s); right one missing.

trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; minimal

uterus (incl. cervix and oviducts) : immature/juvenile



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal: 7 (Continued)

Group: 1

Sex: Female

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; kidney (2); lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); muscle (skeletal, leg); nerve (sciatic); oviducts; pancreas; peyer's patches; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder; vagina



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal: 8	Group: 1	Sex: Female
Species: Cynomolgus Monkey	Strain: Macaca fascicularis	
Study Type: Repeated Dose Toxicity	Route: Intravenous infusion	

Dose: 0 Units/kg		
Death Date: 01/03/2019	Removal Reason: Terminal Sacrifice	
Necropsy Date: 01/03/2019	Study Day (Week) of Death: 12 (2)	

Gross Status: Complete

Histo Status: Complete

Gross Pathology Observations [Correlation]:

infusion site(s) - last dosing : haemorrhagic (subcutaneous) (TGL) [infusion site(s) - last dosing : subcutis; haemorrhage; slight (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

duodenum : mucosa; pigment deposition; multifocal, slight : (comment) Green-brown pigment.

heart (left/right ventricle, septum) : ventricle; myocardium; infiltrate, inflammatory cell, mononuclear; focal, minimal

heart (left/right ventricle, septum) : oil red o staining; minimal

infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; marked

infusion site(s) - last dosing : subcutis; fibrosis; slight

infusion site(s) - last dosing : subcutis; granulation tissue; minimal

infusion site(s) - last dosing : subcutis; haemorrhage; slight [infusion site(s) - last dosing : haemorrhagic (subcutaneous) (G)]

infusion site(s) - last dosing : subcutis; necrosis; slight

infusion site(s) - last dosing : subcutis; (peri-)vasculitis; slight

infusion site(s) - last dosing : subcutis; vessel, intimal thickening; minimal

kidney (2) : oil red o staining; minimal

lacrimal gland (2) : infiltrate, inflammatory cell, mononuclear; right, minimal

liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight

lymph node (1, axillary) : erythrophagocytosis; minimal

lymph node (1, axillary) : pigment deposition; slight

lymph node (1, axillary) : sinus histiocytosis; minimal

mammary gland : mammary acinar development; minimal

thymus : atrophy; moderate

uterus (incl. cervix and oviducts) : immature/juvenile



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	8 (Continued)	Group:	1	Sex:	Female
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Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); lymph node (1, cervical); muscle (skeletal, leg); nerve (sciatic); ovary (2); oviducts; pancreas; peyer's patches; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; vagina



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	11	Group:	2	Sex:	Male
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	35 Units/kg		
Death Date:	22/02/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	22/02/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

infusion site(s) - last dosing : haemorrhagic (subcutaneous) (TGL) [infusion site(s) - last dosing : subcutis; haemorrhage; slight (H)]

thyroid (2) (incl. parathyroids) : left; pale (TGL) [no correlate : to gross pathology (H)]

thyroid (2) (incl. parathyroids) : left; reduced in size (TGL) [no correlate : to gross pathology (H)]

thyroid (2) (incl. parathyroids) : left; soft consistency (TGL) [no correlate : to gross pathology (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

epididymis (2) : aspermia

epididymis (2) : duct(s); contain(s) mucus/debris; left, minimal

heart (left/right ventricle, septum) : oil red o staining; minimal

infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; moderate

infusion site(s) - last dosing : subcutis; granulation tissue; minimal

infusion site(s) - last dosing : subcutis; haemorrhage; slight [infusion site(s) - last dosing : haemorrhagic (subcutaneous) (G)]

infusion site(s) - last dosing : subcutis; necrosis; moderate

infusion site(s) - last dosing : subcutis; (peri-)vasculitis; moderate

kidney (2) : interstitial nephritis; unilateral, slight

liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight

lymph node (1, axillary) : erythrophagocytosis; minimal

lymph node (1, axillary) : pigment deposition; slight

lymph node (1, axillary) : sinus histiocytosis; minimal

testicle (2) : immature

thymus : atrophy; slight

thyroid (2) (incl. parathyroids) : (comment) Left thyroid and parathyroid missing.

no correlate : to gross pathology [thyroid (2) (incl. parathyroids) : left; reduced in size (G) | thyroid (2) (incl. parathyroids) : left; pale (G) | thyroid (2) (incl. parathyroids) : left; soft consistency (G)]



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	11 (Continued)	Group:	2	Sex:	Male
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Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); lymph node (1, cervical); mammary gland; muscle (skeletal, leg); nerve (sciatic); pancreas; peyer's patches; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
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INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	12	Group:	2	Sex:	Male
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	35 Units/kg		
Death Date:	22/02/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	22/02/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

epididymis (2) : aspermia
epididymis (2) : duct(s); contain(s) mucus/debris; left, minimal
heart (left/right ventricle, septum) : oil red o staining; minimal
infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; moderate
infusion site(s) - last dosing : subcutis; fibrosis; slight
infusion site(s) - last dosing : subcutis; granulation tissue; minimal
infusion site(s) - last dosing : subcutis; haemorrhage; slight
infusion site(s) - last dosing : subcutis; necrosis; slight
infusion site(s) - last dosing : subcutis; (peri-)vasculitis; slight
infusion site(s) - last dosing : subcutis; pigment deposition; slight
kidney (2) : interstitial nephritis; unilateral, minimal
kidney (2) : oil red o staining; slight
lacrimal gland (2) : infiltrate, inflammatory cell, mononuclear; bilateral, slight
liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight
lymph node (1, axillary) : erythrophagocytosis; slight
lymph node (1, axillary) : sinus histiocytosis; minimal
nerve (sciatic) : infiltrate, inflammatory cell, mononuclear; focal, slight : (comment) Perivascular.
spleen : pigment deposition; minimal
testicle (2) : immature
testicle (2) : testicular fibrous hypoplasia; right, minimal
thymus : atrophy; moderate
thyroid (2) (incl. parathyroids) : associated ectopic thymus; left
trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; minimal



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	12 (Continued)	Group:	2	Sex:	Male
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Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); lymph node (1, cervical); mammary gland; muscle (skeletal, leg); pancreas; peyer's patches; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); sternum; stomach; tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	13	Group:	2	Sex:	Male
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	35 Units/kg		
Death Date:	22/02/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	22/02/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

infusion site(s) - last dosing : haemorrhagic (subcutaneous) (TGL) [infusion site(s) - last dosing : subcutis; haemorrhage; moderate (H)]
lymph node (1, axillary) : enlarged (TGL) [lymph node (1, axillary) : medulla; lymphoid hyperplasia; moderate (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

epididymis (2) : aspermia
heart (left/right ventricle, septum) : oil red o staining; minimal
infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; slight
infusion site(s) - last dosing : subcutis; fibrosis; slight
infusion site(s) - last dosing : subcutis; granulation tissue; slight
infusion site(s) - last dosing : subcutis; haemorrhage; moderate [infusion site(s) - last dosing : haemorrhagic (subcutaneous) (G)]
kidney (2) : interstitial nephritis; bilateral, minimal
liver (3 sections - left (medial), right (medial) and caudal lobe) : infiltrate, inflammatory cell, mononuclear; multifocal, minimal
liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; moderate
lymph node (1, axillary) : erythrophagocytosis; moderate
lymph node (1, axillary) : medulla; lymphoid hyperplasia; moderate [lymph node (1, axillary) : enlarged (G)]
lymph node (1, axillary) : sinus histiocytosis; slight
spleen : pigment deposition; minimal
testicle (2) : immature
testicle (2) : testicular fibrous hypoplasia; bilateral, marked
thymus : atrophy; moderate
thyroid (2) (incl. parathyroids) : associated ectopic thymus; left
trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; minimal



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	13 (Continued)	Group:	2	Sex:	Male
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Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); lymph node (1, cervical); mammary gland; muscle (skeletal, leg); nerve (sciatic); pancreas; peyer's patches; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); sternum; stomach; tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	14	Group:	2	Sex:	Female
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	35 Units/kg		
Death Date:	01/03/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/03/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

heart (left/right ventricle, septum) : oil red o staining; minimal
infusion site(s) - last dosing : subcutis; haemorrhage; minimal
kidney (2) : oil red o staining; minimal
liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; moderate
lymph node (1, axillary) : erythrophagocytosis; marked
lymph node (1, axillary) : pigment deposition; moderate
lymph node (1, axillary) : sinus histiocytosis; marked
lymph node (1, cervical) : erythrophagocytosis; minimal
lymph node (1, cervical) : sinus histiocytosis; moderate
mammary gland : mammary acinar development; slight
thyroid (2) (incl. parathyroids) : associated ectopic thymus; left
trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; slight
uterus (incl. cervix and oviducts) : immature/juvenile

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); muscle (skeletal, leg); nerve (sciatic); ovary (2); oviducts; pancreas; peyer's patches; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; sternum; stomach; thymus; tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder; vagina



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	15	Group:	2	Sex:	Female
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	35 Units/kg		
Death Date:	01/03/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/03/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

infusion site(s) - last dosing : haemorrhagic (subcutaneous) (TGL) [infusion site(s) - last dosing : subcutis; haemorrhage; minimal (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

heart (left/right ventricle, septum) : oil red o staining; minimal

infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; slight

infusion site(s) - last dosing : subcutis; haemorrhage; minimal [infusion site(s) - last dosing : haemorrhagic (subcutaneous) (G)]

infusion site(s) - last dosing : subcutis; necrosis; minimal

infusion site(s) - last dosing : subcutis; pigment deposition; slight

liver (3 sections - left (medial), right (medial) and caudal lobe) : infiltrate, inflammatory cell, mononuclear; multifocal, minimal

liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight

lymph node (1, axillary) : erythrophagocytosis; slight

lymph node (1, axillary) : sinus histiocytosis; slight

lymph node (1, cervical) : sinus histiocytosis; slight

mammary gland : mammary acinar development; minimal

thymus : atrophy; slight

trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; slight

uterus (incl. cervix and oviducts) : follicular phase

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; kidney (2); lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); muscle (skeletal, leg); nerve (sciatic); ovary (2); oviducts; pancreas; peyer's patches; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder; vagina



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	16	Group:	2	Sex:	Female
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	35 Units/kg		
Death Date:	01/03/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/03/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

infusion site(s) - last dosing : haemorrhagic (subcutaneous) (TGL) [infusion site(s) - last dosing : subcutis; haemorrhage; slight (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

heart (left/right ventricle, septum) : oil red o staining; minimal

infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; slight

infusion site(s) - last dosing : subcutis; haemorrhage; slight [infusion site(s) - last dosing : haemorrhagic (subcutaneous) (G)]

infusion site(s) - last dosing : subcutis; pigment deposition; slight

kidney (2) : interstitial nephritis; unilateral, minimal

liver (3 sections - left (medial), right (medial) and caudal lobe) : infiltrate, inflammatory cell, mononuclear; multifocal, minimal

liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight

lymph node (1, axillary) : erythrophagocytosis; minimal

lymph node (1, axillary) : pigment deposition; minimal

lymph node (1, axillary) : sinus histiocytosis; minimal

mammary gland : mammary acinar development; minimal

thymus : atrophy; moderate

trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; minimal

uterus (incl. cervix and oviducts) : immature/juvenile

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); lymph node (1, cervical); muscle (skeletal, leg); nerve (sciatic); ovary (2); oviducts; pancreas; peyer's patches; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder; vagina



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	17	Group:	3	Sex:	Male
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	110 Units/kg		
Death Date:	22/02/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	22/02/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

infusion site(s) - last dosing : haemorrhagic (subcutaneous) (TGL) [infusion site(s) - last dosing : subcutis; haemorrhage; slight (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

epididymis (2) : aspermia

heart (left/right ventricle, septum) : oil red o staining; slight

infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; slight

infusion site(s) - last dosing : subcutis; haemorrhage; slight [infusion site(s) - last dosing : haemorrhagic (subcutaneous) (G)]

infusion site(s) - last dosing : subcutis; necrosis; slight

infusion site(s) - last dosing : subcutis; (peri-)vasculitis; minimal

infusion site(s) - last dosing : subcutis; pigment deposition; slight

liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; moderate

spleen : pigment deposition; minimal

testicle (2) : immature

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : (comment) Parathyroid(s); right one missing.

thyroid (2) (incl. parathyroids) : associated ectopic thymus; bilateral

trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; minimal

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; kidney (2); lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); lymph node (1, axillary); lymph node (1, cervical); mammary gland; muscle (skeletal, leg); nerve (sciatic); pancreas; peyer's patches; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); sternum; stomach; tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	18	Group:	3	Sex:	Male
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	110 Units/kg		
Death Date:	22/02/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	22/02/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

infusion site(s) - last dosing : haemorrhagic (subcutaneous) (TGL) [infusion site(s) - last dosing : subcutis; haemorrhage; slight (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

heart (left/right ventricle, septum) : oil red o staining; minimal
infusion site(s) - last dosing : subcutis; fibrosis; slight
infusion site(s) - last dosing : subcutis; granulation tissue; minimal
infusion site(s) - last dosing : subcutis; haemorrhage; slight [infusion site(s) - last dosing : haemorrhagic (subcutaneous) (G)]
infusion site(s) - last dosing : subcutis; necrosis; slight
infusion site(s) - last dosing : subcutis; (peri-)vasculitis; slight
infusion site(s) - last dosing : subcutis; pigment deposition; slight
kidney (2) : interstitial nephritis; bilateral, minimal
lacrimal gland (2) : infiltrate, inflammatory cell, mononuclear; right, minimal
liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight
lymph node (1, axillary) : erythrophagocytosis; moderate
lymph node (1, axillary) : sinus histiocytosis; moderate
lymph node (1, cervical) : pigment deposition; moderate : (comment) Black pigment.
muscle (skeletal, leg) : infiltrate, inflammatory cell, acute; multifocal, moderate
thymus : atrophy; slight
trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; minimal

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; epididymis (2); esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); mammary gland; nerve (sciatic); pancreas; peyer's patches; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; sternum; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	19	Group:	3	Sex:	Male
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	110 Units/kg		
Death Date:	22/02/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	22/02/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

infusion site(s) - last dosing : haemorrhagic (subcutaneous) (TGL) [infusion site(s) - last dosing : subcutis; haemorrhage; moderate (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

epididymis (2) : aspermia

heart (left/right ventricle, septum) : oil red o staining; minimal

infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; moderate

infusion site(s) - last dosing : subcutis; fibrosis; minimal

infusion site(s) - last dosing : subcutis; granulation tissue; minimal

infusion site(s) - last dosing : subcutis; haemorrhage; moderate [infusion site(s) - last dosing : haemorrhagic (subcutaneous) (G)]

infusion site(s) - last dosing : subcutis; necrosis; slight

infusion site(s) - last dosing : subcutis; (peri-)vasculitis; slight

infusion site(s) - last dosing : subcutis; pigment deposition; minimal

liver (3 sections - left (medial), right (medial) and caudal lobe) : infiltrate, inflammatory cell, mononuclear; multifocal, minimal

liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight

lymph node (1, axillary) : erythrophagocytosis; slight

spleen : pigment deposition; minimal

testicle (2) : immature

thymus : atrophy; moderate

trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; slight

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; kidney (2); lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); lymph node (1, cervical); mammary gland; muscle (skeletal, leg); nerve (sciatic); pancreas; peyer's patches; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	20	Group:	3	Sex:	Female
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	110 Units/kg		
Death Date:	01/03/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/03/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

infusion site(s) - last dosing : haemorrhagic (subcutaneous) (TGL) [infusion site(s) - last dosing : subcutis; haemorrhage; slight (H)]

ovary (2) : left; cystic (TGL) [ovary (2) : cyst(s); unilateral, two (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

heart (left/right ventricle, septum) : ventricle; myocardium; infiltrate, inflammatory cell, mononuclear; multifocal, minimal

heart (left/right ventricle, septum) : oil red o staining; minimal

infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; marked

infusion site(s) - last dosing : subcutis; haemorrhage; slight [infusion site(s) - last dosing : haemorrhagic (subcutaneous) (G)]

infusion site(s) - last dosing : subcutis; necrosis; slight

infusion site(s) - last dosing : subcutis; (peri-)vasculitis; moderate

infusion site(s) - last dosing : subcutis; vessel, intimal thickening; moderate

liver (3 sections - left (medial), right (medial) and caudal lobe) : infiltrate, inflammatory cell, mononuclear; multifocal, minimal

liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight

lymph node (1, axillary) : erythrophagocytosis; moderate

lymph node (1, axillary) : pigment deposition; slight

lymph node (1, axillary) : sinus histiocytosis; moderate

lymph node (1, cervical) : erythrophagocytosis; minimal

lymph node (1, cervical) : sinus histiocytosis; minimal

mammary gland : mammary acinar development; minimal

ovary (2) : cyst(s); unilateral, two [ovary (2) : left; cystic (G)]

oviducts : (comment) Tissue incomplete; precludes further diagnosis.

thymus : atrophy; moderate

thymus : cyst(s); two

thyroid (2) (incl. parathyroids) : associated ectopic thymus; left

trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; slight

uterus (incl. cervix and oviducts) : immature/juvenile



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	20 (Continued)	Group:	3	Sex:	Female
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Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; kidney (2); lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); muscle (skeletal, leg); nerve (sciatic); oviducts; pancreas; peyer's patches; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; sternum; stomach; tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder; vagina



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	21	Group:	3	Sex:	Female
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	110 Units/kg		
Death Date:	01/03/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/03/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

infusion site(s) - last dosing : haemorrhagic (subcutaneous) (TGL) [infusion site(s) - last dosing : subcutis; haemorrhage; slight (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

heart (left/right ventricle, septum) : oil red o staining; minimal

infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; marked : (comment) Extending into the muscle (fascii),

infusion site(s) - last dosing : subcutis; granulation tissue; slight

infusion site(s) - last dosing : subcutis; haemorrhage; slight [infusion site(s) - last dosing : haemorrhagic (subcutaneous) (G)]

infusion site(s) - last dosing : subcutis; necrosis; slight

infusion site(s) - last dosing : subcutis; (peri-)vasculitis; moderate

infusion site(s) - last dosing : subcutis; pigment deposition; minimal

liver (3 sections - left (medial), right (medial) and caudal lobe) : infiltrate, inflammatory cell, mononuclear; multifocal, minimal

liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight

lymph node (1, axillary) : erythrophagocytosis; moderate

lymph node (1, axillary) : pigment deposition; slight

lymph node (1, axillary) : sinus histiocytosis; moderate

lymph node (1, cervical) : sinus histiocytosis; slight

mammary gland : mammary acinar development; minimal

spleen : pigment deposition; slight

thymus : atrophy; marked

uterus (incl. cervix and oviducts) : immature/juvenile



Provantis

Pathology - Individual Animal Data

INDIVIDUAL ANIMAL PATHOLOGY

35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	21 (Continued)	Group:	3	Sex:	Female
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Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; kidney (2); lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); muscle (skeletal, leg); nerve (sciatic); ovary (2); oviducts; pancreas; peyer's patches; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; vagina



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	22	Group:	3	Sex:	Female
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	110 Units/kg		
Death Date:	01/03/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/03/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

infusion site(s) - last dosing : haemorrhagic (subcutaneous) (TGL) [infusion site(s) - last dosing : subcutis; haemorrhage; slight (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; slight

infusion site(s) - last dosing : subcutis; haemorrhage; slight [infusion site(s) - last dosing : haemorrhagic (subcutaneous) (G)]

infusion site(s) - last dosing : subcutis; (peri-)vasculitis; minimal

infusion site(s) - last dosing : subcutis; pigment deposition; slight

infusion site(s) - last dosing : subcutis; vessel, intimal thickening; minimal

liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight

lymph node (1, axillary) : erythrophagocytosis; moderate

lymph node (1, axillary) : pigment deposition; slight

lymph node (1, axillary) : sinus histiocytosis; moderate

lymph node (1, cervical) : sinus histiocytosis; slight

mammary gland : mammary acinar development; minimal

thymus : atrophy; slight

thyroid (2) (incl. parathyroids) : (comment) Parathyroid(s); left one missing.

uterus (incl. cervix and oviducts) : endometrium; pigment deposition; moderate : (comment) Brown pigment.

uterus (incl. cervix and oviducts) : immature/juvenile

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; heart (left/right ventricle, septum); ileum; jejunum; kidney (2); lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); muscle (skeletal, leg); nerve (sciatic); ovary (2); oviducts; pancreas; peyer's patches; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; vagina



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INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	23	Group:	4	Sex:	Male
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	350/225/200 Units/kg		
Death Date:	22/02/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	22/02/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

infusion site(s) - last dosing : haemorrhagic (subcutaneous) (TGL) [infusion site(s) - last dosing : subcutis; haemorrhage; slight (H)]

spleen : enlarged (TGL) [spleen : follicular cell hyperplasia; slight (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

epididymis (2) : aspermia

heart (left/right ventricle, septum) : oil red o staining; minimal

infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; moderate

infusion site(s) - last dosing : subcutis; fibrosis; slight

infusion site(s) - last dosing : subcutis; haemorrhage; slight [infusion site(s) - last dosing : haemorrhagic (subcutaneous) (G)]

infusion site(s) - last dosing : subcutis; necrosis; slight

infusion site(s) - last dosing : subcutis; (peri-)vasculitis; slight

lacrimal gland (2) : infiltrate, inflammatory cell, mononuclear; left, minimal

liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight

lymph node (1, axillary) : erythrophagocytosis; slight

lymph node (1, axillary) : pigment deposition; minimal

lymph node (1, axillary) : sinus histiocytosis; slight

lymph node (1, cervical) : sinus histiocytosis; minimal

prostate : (comment) Tissue incomplete; precludes further diagnosis.

spleen : follicular cell hyperplasia; slight [spleen : enlarged (G)]

testicle (2) : immature

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : associated ectopic thymus; right

trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; minimal



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INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	23 (Continued)	Group:	4	Sex:	Male
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Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; kidney (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); mammary gland; muscle (skeletal, leg); nerve (sciatic); pancreas; peyer's patches; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); sternum; stomach; tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder



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INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	24	Group:	4	Sex:	Male
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	350/225/200 Units/kg		
Death Date:	22/02/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	22/02/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

infusion site(s) - last dosing : haemorrhagic (subcutaneous) (TGL) [infusion site(s) - last dosing : subcutis; haemorrhage; moderate (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

epididymis (2) : aspermia

heart (left/right ventricle, septum) : oil red o staining; minimal

infusion site(s) - last dosing : subcutis; fibrosis; slight

infusion site(s) - last dosing : subcutis; granulation tissue; minimal

infusion site(s) - last dosing : subcutis; haemorrhage; moderate [infusion site(s) - last dosing : haemorrhagic (subcutaneous) (G)]

infusion site(s) - last dosing : subcutis; necrosis; minimal

infusion site(s) - last dosing : subcutis; pigment deposition; minimal

kidney (2) : oil red o staining; minimal

liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight

lymph node (1, axillary) : erythrophagocytosis; slight

spleen : pigment deposition; slight

testicle (2) : immature

thymus : atrophy; moderate

thymus : cyst(s); three

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); lymph node (1, cervical); mammary gland; muscle (skeletal, leg); nerve (sciatic); pancreas; peyer's patches; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	25	Group:	4	Sex:	Male
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	350/225/200 Units/kg		
Death Date:	22/02/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	22/02/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

infusion site(s) - last dosing : haemorrhagic (subcutaneous) (TGL) [infusion site(s) - last dosing : subcutis; haemorrhage; slight (H)]
lymph node (1, axillary) : enlarged (TGL) [lymph node (1, axillary) : medulla; lymphoid hyperplasia; moderate : (comment) Medullary hyperplasia of lymphocytes and plasma cells in the medullary cords. (H)]
spleen : enlarged (TGL) [no correlate : to gross pathology (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

epididymis (2) : aspermia
heart (left/right ventricle, septum) : oil red o staining; minimal
infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; moderate
infusion site(s) - last dosing : subcutis; fibrosis; slight
infusion site(s) - last dosing : subcutis; granulation tissue; minimal
infusion site(s) - last dosing : subcutis; haemorrhage; slight [infusion site(s) - last dosing : haemorrhagic (subcutaneous) (G)]
infusion site(s) - last dosing : subcutis; necrosis; slight
infusion site(s) - last dosing : subcutis; (peri-)vasculitis; minimal
infusion site(s) - last dosing : subcutis; pigment deposition; minimal
liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight
lymph node (1, axillary) : erythrophagocytosis; slight
lymph node (1, axillary) : medulla; lymphoid hyperplasia; moderate : (comment) Medullary hyperplasia of lymphocytes and plasma cells in the medullary cords. [lymph node (1, axillary) : enlarged (G)]
lymph node (1, axillary) : pigment deposition; slight
testicle (2) : immature
thymus : atrophy; moderate
no correlate : to gross pathology [spleen : enlarged (G)]



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35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	25 (Continued)	Group:	4	Sex:	Male
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Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; kidney (2); lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); lymph node (1, cervical); mammary gland; muscle (skeletal, leg); nerve (sciatic); pancreas; peyer's patches; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	26	Group:	4	Sex:	Male
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	350/225/200 Units/kg		
Death Date:	11/02/2019	Removal Reason:	Premature Sacrifice		
Necropsy Date:	11/02/2019	Study Day (Week) of Death:	1 (1)	Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

lungs (with mainstem bronchi and bronchioles - 3 sections) : emphysematous (TGL) [no correlate : to gross pathology (H)]

lymph node (1, axillary) : enlarged (TGL) [no correlate : to gross pathology (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

heart (left/right ventricle, septum) : oil red o staining; minimal

liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight

lungs (with mainstem bronchi and bronchioles - 3 sections) : congestion; slight

lymph node (1, axillary) : erythrophagocytosis; minimal

lymph node (1, axillary) : sinus histiocytosis; minimal

lymph node (1, cervical) : sinus histiocytosis; slight

spleen : follicular cell hyperplasia; slight

thymus : atrophy; slight

no correlate : to gross pathology [lymph node (1, axillary) : enlarged (G) | lungs (with mainstem bronchi and bronchioles - 3 sections) : emphysematous (G)]

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; epididymis (2); esophagus; eye with optic nerve (2); gall bladder; ileum; infusion site(s) - last dosing; jejunum; kidney (2); lacrimal gland (2); larynx; mammary gland; muscle (skeletal, leg); nerve (sciatic); pancreas; peyer's patches; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); sternum; stomach; testicle (2); thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder



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35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	27	Group:	4	Sex:	Male
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	350/225/200 Units/kg		
Death Date:	11/02/2019	Removal Reason:	Premature Sacrifice		
Necropsy Date:	11/02/2019	Study Day (Week) of Death:	1 (1)	Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

adrenal gland (2) : enlarged (TGL) [no correlate : to gross pathology (H)]
 lower legs : subcutaneous tissue; haemorrhagic; bilateral (TGL) [lower legs : inflammation; phlegmonous, diffuse, slight : (comment) Acute inflammation with interstitial oedema and minimal haemorrhage. (H)]
 lower legs : subcutaneous tissue; oedematous; bilateral (TGL) [lower legs : inflammation; phlegmonous, diffuse, slight : (comment) Acute inflammation with interstitial oedema and minimal haemorrhage. (H)]
 lymph node (1, axillary) : enlarged (TGL) [no correlate : to gross pathology (H)]
 lymph node (1, cervical) : enlarged (TGL) [no correlate : to gross pathology (H)]
 thighs : subcutaneous tissue; haemorrhagic; bilateral (TGL) [thighs : inflammation; phlegmonous, diffuse, slight : (comment) Acute inflammation with interstitial oedema and minimal haemorrhage. (H)]
 thighs : subcutaneous tissue; oedematous; bilateral (TGL) [thighs : inflammation; phlegmonous, diffuse, slight : (comment) Acute inflammation with interstitial oedema and minimal haemorrhage. (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

epididymis (2) : aspermia
 kidney (2) : interstitial nephritis; unilateral, minimal
 liver (3 sections - left (medial), right (medial) and caudal lobe) : infiltrate, inflammatory cell, mononuclear; multifocal, minimal
 liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight
 lower legs : haemorrhage; minimal
 lower legs : inflammation; phlegmonous, diffuse, slight : (comment) Acute inflammation with interstitial oedema and minimal haemorrhage. [lower legs : subcutaneous tissue; haemorrhagic; bilateral (G) | lower legs : subcutaneous tissue; oedematous; bilateral (G)]
 lymph node (1, axillary) : pigment deposition; slight
 lymph node (1, axillary) : sinus histiocytosis; slight
 lymph node (1, cervical) : sinus histiocytosis; minimal
 pituitary : pars distalis; cyst(s); two : (comment) Small.
 spleen : pigment deposition; minimal
 testicle (2) : immature
 thighs : haemorrhage; minimal



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35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal: 27 (Continued)	Group: 4	Sex: Male
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Histopathology Observations [Correlation] (Continued):

thighs : inflammation; phlegmonous, diffuse, slight : (comment) Acute inflammation with interstitial oedema and minimal haemorrhage. [thighs : subcutaneous tissue; haemorrhagic; bilateral (G) | thighs : subcutaneous tissue; oedematous; bilateral (G)]

trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; minimal

no correlate : to gross pathology [lymph node (1, cervical) : enlarged (G) | lymph node (1, axillary) : enlarged (G) | adrenal gland (2) : enlarged (G)]

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; heart (left/right ventricle, septum); ileum; infusion site(s) - last dosing; jejunum; lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); mammary gland; muscle (skeletal, leg); nerve (sciatic); pancreas; peyer's patches; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); sternum; stomach; thymus; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder



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35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal: 28	Group: 4	Sex: Female
Species: Cynomolgus Monkey	Strain: Macaca fascicularis	
Study Type: Repeated Dose Toxicity	Route: Intravenous infusion	

Dose: 350/225/200 Units/kg		
Death Date: 01/03/2019	Removal Reason: Terminal Sacrifice	
Necropsy Date: 01/03/2019	Study Day (Week) of Death: 12 (2)	

Gross Status: Complete

Histo Status: Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

adrenal gland (2) : accessory (adrenal) cortical nodule(s); unilateral, one
heart (left/right ventricle, septum) : oil red o staining; minimal
infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; minimal
infusion site(s) - last dosing : subcutis; granulation tissue; minimal
infusion site(s) - last dosing : subcutis; haemorrhage; slight
infusion site(s) - last dosing : subcutis; pigment deposition; slight
liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight
lymph node (1, axillary) : sinus histiocytosis; minimal
lymph node (1, cervical) : sinus histiocytosis; slight
mammary gland : mammary acinar development; minimal
thymus : atrophy; moderate
thyroid (2) (incl. parathyroids) : associated ectopic thymus; right
trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; slight
uterus (incl. cervix and oviducts) : immature/juvenile

Histopathology - The following Tissues were Within Normal Limits:

aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; kidney (2); lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); muscle (skeletal, leg); nerve (sciatic); ovary (2); oviducts; pancreas; peyer's patches; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; sternum; stomach; tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder; vagina



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INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	29	Group:	4	Sex:	Female
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	350/225/200 Units/kg		
Death Date:	01/03/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/03/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

infusion site(s) - last dosing : haemorrhagic (subcutaneous) (TGL) [infusion site(s) - last dosing : subcutis; haemorrhage; slight (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

heart (left/right ventricle, septum) : oil red o staining; minimal

infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; slight

infusion site(s) - last dosing : subcutis; haemorrhage; slight [infusion site(s) - last dosing : haemorrhagic (subcutaneous) (G)]

infusion site(s) - last dosing : subcutis; necrosis; minimal

infusion site(s) - last dosing : subcutis; (peri-)vasculitis; minimal

infusion site(s) - last dosing : subcutis; pigment deposition; slight

kidney (2) : oil red o staining; minimal

liver (3 sections - left (medial), right (medial) and caudal lobe) : infiltrate, inflammatory cell, mononuclear; multifocal, minimal

liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight

lymph node (1, axillary) : erythrophagocytosis; moderate

lymph node (1, axillary) : sinus histiocytosis; moderate

mammary gland : mammary acinar development; minimal

thymus : atrophy; marked

trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; slight

uterus (incl. cervix and oviducts) : immature/juvenile

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); lymph node (1, cervical); muscle (skeletal, leg); nerve (sciatic); ovary (2); oviducts; pancreas; peyer's patches; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder; vagina



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INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	30	Group:	4	Sex:	Female
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	350/225/200 Units/kg		
Death Date:	01/03/2019	Removal Reason:	Terminal Sacrifice		
Necropsy Date:	01/03/2019	Study Day (Week) of Death:	12 (2)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

thymus : reduced in size (TGL) [thymus : atrophy; marked (H)]

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

adrenal gland (2) : accessory (adrenal) cortical nodule(s); unilateral, one
heart (left/right ventricle, septum) : oil red o staining; slight
infusion site(s) - last dosing : subcutis; infiltrate, inflammatory cell, acute; slight
infusion site(s) - last dosing : subcutis; fibrosis; slight
infusion site(s) - last dosing : subcutis; granulation tissue; minimal
infusion site(s) - last dosing : subcutis; haemorrhage; minimal
infusion site(s) - last dosing : subcutis; (peri-)vasculitis; minimal
kidney (2) : oil red o staining; marked
lacrimal gland (2) : infiltrate, inflammatory cell, mononuclear; right, slight
liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; marked
lymph node (1, axillary) : sinus histiocytosis; moderate
mammary gland : mammary acinar development; minimal
muscle (skeletal, leg) : infiltrate, inflammatory cell, mononuclear; multifocal, slight
spleen : pigment deposition; slight
thymus : atrophy; marked [thymus : reduced in size (G)]
thyroid (2) (incl. parathyroids) : associated ectopic thymus; right
uterus (incl. cervix and oviducts) : immature/juvenile

Histopathology - The following Tissues were Within Normal Limits:

aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; jejunum; larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); lymph node (1, cervical); nerve (sciatic); ovary (2); oviducts; pancreas; peyer's patches; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); sternum; stomach; tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; vagina



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	4	Group:	1R	Sex:	Male
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	0 Units/kg		
Death Date:	08/03/2019	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	08/03/2019	Study Day (Week) of Death:	26 (4)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

epididymis (2) : aspermia

heart (left/right ventricle, septum) : oil red o staining; minimal

kidney (2) : oil red o staining; minimal

liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight

lymph node (1, axillary) : erythrophagocytosis; minimal

lymph node (1, axillary) : sinus histiocytosis; slight

testicle (2) : immature

testicle (2) : testicular fibrous hypoplasia; bilateral, marked

thymus : atrophy; moderate

trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; minimal

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; infusion site(s) - last dosing; jejunum; lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); lymph node (1, cervical); mammary gland; muscle (skeletal, leg); nerve (sciatic); pancreas; peyer's patches; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); spleen; sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	5	Group:	1R	Sex:	Male
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	0 Units/kg		
Death Date:	08/03/2019	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	08/03/2019	Study Day (Week) of Death:	26 (4)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

epididymis (2) : aspermia
heart (left/right ventricle, septum) : oil red o staining; minimal
kidney (2) : interstitial nephritis; unilateral, minimal
lacrimal gland (2) : infiltrate, inflammatory cell, mononuclear; left, slight
liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight
lymph node (1, axillary) : pigment deposition; slight
lymph node (1, axillary) : sinus histiocytosis; minimal
lymph node (1, cervical) : sinus histiocytosis; slight
spleen : pigment deposition; minimal
testicle (2) : immature
thymus : atrophy; moderate
thyroid (2) (incl. parathyroids) : associated ectopic thymus; right
trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; minimal

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; infusion site(s) - last dosing; jejunum; larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); mammary gland; muscle (skeletal, leg); nerve (sciatic); pancreas; peyer's patches; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); sternum; stomach; tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	9	Group:	1R	Sex:	Female
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	0 Units/kg		
Death Date:	15/03/2019	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	15/03/2019	Study Day (Week) of Death:	26 (4)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

kidney (2) : oil red o staining; moderate
liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight
lymph node (1, axillary) : erythrophagocytosis; minimal
lymph node (1, axillary) : pigment deposition; slight
lymph node (1, axillary) : sinus histiocytosis; moderate
lymph node (1, cervical) : erythrophagocytosis; minimal
lymph node (1, cervical) : sinus histiocytosis; minimal
mammary gland : mammary acinar development; minimal
spleen : pigment deposition; minimal
thymus : atrophy; moderate
trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; slight
uterus (incl. cervix and oviducts) : follicular phase

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; heart (left/right ventricle, septum); ileum; infusion site(s) - last dosing; jejunum; lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); muscle (skeletal, leg); nerve (sciatic); ovary (2); oviducts; pancreas; peyer's patches; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder; vagina



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	10	Group:	1R	Sex:	Female
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	0 Units/kg		
Death Date:	15/03/2019	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	15/03/2019	Study Day (Week) of Death:	26 (4)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

heart (left/right ventricle, septum) : oil red o staining; minimal
lacrimal gland (2) : infiltrate, inflammatory cell, mononuclear; bilateral, slight
liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; slight
lymph node (1, axillary) : erythrophagocytosis; minimal
lymph node (1, axillary) : pigment deposition; moderate
lymph node (1, axillary) : sinus histiocytosis; moderate
lymph node (1, cervical) : sinus histiocytosis; slight
mammary gland : mammary acinar development; minimal
pituitary : (comment) Pars intermedia missing.
spleen : pigment deposition; minimal
thymus : atrophy; moderate
uterus (incl. cervix and oviducts) : follicular phase

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; infusion site(s) - last dosing; jejunum; kidney (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); muscle (skeletal, leg); nerve (sciatic); ovary (2); oviducts; pancreas; peyer's patches; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; vagina



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	33	Group:	4R	Sex:	Male
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	350/225/200 Units/kg		
Death Date:	15/03/2019	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	15/03/2019	Study Day (Week) of Death:	26 (4)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

epididymis (2) : aspermia
heart (left/right ventricle, septum) : oil red o staining; slight
kidney (2) : oil red o staining; slight
lacrimal gland (2) : infiltrate, inflammatory cell, mononuclear; bilateral, minimal
liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; moderate
lymph node (1, axillary) : pigment deposition; slight
lymph node (1, axillary) : sinus histiocytosis; slight
spleen : pigment deposition; moderate
testicle (2) : immature
thymus : atrophy; slight
thymus : cyst(s); a few
thyroid (2) (incl. parathyroids) : associated ectopic thymus; left
trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; slight

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; infusion site(s) - last dosing; jejunum; larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); lymph node (1, cervical); mammary gland; muscle (skeletal, leg); nerve (sciatic); pancreas; peyer's patches; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); sternum; stomach; tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	34	Group:	4R	Sex:	Male
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	350/225/200 Units/kg		
Death Date:	15/03/2019	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	15/03/2019	Study Day (Week) of Death:	26 (4)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

epididymis (2) : aspermia
epididymis (2) : duct(s); contain(s) mucus/debris; left, minimal
heart (left/right ventricle, septum) : oil red o staining; minimal
kidney (2) : oil red o staining; minimal
liver (3 sections - left (medial), right (medial) and caudal lobe) : infiltrate, inflammatory cell, mononuclear; multifocal, slight
liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; moderate
lymph node (1, axillary) : sinus histiocytosis; slight
lymph node (1, cervical) : sinus histiocytosis; slight
spleen : pigment deposition; minimal
testicle (2) : immature
thymus : atrophy; moderate
thymus : cyst(s); one
trachea (incl. larynx) : lamina propria; infiltrate, inflammatory cell, mononuclear; minimal

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; infusion site(s) - last dosing; jejunum; lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); mammary gland; muscle (skeletal, leg); nerve (sciatic); pancreas; peyer's patches; pituitary; prostate; rectum; salivary glands (mandibular, parotid, sublingual); seminal vesicle; skin (left flank); spinal cord (3 sections); sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); ureter (2); urinary bladder



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	31	Group:	4R	Sex:	Female
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	350/225/200 Units/kg		
Death Date:	15/03/2019	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	15/03/2019	Study Day (Week) of Death:	26 (4)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

kidney (2) : oil red o staining; slight

liver (3 sections - left (medial), right (medial) and caudal lobe) : infiltrate, inflammatory cell, mononuclear; multifocal, slight

liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; moderate

mammary gland : mammary acinar development; minimal

thymus : atrophy; moderate

thyroid (2) (incl. parathyroids) : (comment) Parathyroid(s); left one missing.

uterus (incl. cervix and oviducts) : follicular phase

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; heart (left/right ventricle, septum); ileum; infusion site(s) - last dosing; jejunum; lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); lymph node (1, axillary); lymph node (1, cervical); muscle (skeletal, leg); nerve (sciatic); ovary (2); oviducts; pancreas; peyer's patches; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; vagina



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Animal:	32	Group:	4R	Sex:	Female
Species:	Cynomolgus Monkey	Strain:	Macaca fascicularis		
Study Type:	Repeated Dose Toxicity	Route:	Intravenous infusion		
		Dose:	350/225/200 Units/kg		
Death Date:	15/03/2019	Removal Reason:	Recovery Sacrifice		
Necropsy Date:	15/03/2019	Study Day (Week) of Death:	26 (4)		
				Gross Status:	Complete
				Histo Status:	Complete

Gross Pathology Observations [Correlation]:

No observations found

Any remaining protocol required tissues, which have been examined, have no visible lesions

Histopathology Animal Details:

No animal details found

Histopathology Observations [Correlation]:

heart (left/right ventricle, septum) : oil red o staining; minimal

kidney (2) : oil red o staining; marked

liver (3 sections - left (medial), right (medial) and caudal lobe) : oil red o staining; moderate

mammary gland : mammary acinar development; minimal

thymus : atrophy; moderate

uterus (incl. cervix and oviducts) : follicular phase

Histopathology - The following Tissues were Within Normal Limits:

adrenal gland (2); aorta abdominalis; bone (os femoris with joint); bone marrow (os femoris); brain (cerebrum, cerebellum, brain stem, hippocampus, paraventricular parts); caecum; colon; duodenum; esophagus; eye with optic nerve (2); gall bladder; ileum; infusion site(s) - last dosing; jejunum; lacrimal gland (2); larynx; lungs (with mainstem bronchi and bronchioles - 3 sections); lymph node (1, axillary); lymph node (1, cervical); muscle (skeletal, leg); nerve (sciatic); ovary (2); oviducts; pancreas; peyer's patches; pituitary; rectum; salivary glands (mandibular, parotid, sublingual); skin (left flank); spinal cord (3 sections); spleen; sternum; stomach; thyroid (2) (incl. parathyroids); tissue masses or tumours (including regional lymph nodes); tongue (incl. base); trachea (incl. larynx); ureter (2); urinary bladder; vagina



Provantis
Pathology - Individual Animal Data
INDIVIDUAL ANIMAL PATHOLOGY
35015 - 2-Week Toxicity Study of Allogenic APOSEC™ by
Repeated Twice Weekly Intravenous Infusion to Cynomolgus Monkeys
Followed by a 2-Week Treatment-Free Period - Multi-Site Study -

Key Page

Codes

(TGL) = Trackable Gross Lesion, (MPF) = Major Pathological Finding, (?) = Questionable, (E) = Excluded,
(C) = Clinical Observation, (M) = Mass, (G) = Gross Pathology, (H) = Histopathology

Report Request Items

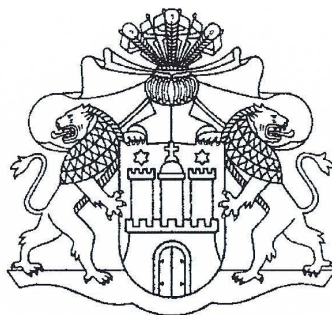
Animals Included:	All
Groups:	All
Observation Type:	Gross and Histo
Tissues:	All
Removal Reasons:	All

Group Information

<u>Short Name</u>	<u>Long Name</u>
1	Gr. 1
2	Gr. 2
3	Gr. 3
4	Gr. 4
1R	Gr. 1 Rec.
4R	Gr. 4 Rec.

A P P E N D I X 4

GLP Certificate of the Test Facility LPT



FREIE UND HANSESTADT HAMBURG
Behörde für Gesundheit und Verbraucherschutz

Gute Laborpraxis / Good Laboratory Practice

GLP – Bescheinigung / Statement of GLP Compliance

(gemäß/according to § 19b (1) Chemikaliengesetz)

Eine GLP-Inspektion zur Überwachung der Einhaltung der GLP-Grundsätze gemäß Chemikaliengesetz bzw. Richtlinie 2004/9/ EG wurde durchgeführt in:

Assessment of conformity with GLP according to Chemikaliengesetz and Directive 2004/9/ EEC at:

☒ Prüfeinrichtung/ Test facility

☐ Prüfstandort/ Test site

LPT Laboratory of Pharmacology and Toxicology GmbH & Co. KG

Redderweg 8

21147 Hamburg

(Unverwechselbare Bezeichnung und Adresse/Unequivocal name and address)

Prüfungen nach Kategorien/ Areas of Expertise

(gemäß/according ChemVwV-GLP Nr. 5.3/OECD guidance)

Kategorie 2, 3, 4 und 9 (Sicherheitspharmakologie und Auftragsarchiv)

Datum der Inspektion (Abschluss)

Datum der Inspektion/ Date of Inspection:

07. Juli 2016

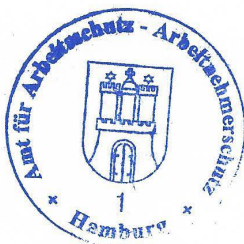
Die/Der genannte Prüfeinrichtung /Prüfstandort befindet sich im nationalen GLP-Überwachungsverfahren und wird regelmäßig auf Einhaltung der GLP-Grundsätze überwacht.

Auf der Grundlage des Inspektionsberichtes wird hiermit bestätigt, dass in dieser Prüfeinrichtung/ diesem Prüfstandort die oben genannten Prüfungen unter Einhaltung der GLP-Grundsätze durchgeführt werden können.

The above mentioned test facility/test site is included in the national GLP Compliance Programme and is inspected on a regular basis.

Based on the inspection report it can be confirmed, that this test facility/ test site is able to conduct the aforementioned studies in compliance with the Principles of GLP

Hamburg, den 8. Mai 2017



Dr. Volker Kregel
Direktor des Amtes für Arbeitsschutz