



Horizon 2020

Call: H2020-SMEInst-2016-2017

(Horizon 2020 dedicated SME Instrument 2016-2017)

Topic: SMEInst-05-2016-2017

Type of action: SME-2
(SME instrument phase 2)

Proposal number: 806344

Proposal acronym: APOSEC

Deadline Id: H2020-SMEINST-2-2016-2017

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How to fill in the forms

The administrative forms must be filled in for each proposal using the templates available in the submission system. Some data fields in the administrative forms are pre-filled based on the previous steps in the submission wizard.

Proposal ID 806344

Acronym APOSEC

1 - General information

Topic SMEInst-05-2016-2017

Call Identifier H2020-SMEInst-2016-2017

Type of Action SME-2

Deadline Id H2020-SMEINST-2-2016-2017

Acronym APOSEC

Proposal title* APOSEC – Novel Secretome Based Regenerative Therapy

Note that for technical reasons, the following characters are not accepted in the Proposal Title and will be removed: < > " &

Duration in months 36

Fixed keyword 1 Clinical trials

Add

Fixed keyword 2 Certification, Verification, Validation, Technical Compliance, Stan

Add

Remove

Fixed keyword 3 SME support

Add

Remove

Free keywords regenerative medicine, advanced wound healing, chronic wounds, diabetic food ulcer,

Abstract

APOSEC is a project driven by the company APOSCIENCE AG, an Austrian SME, focusing on providing innovative therapeutics for regenerative medicine in chronic cutaneous wound healing, and in patients with myocardial infarction. The product named APOSECTM is based on the secretome of apoptotic white blood cells isolated from peripheral blood. Millions of patients are suffering of poorly healing wounds (diabetic foot ulcers-DFU, ischemic ulcerations, pressure ulcers). Chronic wounds are an important burden to patients and healthcare systems. In the US alone, chronic wounds account for more than \$20 billion in healthcare cost. There is a huge unmet medical need for chronic wounds. APOSCIENCE has pioneered a proprietary cutting edge technology, which is a potential game-changer in the treatment of chronic wounds. Chronic wounds are a challenge to treaters, wound care professionals, and consume a great deal of healthcare resources around the globe. The current problem is that the treatment of chronic wounds are not resulting in a optimal closure of the wound, which results in poor quality of life of the patients. A main challenge is to provide an efficient therapy and treatment that reduces the hospitalization periods of patients dramatically. The whole concept for the APOSECTM project is based on a well-planned clinical development strategy and a technology innovation plan to upscale the production of the APOSECTM product(s) for market introduction and to develop a CE marked reconstitution and delivery device. The clinical development plan has been established for the indication of DFU up to a potential market authorization and product launch. Technical developments are needed within the production process to be more cost-efficient and integrate a higher automation grade. The main users of the APOSEC therapy products are not the patients but the hospitals and health centres with doctors, wound care specialists, surgeons, dermatologists, nurses, podiatrists.

Remaining characters 14



Proposal ID **806344**

Acronym **APOSEC**

Has this proposal (or a very similar one) been submitted in the past 2 years in response to a call for proposals under Horizon 2020 or any other EU programme(s)?

☐ Yes ☒ No



Proposal ID 806344

Acronym APOSEC

Declarations

1) The coordinator or sole applicant declares to have the explicit consent of all applicants on their participation and on the content of this proposal.	☒
2) The information contained in this proposal is correct and complete.	☒
3) This proposal complies with ethical principles (including the highest standards of research integrity — as set out, for instance, in the European Code of Conduct for Research Integrity — and including, in particular, avoiding fabrication, falsification, plagiarism or other research misconduct).	☒
4) The coordinator or sole applicant confirms:	
- to have carried out the self-check of the financial capacity of the organisation on https://ec.europa.eu/research/participants/portal/desktop/en/organisations/lfv.html . Where the result was “weak” or “insufficient”, the coordinator confirms being aware of the measures that may be imposed in accordance with the H2020 Grants Manual (Chapter on Financial capacity check); or	☐
- is exempt from the financial capacity check being a public body including international organisations, higher or secondary education establishment or a legal entity, whose viability is guaranteed by a Member State or associated country, as defined in the H2020 Grants Manual (Chapter on Financial capacity check); or	☐
- as sole participant in the proposal is exempt from the financial capacity check.	☒
5) The coordinator or sole applicant hereby declares that each applicant has confirmed:	
- they are fully eligible in accordance with the criteria set out in the specific call for proposals; and	☒
- they have the financial and operational capacity to carry out the proposed action.	☒
The coordinator is only responsible for the correctness of the information relating to his/her own organisation. Each applicant remains responsible for the correctness of the information related to him and declared above. Where the proposal is to be retained for EU funding, the coordinator and each beneficiary applicant will be required to present a formal declaration in this respect.	

According to Article 131 of the Financial Regulation of 25 October 2012 on the financial rules applicable to the general budget of the Union (Official Journal L 298 of 26.10.2012, p. 1) and Article 145 of its Rules of Application (Official Journal L 362, 31.12.2012, p.1) applicants found guilty of misrepresentation may be subject to administrative and financial penalties under certain conditions.

Personal data protection

The assessment of your grant application will involve the collection and processing of personal data (such as your name, address and CV), which will be performed pursuant to Regulation (EC) No 45/2001 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data. Unless indicated otherwise, your replies to the questions in this form and any personal data requested are required to assess your grant application in accordance with the specifications of the call for proposals and will be processed solely for that purpose. Details concerning the purposes and means of the processing of your personal data as well as information on how to exercise your rights are available in the [privacy statement](#). Applicants may lodge a complaint about the processing of their personal data with the European Data Protection Supervisor at any time.

Your personal data may be registered in the Early Detection and Exclusion system of the European Commission (EDES), the new system established by the Commission to reinforce the protection of the Union's financial interests and to ensure sound financial management, in accordance with the provisions of articles 105a and 108 of the revised EU Financial Regulation (FR) (Regulation (EU, EURATOM) 2015/1929 of the European Parliament and of the Council of 28 October 2015 amending Regulation (EU, EURATOM) No 966/2012) and articles 143 - 144 of the corresponding Rules of Application (RAP) (COMMISSION DELEGATED REGULATION (EU) 2015/2462 of 30 October 2015 amending Delegated Regulation (EU) No 1268/2012) for more information see the [Privacy statement for the EDES Database](#).



Proposal ID **806344**

Acronym **APOSEC**

List of participants

#	Participant Legal Name	Country
1	Aposcience AG	Austria



Proposal ID **806344**

Acronym **APOSEC**

Short name **APOSCIENCE AG**

2 - Administrative data of participating organisations

PIC	Legal name
911933279	Aposcience AG

Short name: **APOSCIENCE AG**

Address of the organisation

Street Mariannengasse 14/9

Town Vienna

Postcode 1090

Country Austria

Webpage www.aposcience.at

Legal Status of your organisation

Research and Innovation legal statuses

Public body no

Legal person yes

Non-profit no

International organisation no

International organisation of European interest no

Secondary or Higher education establishment no

Research organisation no

Enterprise Data

SME self-declared status..... 31/12/2015 - yes

SME self-assessment 31/12/2015 - yes

SME validation sme unknown

Based on the above details of the Beneficiary Registry the organisation is an SME (small- and medium-sized enterprise) for the call.



Proposal ID **806344**

Acronym **APOSEC**

Short name **APOSCIENCE AG**

Department(s) carrying out the proposed work

No department involved

Department name

☒ not applicable

☐ Same as organisation address

Street

Please enter street name and number.

Town

Postcode

Country



Proposal ID **806344**

Acronym **APOSEC**

Short name **APOSCIENCE AG**

Person in charge of the proposal

The name and e-mail of contact persons are read-only in the administrative form, only additional details can be edited here. To give access rights and basic contact details of contact persons, please go back to Step 4 of the submission wizard and save the changes.

Title

Mr.

Sex

☒ Male

☐ Female

First name

Last name

E-Mail

Position in org.

Project Manager

Department

Aposcience AG

☒ Same as organisation

☒ Same as organisation address

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Mariannengasse 14/9

Town

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Post code

1090

Country

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Website

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Phone 1

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Phone 2

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Fax

+xxx xxxxxxxxxx

Other contact persons

First Name	Last Name	E-mail	Phone
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Acronym APOSEC

3 - Budget for the proposal

No	Participant	Country	(A) Direct personnel costs/€	(B) Other direct costs/€	(C) Direct costs of sub- contracting/€	(D) Direct costs of providing financial support to third parties/€	(E) Costs of inkind contributions not used on the beneficiary's premises/€	(F) Indirect Costs / € (=0.25(A+B-E))	(G) Special unit costs covering direct & indirect costs / €	(H) Total estimated eligible costs / € (=A+B+C+D+F +G)	(I) Reimburse- ment rate (%)	(J) Max.EU Contribution / € (=H*I)	(K) Requested EU Contribution/ €
			?	?	?	?	?	?	?	?	?	?	?
1	Aposcience Ag	AT											
	Total												

Please note that budget amounts are represented in full, NOT as multiples of 1000.

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Acronym APOSEC

4 - Ethics issues table

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Does your research involve Human Embryonic Stem Cells (hESCs) ?	☐ Yes ☒ No	
Does your research involve the use of human embryos?	☐ Yes ☒ No	
Does your research involve the use of human foetal tissues / cells?	☐ Yes ☒ No	
2. HUMANS		Page
Does your research involve human participants?	☒ Yes ☐ No	8,24
Are they volunteers for social or human sciences research?	☐ Yes ☒ No	
Are they persons unable to give informed consent?	☐ Yes ☒ No	
Are they vulnerable individuals or groups?	☐ Yes ☒ No	
Are they children/minors?	☐ Yes ☒ No	
Are they patients?	☒ Yes ☐ No	8,24
Are they healthy volunteers for medical studies?	☒ Yes ☐ No	8,24
Does your research involve physical interventions on the study participants?	☒ Yes ☐ No	8,24
Does it involve invasive techniques?	☒ Yes ☐ No	8,24
Does it involve collection of biological samples?	☒ Yes ☐ No	8,24
If your research involves processing of genetic information, see also section 4.		
3. HUMAN CELLS / TISSUES		Page
Does your research involve human cells or tissues (other than from Human Embryos/ Foetuses, i.e. section 1)?	☒ Yes ☐ No	5,6
Are they available commercially?	☐ Yes ☒ No	
Are they obtained within this project?	☒ Yes ☐ No	5,6
Are they obtained from another project, laboratory or institution?	☐ Yes ☒ No	
Are they obtained from biobank?	☐ Yes ☒ No	
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Does your research involve personal data collection and/or processing?	☐ Yes ☒ No	
Does your research involve further processing of previously collected personal data (secondary use)?	☐ Yes ☒ No	
5. ANIMALS		Page
Does your research involve animals?	☐ Yes ☒ No	
6. THIRD COUNTRIES		Page
In case non-EU countries are involved, do the research related activities undertaken in these countries raise potential ethics issues?	☐ Yes ☒ No	
Do you plan to use local resources (e.g. animal and/or human tissue samples, genetic material, live animals, human remains, materials of historical value, endangered fauna or flora samples, etc.)?	☐ Yes ☒ No	
Do you plan to import any material - including personal data - from non-EU countries into the EU?	☐ Yes ☒ No	
Do you plan to export any material - including personal data - from the EU to non-EU countries?	☐ Yes ☒ No	
In case your research involves low and/or lower middle income countries , are any benefits-sharing actions planned?	☐ Yes ☒ No	
Could the situation in the country put the individuals taking part in the research at risk?	☐ Yes ☒ No	
7. ENVIRONMENT & HEALTH and SAFETY		Page
Does your research involve the use of elements that may cause harm to the environment, to animals or plants?	☐ Yes ☒ No	
Does your research deal with endangered fauna and/or flora and/or protected areas?	☐ Yes ☒ No	
Does your research involve the use of elements that may cause harm to humans, including research staff?	☐ Yes ☒ No	
8. DUAL USE		Page
Does your research involve dual-use items in the sense of Regulation 428/2009, or other items for which an authorisation is required?	☐ Yes ☒ No	
9. EXCLUSIVE FOCUS ON CIVIL APPLICATIONS		Page
Could your research raise concerns regarding the exclusive focus on civil applications?	☐ Yes ☒ No	
10. MISUSE		Page
Does your research have the potential for misuse of research results?	☐ Yes ☒ No	



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11. OTHER ETHICS ISSUES		Page
Are there any other ethics issues that should be taken into consideration? Please specify	☐ Yes ☒ No	

I confirm that I have taken into account all ethics issues described above and that, if any ethics issues apply, I will complete the ethics self-assessment and attach the required documents.



[How to Complete your Ethics Self-Assessment](#)

Proposal ID 806344

Acronym APOSEC

3 - Call specific questions

Call specific declaration(s)

I declare on my honour that: Neither I nor any of the members of the consortium (if relevant) are involved in concurrent submission or implementation with another SME instrument Phase 1 or Phase 2 project.



Does your proposal build on a SME instrument Phase 1 project? Please indicate.

☐ Yes ☒ No

Excluded Reviewers

You can provide up to three names of persons that should not act as an evaluator in the evaluation of the proposal for potential competitive reasons.

Extended Open Research Data Pilot in Horizon 2020

If selected, applicants will by default participate in the [Pilot on Open Research Data in Horizon 2020¹](#), which aims to improve and maximise access to and re-use of research data generated by actions.

However, participation in the Pilot is flexible in the sense that it does not mean that all research data needs to be open. After the action has started, participants will formulate a [Data Management Plan \(DMP\)](#), which should address the relevant aspects of making data FAIR – findable, accessible, interoperable and re-usable, including what data the project will generate, whether and how it will be made accessible for verification and re-use, and how it will be curated and preserved. Through this DMP projects can define certain datasets to remain closed according to the principle "as open as possible, as closed as necessary". A Data Management Plan does not have to be submitted at the proposal stage.

Furthermore, applicants also have the possibility to opt out of this Pilot completely at any stage (before or after the grant signature). In this case, applicants must indicate a reason for this choice (see options below).

Please note that participation in this Pilot does not constitute part of the evaluation process. Proposals will not be penalised for opting out.

We wish to opt out of the Pilot on Open Research Data in Horizon 2020.

☐ Yes

☒ No

Applicants in calls of the Work Programme "Secure societies – Protecting freedom and security of Europe and its citizens" are reminded that their proposals are subject to a Security Scrutiny and that they may find more appropriate to opt out of the Extended Pilot on Open Research Data in Horizon 2020.

Further guidance on open access and research data management is available on the participant portal: http://ec.europa.eu/research/participants/docs/h2020-funding-guide/cross-cutting-issues/open-access-dissemination_en.htm and in general annex L of the Work Programme.

¹ According to article 43.2 of Regulation (EU) No 1290/2013 of the European Parliament and of the Council, of 11 December 2013, laying down the rules for participation and dissemination in "Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)" and repealing Regulation (EC) No 1906/2006.

COVER PAGE



Title of Proposal: APOSEC™ – Novel Secretome Based Regenerative Therapy

List of participants

Participant No *	Participant organisation name	Country
1 (Coordinator)	APOSCIENCE AG	AT

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1. Excellence

1.1 Objectives

Specific objectives for the project

This proposal describes a project driven by the company APOSCIENCE AG, an Austrian SME, focusing on providing innovative therapeutics for **regenerative medicine** in chronic cutaneous wound healing, and in patients suffering of myocardial infarction, myocarditis, stroke, and spinal cord injury. The product named APOSEC™ is based on the secretome of apoptotic **white blood cells** isolated from peripheral blood mononuclear cells (PBMC). The team of APOSCIENCE AG started to shift the paradigm “**from cellular therapy to secretome based therapy**” as early as in 2008. The secretome released by cultured, stressed **peripheral blood mononuclear cells (PBMC)** is termed APOSEC™. Analysis showed that APOSEC™ consists of proteins, exosomes, lipids, phospholipids, cholesterol as well as antimicrobial peptides (AMPs). It was shown in small and large preclinical animal models that the **topical application** of APOSEC™ augments **wound healing** whereas the **intravenous administration** prevents hypoxia induced cell damage in acute **myocardial infarction, myocarditis, stroke and spinal cord injury**. In vitro mode of action (MOA) investigations revealed that APOSEC™ causes platelet inhibition, vasodilation, augments cytoprotective and anti-apoptotic gene products in primary cultured human cells, induces migration of fibroblasts, keratinocytes and proliferation of endothelial cells; suppresses proliferation of highly purified CD4+ T cells, causes aortic and spinal cord endothelial cell sprouting and provides antibacterial activity. Chronic wound healing problems are pestering our society in a large extent. For example, **diabetic foot ulcer (DFU)**, a most prominent complication of diabetes mellitus is the the most frequent reasons for hospitalisation in Europa (**811.000 patients in EU** per year and a growth rate of 1.35%). The delayed healing of DFU is the primary factor leading to lower extremity amputation. Once amputation occurs, 50 % of the patients develop an ulcer in the contralateral limb within 18 months of amputation. Moreover, nearly half of all unhealed neuropathic ulcers lead to death within 5 years. The treatment and the outcome depend very much on the presence or extent of arterial insufficiency, the degree of neuropathy, the ulcer location, and the persistent propensity to infection. **Current therapies** and treatments **are not satisfactory** and are accompanied by reduced quality of life and high morbidity due to symptoms such as pain for the patients. APOSCIENCE AG has found that the mixture of active components secreted from cultured apoptotic peripheral white blood mononuclear cells (PBMCs) has superior efficacy in **promoting wound healing and skin regeneration**. The product has this effect by stimulating migration of keratinocytes and fibroblasts into the wounded area, as well as by promoting neovascularization of the wound and improving blood and oxygen supply. Of most importance is that APOSEC™ contains antimicrobial capability, since it is known that DFU is >70% superinfected with gram negative germs. APOSCIENCE AG **expects** that their **product APOSEC™ derived from PBMCs** will have a **significant impact in the care for patients** who are suffering from poorly healing wounds (diabetic foot ulcers, ischemic ulcerations, pressure ulcers) and therefore present a very **important market opportunity in Europa** with a potential annual turnover of well over 1 billion Euros. The specific objectives of the APOSEC™ project are:

1. **To implement a clinical development program with the lead product APO-2 (allogenic APOSEC™ for topical application) for healing of diabetic foot ulcer and chronic wound healing.**

APOSEC™ in association with a hydrogel as carrier matrix is aimed to promote and accelerate wound granulation and thereby the healing of full-thickness wounds in neuropathic and chronic diabetic ulcers. A Phase I study with topical autologous APOSEC™ has been successfully completed in a small sample size of healthy male volunteers to evaluate safety and local tolerability. The clinical development will be followed by the **planned first in human/Phase**

II study with GMP “off the shelf” allogenic APO-2 consisting of a combined 4-week exploratory efficacy/dose finding/safety study in patients with DFU with an 8-week follow-up. 120 patients with chronic diabetic foot ulcers will be enrolled and randomized in a 3:1 ratio (active treatment versus placebo). First patients will be enrolled in the beginning of Q3/2018, study completion is planned by end 2019.

2. Development of a reconstitution and delivery device

Goller Systems, a partnering company in Austria, has manufactured prototypes of the reconstitution and delivery device. Further development to a commercial device with CE mark is planned within the next three years and in order to apply this device within the upcoming phase III trials. The goal is to develop a reconstitution and delivery device that consists just of one piece. Based on the opinion of the regulatory authority of Austria (AGES) a “one-piece system” for the reconstitution and delivery device is feasible to prevent microbial contaminations in the make ready of APOSEC™.

3. Develop a strategy for upscaling manufacturing capacity for phase III clinical study and market introduction

The current production process has the capacity to produce enough APOSEC™ product for the phase II study in wound healing, as well as for a phase I trial of intravenous application of APOSEC in healthy man. This study constitutes the prerequisite of Phase II trials in AMI, stroke, spinal cord injury and myocarditis. For further studies, the phase III study and a market introduction, higher capacities are needed. Therefore, the production process needs to be optimised, automatized and up scaled. New technologies currently applied in bone marrow and umbilical cord issues will be tested and assessed to be utilized within the APOSEC™ production process. The anticipated advantage is that with closed systems the requirement of a high-level cleanroom will no longer be needed. Additionally, higher capacities of APOSEC™ require more amounts of the PBMC raw material from transfusion units. A common standard needs to be defined on how the raw material will be produced and transported to the production unit.

Currently, the production capacity is designed to deliver enough APOSEC™ material to be used for the planned clinical trials. The current GMP certified production site is able to produce about half of the required APOSEC™ for Austrian patients - or about 1% for all patients in the EU (based on a calculation of a 30% market share in future).

4. To implement a First in man (FIM) clinical phase I study with intravenous (i.v) APOSEC™ (APO-1)

The second main indication of the APOSEC™ therapy is the potential treatment of patients with acute myocardial infarction, stroke, spinal cord injury and myocarditis. We therefore designed a phase I study with healthy volunteers to conduct and assess safety and tolerability of intravenous administration of APOSEC™ in vivo by Q3/2018 with the clinical pharmacology of the Medical University of Vienna. This study is a pre-requisite for later phase II studies in diseases with hypoxia induced damage.

5. Ensure regulatory requirements and IPR issues

It is necessary to fulfil all national and supranational regulatory requirements within the clinical studies and technology optimisations in order to proof a safe, efficient and ease-to-use therapy product. CE marks complied with notified bodies are needed to be addressed.

Industrial/economic/social challenges to overcome the business opportunity

Millions of patients are suffering of **poorly healing wounds** (diabetic foot ulcers, ischemic ulcerations, pressure ulcers). Chronic wounds are an important burden to patients and healthcare systems. In the US alone, chronic wounds account for more than \$20 billion in healthcare costs and represent a **huge unmet medical need**. APOSCIENCE AG has pioneered a proprietary cutting edge technology, which represents a **potential game-changer** in the treatment of chronic wounds. The mixture of active components secreted from cultured apoptotic PBMC (the secretome) has

superior efficacy in promoting wound healing and has the potential to transform regenerative medicine far beyond cutaneous tissue repair. Furthermore, there is also a high-unmet need in defects caused by ischemia/reperfusion of internal organs, e.g. myocardial infarction, stroke, spinal cord injury and myocarditis, wherein APOSEC™ can be applied. Within **advanced wound healing** APOSCIENCE AG targets the challenges within the following indications:

- Diabetic foot ulcer (DFU):

The number of diabetes patients is constantly growing within the industrialized world by 1.35-1.45%. About 8% of the industrialized world's population (382 million) are suffering from diabetes¹. One of the most common complications for a person with diabetes is foot ulceration. This causes wounds that do not heal and cause infections as leading cause for hospitalization and morbidity. The clinical challenge is to provide a therapy that accelerates the closure of these ulcers. By adding an efficient therapy, hospitalization times and treatment costs of DFU patients can be reduced.

- Venous leg ulcers (VLU):

Leg ulcers occur due to impairment of the circulation in the leg and it can take up to a full year to heal. VLUs are a very common type of chronic wounds with an overall prevalence² of 1%. According to a study by MedMarket Diligence, a need for treatment of about 11 million VLU patients would cost 14.9 billion Dollars.³

- Pressure ulcers (PU):

Pressure ulcers mainly occur when a person is immobilized and sustained pressure can reduce circulation and oxygen delivery to the skin. In the US more than two million pressure ulcers occur each year with an annual cost greater than 1.3 billion dollars. According to a study by MedMarket Diligence a need for treatment of about 7.4 million PU patients is calculated.

- Burns:

Burns are often life-threatening and are expensive and difficult to treat because of the risk of infection, dehydration and pain. For complex burns the costs increase dramatically due to long hospitalization periods, surgical procedures, medications and antibiotics. MedMarket Diligence estimates that approximately 3.3 million burns in this category do enter the outpatient health service system and receive some level of medical attention.

Chronic wounds are a challenge to physicians, wound care professionals, and consume a great deal of healthcare resources around the globe. The current problem is that the treatment of chronic wounds is not resulting in an optimal closure of the wound, which results in poor quality of life for the disease ridden patients. A main challenge is to provide an efficient therapy and treatment that **reduces the hospitalization periods** of patients dramatically. Both, shorter and more efficient treatments in combination with less hospitalization and re-hospitalization can reduce the economic burden to governments.

APOSCIENCE AG Solution to solve the stated problem

Explanation video APOSEC™: youtube: <https://www.youtube.com/watch?v=LaSzmzGvxnk&t=3s>

APOSCIENCE AG is a biotech-company producing biological products to be applied in regenerative medicine. The solutions provided by APOSCIENCE AG are products derived from its proprietary APOSEC™ technology platform:

- **APO-1** formulated as a systemic treatment (intra venous, i.v.) for the potential application in acute myocardial infarction, stroke, spinal cord injury and myocarditis.

¹ IDF Atlas, 6th edition, 2013

² Prevalence – Number or Percentage of cases with a certain disease per population within a year

³ Rice et al. Burden of venous leg ulcers in the United States. J Med Econ. 2014 May;17(5):347-56.

- **APO-2** is the **lead product** intended to accelerate healing of acute and chronic wounds, in particular DFU, and is formulated in an alginate hydrogel (ready to use) for topical application.

APO-1 is indicated for defects caused by ischemia/reperfusion of internal organs, e.g. myocardial infarction, myocarditis, as well as ischemic stroke or nerve damage caused by trauma, e.g. spinal cord injury. All these indications have a high-unmet need, and represent multi-billion dollar markets world-wide. The company has generated proof-of-concept (PoC) *in vivo* utilizing APO-1 in relevant state-of-the-art animal models.⁴

APO-2 is a highly innovative, differentiated **topical wound care product** that is manufactured from a waste fraction of blood banking (buffy coat containing PBMCs). APO-2 has been **granted worldwide patents**, the first of which will expire in 2028. APO-2 has demonstrated safety and efficacy in compassionate use cases. DFUs refractory to healing under standard of care have shown wound size reduction over 50% up to wound closure within 20 to 28 days. APO-2 offers efficacy second to none, **is easy to use, and is a cost-effective product**, which is an advantage to payors, physicians and patients in need. APO-2 has the clear potential to become **best in class** for the advanced wound care market.

The proteomic content of APOSEC™ has been extensively studied by bioanalytical methods. APOSEC™ contains a myriad of cytokines, exosomes, lipids, cholesterol, growth factors and albumin. In (rodent and pig) **models** of cutaneous wounds, APOSCIENCE AG has found that APOSEC™ vs control condition (lyophilized culture medium) **stimulates migration of keratinocytes and fibroblasts**, as well as neoangiogenesis – thereby **contributing to accelerated wound closure**, and increased epidermal thickness. In preclinical models of myocardial infarction, protection of cardiomyocytes, platelet inhibition and induction of the growth of new blood vessels were found, contributing to a reduction of infarct size and attenuated remodelling of the left ventricle. Eventually, this will result in a reduction of the incidence of cardiac death and congestive heart failure. The very same mechanism is also highly relevant in diabetic foot ulcers where restoration of microcirculation is paramount to induce healing. The drug substance of APOSEC™ is the freeze-dried supernatant (secretome) of human apoptotic peripheral blood mononuclear cells (PBMCs) cultured in medium. Hence, the APOSEC™ product is devoid of any mononuclear cells. It is presented as a “off the shelf” lyophilized cake of white powder. The product is reconstituted with 0.9 % NaCl prior to utilization. Besides **cost-efficiency** of therapies, wound care products ideally work in an **outpatient setting**, not necessitating any change to the conduct of good standard of care. In the case of DFU, this is moist wound care with two to three times’ weekly change of bandages. Preparation time (time-to-table) and ease-of-use are important parameters. The **solutions** provided by **APOSCIENCE AG** will provide second-to-none efficacy combined with **superior ease-of-use**, which will be main drivers for APO-2. The planned pricing for APO-2 has been oriented at the pricing level of the only approved advanced wound care pharmaceutical product in Europe, Regranex. The product Regranex has been withdrawn in 2012 due to a potential cancer risk in the USA but is the only product in Europe that was approved in the area of advanced wound care.

1.2 Relation to the work programme

The APOSEC project relates to the topic: “Supporting innovative SMEs in the healthcare biotechnology sector; a) Cell technologies in medical applications”. The company is developing proprietary, innovative therapeutics based on white blood cells (PBMCs, leukocytes) isolated from peripheral blood. The cell-free active pharmaceutical ingredient (API) of all of the company’s products has been termed APOSEC™, which is an acronym of **APO**ptotic **SE**Cretome derived

⁴ Lichtenauer 2011, Hoetzenecker 2015, Altmann 2015, Haider 2015

from stressed PBMCs. APOSEC™ contains a complex mixture of cytokines, anti-inflammatory and pro-angiogenic proteins, lipids, exosomes, and anti-microbial peptides. This complex mixture exerts a pleiotropic mechanism of action that renders the production of a very potent experimental drug compound. The potential medical applications of APOSEC™ products are therapies for wound healing (topic application) and diseases related to hypoxia induced damage. In conclusion: APOSEC™ is produced derived from PBMCs, but the final drug product (DP) is cell free, safe, (underwent mandatory double viral clearance) and is easy-to-apply. APOSCIENCE AG poses challenges for bringing the safe, reliable, regulatory-compliant and cost-effective APOSEC™ product to the market. This will be achieved through cost-intensive PoC studies in humans, upscaling of DP production, development of a CE marked delivery technology for topical application and the fulfilment of all necessary regulatory requirements for market introduction.

1.3 Concept and approach

Current stage of development and key milestones achieved so far

Milestone 1: Good manufacturing practice (GMP) production line

APOSEC™ drug product is the freeze-dried supernatant (secretome) of human apoptotic peripheral blood mononuclear cells (PBMCs) in cell culture medium. Therefore, APOSEC™ drug product does not contain any cells, though its manufacture requires culture periods with freshly obtained PBMCs. PBMCs are isolated from allogeneic blood donations as starting material, irradiated and cultured for 24 hrs. Thereafter, PBMC are discarded and obtained cultured medium (CM) is pooled for viral clearance and lyophilisation. The Chemistry, Materials & Controls (CMC) Document has been presented to the Austrian Health Authorities in April 2017 which is a prerequisite for a later market authorisation. This **CMC document** defines the **pharmaceutical product APOSEC™** based on the production process and describes quality parameters. APOSCIENCE AG has a framework agreement with the Austrian Red Cross organisation in Upper Austria, Linz, and the Blood Center Linz where the drug product APOSEC™ is manufactured. A GMP validated production line for APOSEC™ has been implemented in their blood bank. The capacity is sufficient for the implementation of the upcoming phase II clinical study with APO-2 for DFU treatment and intravenous (systemic) first in man. APOSEC™ is produced based on the process depicted in the following diagram⁵.

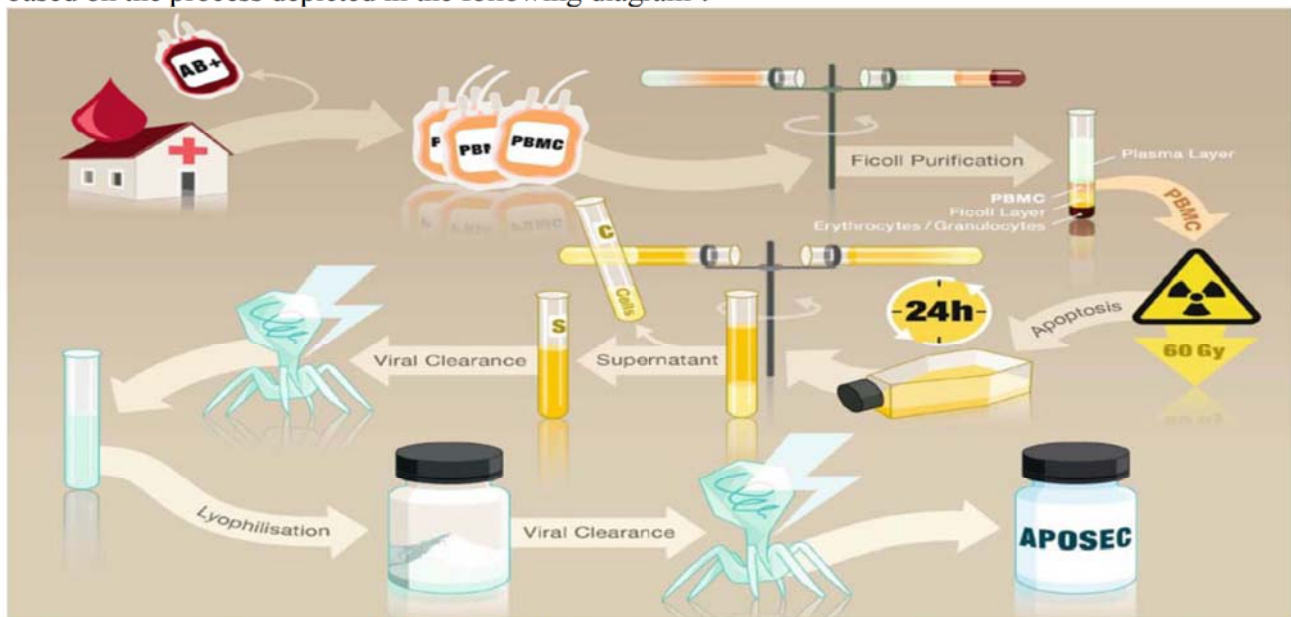


Fig.1: Production of APOSEC™ – the lyophilized secretome of apoptotic PBMC. Buffy coats from 12 donors are obtained from a blood donor center and the peripheral blood mononuclear cells (PBMC) are

⁵ [Apoptosis](#). 2016 Dec;21(12):1336-1353.

isolated in a good manufacturing practice (GMP) facility. Apoptosis is induced by irradiation and the cells are incubated in culture medium at a concentration of 25×10^6 cells per ml in an incubator. After 24 hours, the cells are separated and discarded and the supernatant (conditioned medium) with the secreted factors of the dying PBMCs passes two virus inactivation steps and is lyophilized to get a white powder which is well suitable for storage. (DOI 10.1007/s10495-016-1292-8)

The National Austrian Health Authority, AGES, has **certified the GMP** process and thus the high quality process was confirmed. With the current process, 12 buffy coats (about 50 ml per donor) can be processed at once (for one batch). A buffy coat includes mainly leucocytes, erythrocytes, thrombocytes and plasma. This results in about 250-330 ml APOSEC™ per batch. One batch needs to consist of 4.500 – 6.500 millions of cells. The entire process is based on several time-consuming handwork steps and requests a long time until the APOSEC™ product is ready to be used. Currently five days can be calculated for the whole production process (see Fig. 1); in addition further 2 weeks for logistics, performance of potency assays in GLC laboratories and microbiology for final batch release can be anticipated. Given the nature of the product (consisting of a complex mixture of components) specific attention is paid by APOSCIENCE AG to control starting materials, in-process controls, validation and control of viral safety, and finally to ensure batch to batch consistency.

Milestone 2: Good laboratory practise (GLP) potency assays:

Potency assays are needed to assess a) the biological activity of the product after a certain duration of storage; b) to determine the minimum of shelf life; and c) determine DP criteria for a release into the market. Such GLP Potency assays have already been qualified and were approved by APOSCIENCE AG. Therefore, it can be argued that APOSEC™ is always produced in the same quality. Non-GLP stability testing evidenced that APOSEC™ has an exceptional stability range (up to 12 month) at minus 80°C and minus 20°C. **AGES agreed** within a National **Scientific Advice** to the **approach to the planned quality assurance** of APOSEC™ was just.

Milestone 3: pre- and clinical work

Seven final reports verified that APOSEC™ did not have any adverse effects in GLP toxicology studies: 1. Single dose toxicity (acute toxicity study) in rats; 2. LLNA-Local Lymph Node Assay; 3. Irwin Test in Rats; 4. Dose range finder study (DRF) in rats i.v.; 5. Dose range finder study (DRF) in dogs i.v.; 6. Dose range finder study (DRF) in dogs s.c.; 7. Repeated dose (4 weeks) in mice i.v. . The final 8th study is ongoing (Repeated dose (4 weeks) in minipigs sc. (finished in January 2017). A Clinical phase I study with 10 patients – MARSYAS I was performed in 2015: This first in man (FIM) study was a prospective randomized double-blinded placebo controlled, explorative **phase I trial** to investigate the **safety and tolerability** of two different doses of topically administered APOSEC™ (autologous) in **healthy male subjects** with artificial dermal wounds.⁶ It results indicated that APOSEC™ mixed with the carrier hydrogel NU-GEL™ is **safe and tolerable** for topical administration.

Milestone 4: Scientific Advice at the Austrian national regulatory agency (AGES)⁷

The Austrian Federal Office, **AGES**, has provided APOSCIENCE AG with a Scientific Advice pertaining to APOSEC™. The APOSCIENCE AG briefing book summarizes the status of the current DP development and provided an overview of completed non-clinical and clinical studies, the current status of the manufacturing process and the assurance of product quality. The National Authority **agreed with APOSCIENCE's design of the clinical development of the DP, supported the non-clinical program and endorsed the measures of quality assurance. Based on the current pre-clinical pharmacology and preclinical GLC toxicology results, data from the MARSYAS I study, and clinical experience with compassionate use of APOSEC™, no safety concerns have been raised in order to follow the envisioned development program.** The next steps will be to finalise

⁶ Marsyas I: A Prospective Randomized Double-Blinded Placebo controlled, explorative Phase I trial to investigate the Safety and Tolerability of two different doses of Topically Administered APOSECTM in Healthy male subjects with Artificial Dermal Wounds, (ClinicalTrials.gov Identifier: NCT02284360) initiated on 23 October 2014 was completed on 5 February 2016; relevant DOI publication number: DOI: [10.1038/s41598-017-06223-x](https://doi.org/10.1038/s41598-017-06223-x)

⁷ Relevant document can be found as Annex document.

toxicology testing and to prepare for the multinational, multicentre **phase II** clinical trial in 120 patients for the indication of **diabetes food ulcer (DFU)** – the MARSYAS II study. This study will commence in **Q3/2018**, thus in line with a potential start of the SME instrument project. If we can reach the primary end points in this Phase II Study, a **phase III** studies for **indication DFU** will be launched in **2020**. For sure, when entering the market (reaching market authorisation) an upscaled and optimised production process is warranted. In parallel to the phase II study, the CE marked delivery device will be developed and prepared for market introduction. In 2018 (Q3/2018), we anticipate to initiate a phase I trial of systemic (i.v.) application of APOSEC™ in order to prove safety and tolerability in healthy young men. This “first in human (FIH) study” is the mandatory prelude for phase II studies in **acute myocardial infarction (AMI), stroke, spinal cord injury and myocarditis**. In parallel, an **upscaling of the production process** of APOSEC™ will be prepared and assessed.

Positioning of the business innovation project

The APOSEC project has two pillars, the clinical and the technological. The pipeline of **clinical development** will initiate in parallel in a **Phase II study for topical application** in treatment of diabetic foot ulcers and in a **Phase I study (first-in-man) with healthy volunteers** for systemic application in treatment of **with AMI, stroke, spinal cord injury and myocarditis**. Reports of the ongoing preclinical toxicology studies will be completed Q1/2018 in order to allow the translation of APOSEC™ into the realm of clinical development. The promising safety profile of the completed MARSYAS I study opens the path of APO-2 into the Phase II development in patients with DFU.

For market authorization, APOSCIENCE AG aims to perform only one pivotal phase III study (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). From the technology and production purpose the project is already in a stage of TRL 6. Hence, the production of the APOSEC™ product is already validated in a GMP facility. This GMP certified production plant for APOSEC™ is accepted by the Austrian Health Authority (AGES) and APOSEC™ was approved as experimental drug compound for clinical trials.

Concept and the approach/activities

The whole concept for the APOSEC™ project is based on a **well-planned clinical development strategy** and a **technology innovation plan to upscale the production** of the APOSEC™. Before market introduction we want to **develop a CE marked reconstitution and delivery device**. The clinical development plan has been established for the indication of DFU up to a potential market authorization and product launch. Technical developments are needed within the **production process to be more cost-efficient and integrate a higher automation grade**. The concept for this SME project fits very well into the whole strategy of the company to market a new product for the treatment of DFU, chronic wounds and burns. Furthermore, we want to initiate a phase I trial of APOSEC™ in healthy volunteers (FIH) to prove safety and tolerability. This will set the stage for further Phase II trials in diseases related to hypoxia induced damage (e.g. AMI, stroke, spinal cord injury, and others).

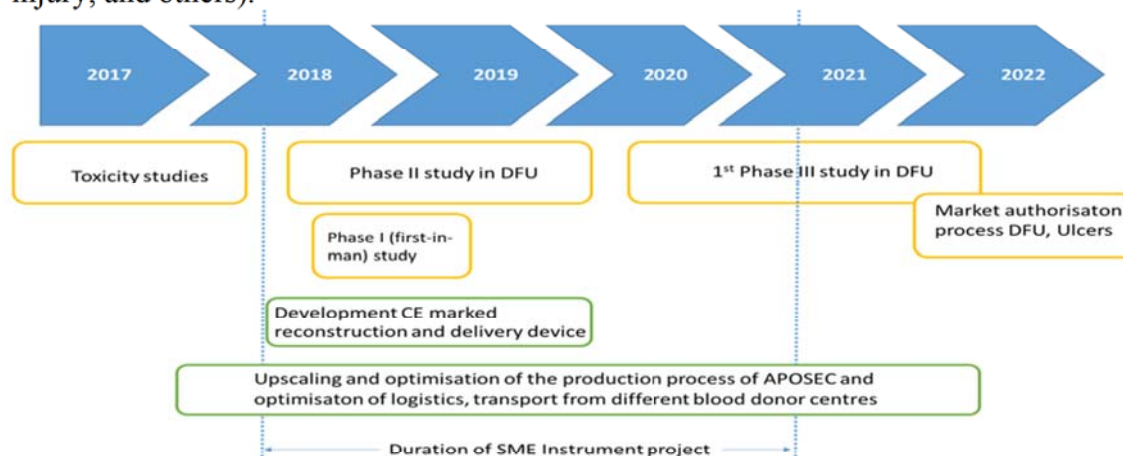


Fig.2: concept and structure of the APOSCIENCE AG development path

The **upscaling and automatization plan** is mainly based on reducing the steps that have to be performed by handwork in high sterility surrounding. Besides automatization, it would be of great interest to omit the requirement of a full clean room (the current need). The potential conservation of APOSEC™ production to a GMP D-class clean room environment would result in much less cost-intensive conditions than a B-class clean room (or A in B, respectively). Currently a B-Class is mandatory. With the application of new separation technologies, such as the SEPAX system (by General Electric) - which is currently in use for PBMC separation for umbilical cord blood – would lead to such a clean room class reduction. From our current insight, such a technology optimisation should lead to higher recovery rates of PBMCs (up to 90% as compared currently 50%). The following issues have to be investigated:

- **Technological optimisation of handling:**

Separation technologies need to be tested, adapted and integrated into the current process of APOSEC™ production. These CE marked technologies (e.g. SEPAX) are currently utilized in bone marrow and umbilical cord blood procurement. The validated manufacturing of APOSEC™ is currently performed within a cleanroom class B; employees have to adhere to the strictest cleanroom conditions. These new technologies might be of interest for “in-line APOSEC™ production”, since closed bag systems and PBMC separation columns might make the DP production more feasible.

Estimation of the market need for APOSEC™ in comparison to the current production capacity at the [REDACTED] (need for upscaling and automatization)

The current GMP certified production process is able to deliver about 2.5 batches per week or 130 batches per year, each equalling 8,000 U (= units). After subtraction of 23 vials for testing and retain samples (=2,300 U; current estimation, could change after optimization (pooling) of the production process), 5,700 U per batch can be utilized for application on the patient. The current production capacity per year at the [REDACTED] therefore sums up to 741,000 U. The current production capacity at the [REDACTED] is able to cover 0.25% (calculation for the middle dose, 25 U/ml) of a presupposed 30% share of the European DFU market. The current [REDACTED] production capacity would sum up to 15% (calculation for the middle dose 25 U/ml) of a presupposed 30% market share for the Austrian market (8,8 million inhabitants, 14,080 DFU patients/year, 30% market share: 4,224 patients/year).

Estimation of the amount of APOSEC™ that could be produced from the leucocytes discarded per year by Austrian blood banks (according to [REDACTED])

[REDACTED]: Approximately 330,000 blood samples are donated each year in Austria (Basis 2016) and 264,000 of these blood samples could be used for the production of APOSEC™ (20% are used for the production of thrombocyte concentrates). The amount of APOSEC™ produced utilizing the leucocytes discarded annually by Austrian blood banks could cover (theoretically) around 43% of a presupposed 30% market share of the European DFU market.

No gender-specific differences are predicted in the studies, neither in primary nor in the secondary end points. The clinical development program will include patients of both genders as represented in typical populations of patients with diabetic foot ulcer. In the first in man study of APOSEC™ i.v. only healthy men will be included.

1.4 Ambition

Novelty of the innovation business project and APOSEC™

In the field of chronic non-healing wounds resulting from diabetes **no satisfactory treatments and therapies are currently available**. Especially, the German guidelines on wound healing “S3-Leitlinien der Deutschen Gesellschaft für Wundheilung und Wundbehandlung e.V.” suggest treatments

based on wound dressing but no other suggestion on therapeutic agents are provided. Alternatively, there is a so-called vacuum-therapy available but treatment is depending on a specific device. This shows that the **opportunities to treat DFU are currently limited**. The main problem is that the **wound does not heal** and the only real medical solution is only an amputation that again results in a wound that might have difficulties to heal. The uniqueness of APOSEC™ is that this product and treatment induces a healing process that is expected to be finalised within 4 weeks. A further novum to other cell based therapies is that only the secretome is the therapeutic agent.

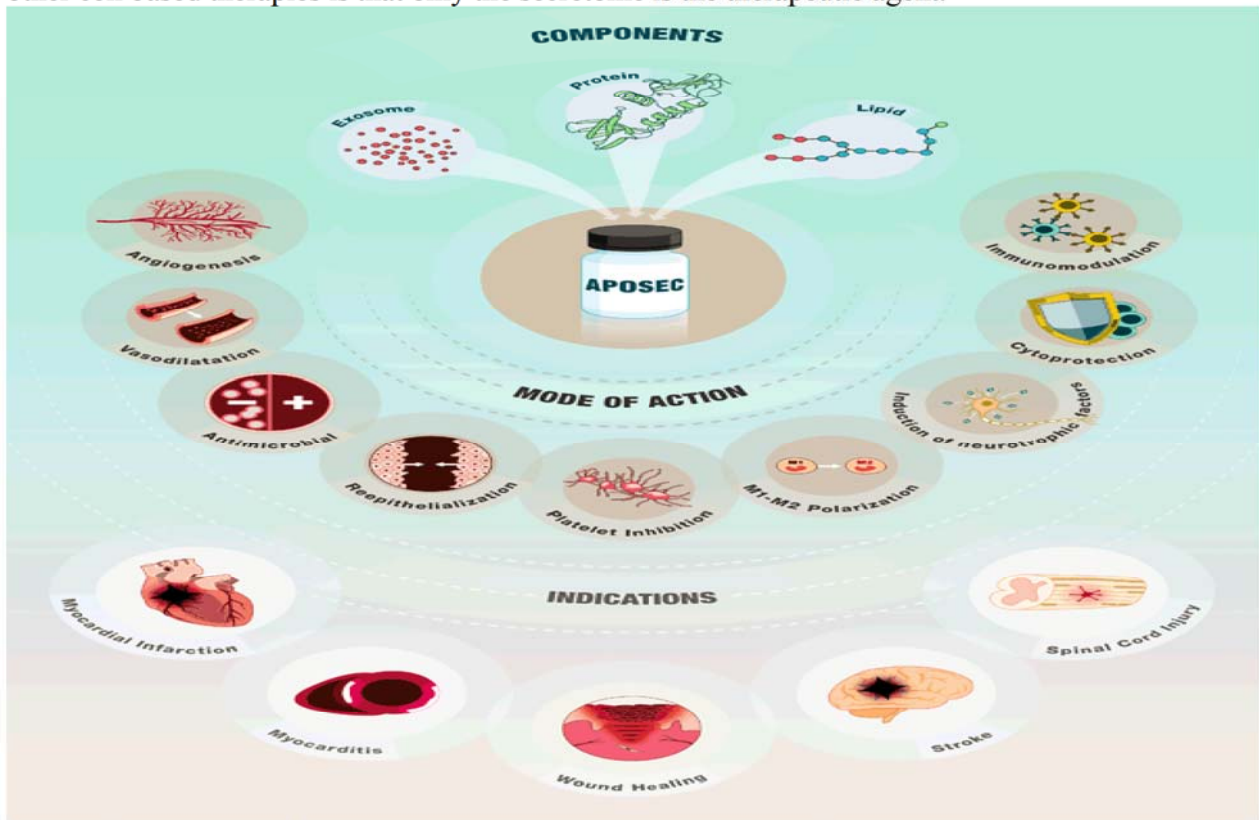


Fig. 3: APOSEC™ and its advantages and treatment opportunities⁸ (DOI 10.1007/s10495-016-1292-8)

Novelty within the APOSEC™ project and company APOSCIENCE AG is based on a shift of paradigm: “from cellular therapy to PBMC secretome based therapy”. In the last 10 years the main approach in the scientific world was to apply GMP manufactured living cell compartments (e.g. mesenchymal stem cells, placenta cells, and others). Currently it is accepted by researchers and product developers that not the cells (by themselves) but their secretory capacity is responsible for any documented clinical effects in human trials. One of the main novelties of the APOSCIENCE AG approach is the finding that **white blood cells** (PBMC), a current waste product at transfusion units (and not stem cells), is the starting material for the production of APOSEC™. These PBMC produce beneficial paracrine factors whilst getting into the apoptotic state. In vitro and vivo scientific results have evidenced that those PBMC in apoptosis secrete factors that are immunosuppressive, attenuate inflammation and augments reparative mechanisms in hypoxic tissues. The **concept of using paracrine factors** of apoptotic PBMC in a therapeutic context in regenerative medicine can be seen as a game changer which was developed and patented in Europa. The application of stem cells is facing a disillusion based on clinical trials⁹. The diagram (Fig.3) shows the components of the cell secretome (proteins, lipids, exosomes), the different mode of actions and consequently relevant

⁸ DOI 10.1007/s00395-011-0224-6

⁹ 10.1161/CIRCRESAHA.116.304346

indications that were examined in preclinical experiments¹⁰. Paracrine factors derived from apoptotic PBMCs have been shown to **induce angiogenesis and vasodilation, exert antimicrobial activity, enhance re-epithelialization, inhibit platelet coagulation, induce M1–M2 polarization, augment the release of neurotropic factors, exhibit cytoprotective capacities** due to the up-regulation of anti-apoptotic proteins, **and act in an immunomodulatory manner**. Based on these biological effects, the PBMC secretome **has been successfully tested** in multiple preclinical animal models of acute myocardial infarction, chronic heart failure, myocarditis, skin ulcer, stroke, and spinal cord injury. The use of human PBMCs as bioreactors for secretome-based therapies can be seen as an extension of the original concept of stem cell-based therapies to enable clinical applications. A large number of studies of **transplanted stem cells** have **failed** to show any significant integration and differentiation of injected cells into mature (cardiac) cells¹¹. In addition, there is a considerable loss of injected cells immediately after translation. By utilizing the secretome of apoptotic PBMCs (AMPOSEC™) instead of stem cells, we could promote tissue repair and regeneration in multiple pre-clinical indications with the identification of a variety of mode of actions (MOAs). Furthermore, stem cells are rare and their isolation and cultivation in large numbers is neither simple nor practical under GMP conditions. Hence, the more easily obtainable white blood cell-fraction (PBMC) will serve as “bioreactor” for the secretome production. This introduction of patented technology will instigate a new area in “cell free” regenerative medicine when clinical studies prove efficacy. PBMCs release pleiotropic paracrine factors that **augment tissue regeneration**, and their usage has the following **advantages**.

- (I) PBMCs are a current **waste product** from each red blood donation at transfusion units, so their **amount is potentially unrestricted** as compared to any stem cell population used thus far.
- (II) PBMCs are **obtained from healthy persons (regular blood donation with mandatory screening)**, avoiding any disease- or age-dependent disadvantage in the PBMC secretome; blood donations are highly regulated according to the western world standard.
- (III) Allogeneic samples with the pooled secretomes of PBMCs (conditioned medium from multiple individuals) can be utilized in human trials. In addition, double viral clearance (eg. methylene blue and gamma irradiation) guarantees additional safety to patients.
- (IV) The use of PBMCs does **not** comprise significant **ethical problems**, unlike the use of fetal stem cells. In conclusion: the PBMC secretome (APOSEC™) may potentially revolutionize regenerative medicine if appropriate proof of concept (PoC) studies in various indications are performed in humans.

Novelty is also based on the following issues that **have been proven** within treatment using APOSEC™:

- Prevents platelet aggregation and thus obstruction of microvasculature
- Induces vasodilatation and thus increases blood supply to hypoxic tissue
- Causes cyto protection and induces anti-apoptotic effects
- Promotes the angiogenesis and thus is important for wound healing and tissue regeneration
- Promotes the keratinocytes and fibroblast migration – important for faster closing of wounds
- Promotes proliferation of endothelial cells which is also important for wound healing
- Exerts anti-microbial effects in limiting the growth of gram-negative and gram-positive bacteria by 60-100% taking into account that 70% of DFU are highly contaminated.

Expected key market application(s) and expected performance

The first main market to be addressed is the **advanced wound care market**, the first tackled indication for APOSCIENCE AG is the **Diabetic Foot Ulcer, DFU**. As this indication is the first

¹⁰ Lucian Beer, Michael Mildner, Mariann Gyöngyösi, Hendrik Jan Ankersmit, Review “Peripheral blood mononuclear cell secretome for tissue repair”, Apoptosis, Dec. 2016, Vol 21, issue 12, pp 1336-1353;

¹¹ 10.1161/CIRCRESAHA.116.304346

anticipated clinical trials, it is expected that the lead product APO-2 will be the first one with market authorization. The main risks are that the product might fail during the proof of concept study (PoC). A **well-developed clinical study plan** performed by well-trained investigators will ensure a high quality of conduct of this clinical trial. The novel drug candidate APOSEC™ promises to be a great improvement to comparable treatments of chronic wounds. Chronic wounds are painful, need a long time to heal and often results in amputation surgery. The current treatment options of chronic wounds require the use of significant resources such as treatment materials, nursing time, multiple hospitalisation which merits only limited success. Treatments including APOSEC™ will provide an added value to the world of wound management. It will be easy-to-use, due the fact that APOSEC™ will be applied with a currently accepted (medical device) carrier substance (alginate NU-GEL™¹²). The economic add on of this novel treatment would be decreased hospitalisation times, reduced need for amputation and increased wellbeing of patients.

2. Impact

2.1 Expected Impacts

a) Users / Market

User needs identified (Targeted users of the final solution)

The main appliers of the APOSEC™ therapy products are not the patients but **the hospitals and health centres with doctors, wound care specialists, surgeons, dermatologists, nurses, podiatrists and social insurance companies**. Listing the products and reimbursement is only possible when **efficacy and ease-of-use are guaranteed**. APOSEC™ fulfils both. Users are faced with an **unmet medical need** in the field of chronic wound care, especially in treating DFU, VLU and decubitus ulcers. There is a **high need for therapies** that accelerate the sustainable closure of these cutaneous ulcers. Conventional procedures to treat DFU are often inefficient, not satisfactory and combined with stress and pain for the patients. APO-2 is a highly innovative, differentiated topical wound care product and has demonstrated safety and efficacy in compassionate use cases. **Chronic wounds can be healed with APOSEC™ within 20 to 28 days**. It is **easy-to-use and will be delivered** onto the wound in combination with an alginate (e.g. NU-GEL™). It is a **cost-effective product** and has the clear potential to become **best-in-class for the advanced wound care**. Within the project a **phase II clinical study** with APO-2 in DFU will be implemented. The primary objective to determine doses response in **clinical efficacy in patients** with DFU. This study will be a prospective, multi-center, randomized, double-blind, parallel group, placebo-controlled phase II study. It will start in Q3 of 2018 and will be finished Q4 2019 with 15-18 centres in 4 countries in Europa. Relevant positive safety and efficacy data will increase the interest of the relevant user groups for the APOSEC™ products. After the phase II study a phase III study needs to be done with approximately 200-250 patients to determine clinical efficacy (sample size will be driven from the results of the Phase II study). After these studies a **market authorisation with one pivotal study (according to EMA guidance:**

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003657.pdf)

at the authorities and introduction can be planned the earliest in 2022 and 2024. The foreseen activities within this project will be clinical studies (Phase II in DFU) and a Phase I first-in-man study for systemic (i.v.) application of APOSEC™ in healthy men. This study is the prerequisite for phase II trials in AMI, stroke, spinal cord injury and myocarditis. The more technical part will be the **upscaling of the production process** in order to be able to produce enough APOSEC™ products for the future planned clinical trials and market introduction. In addition, in order to ensure an easy-to-use approach for the users an APOSEC™ a **reconstitution and application/delivery set**

¹² For topical administration of APOSEC™: Lyophilisate is suspended in NaCl. The complete dissolved lyophilised APOSEC™ is mixed with NUGEL (Hydrogel).

needs to be provided to clinicians. Such a set will be developed within this project and prepared to be tested during the phase III trial.

Main economic benefits for the users

DFU (first indication to be addressed in a Proof of Concept study) is a major **complication of diabetes mellitus** with a **huge economic burden**. Long hospitalisation periods and long treatment procedures are cost drivers. The current therapy costs are between **7.500 – 20.000 USD per hospital stay**¹³. The main benefits are mainly **the reduction of treatment costs, hospitalisation time, ease-of-use** will reduce both nursing time and re-hospitalisation. Important is a study that showed that the calculated costs are 13.179 USD per treatment period on average in DFU patients¹⁴. The costs of an amputation are very diverse depending if the surgery costs are calculated alone or together with the rehabilitation costs. Long-term costs after amputation are between 43.100 and 63.100 USD¹⁵.

Contribution to important benefits to society

Chronic wounds represent a significant burden to patients, health care professionals, and the health care systems: in the US alone, **chronic wounds affect 5.7 million patients** and cost an estimated **20 billion dollars annually**, not including the additional costs to society in terms of lost workdays or productivity. One social problem is that patients have to stay in hospital for a long time and cannot access their social life. The challenge is to **shorten the hospital stay** in order to bring patients back to home into their familiar, social surroundings and back to work. Wound healing problems over a long time induces pain and psychological challenges for all in the family. It can be stated that **no efficient therapy and treatment** in DFU is currently available to overcome all the above mentioned challenges. There are some products in the pipelines of **competing companies** but most of them **failed on their way to market introduction**.

Type of market - Advanced wound care market

The number of diabetes patients is currently 300 million, and growing with a CAGR¹⁶ of 5%. It is expected to reach **600 million by 2030**. It is estimated that **annually 2%** (some estimates go up to even 4%) of diabetes patients will develop a foot ulceration. Therefore, the annual incidence of these events can be estimated to reach **6 to 12 million cases**. An important field where improved therapy will be important is skin regeneration after burns of all causes. These range from mild sun burns to 3rd degree burns covering large parts of the body. Burns lead to approx. 700,000 emergency department visits per year in the US alone. The **chronic wound market is large**, yet fragmented. Treaters differ between surgeons, nurses, podiatrists, and dermatologists. The market is large, but **underserved with effective treatments**. The market for advanced and active wound care products grows double-digit. The worldwide wound-care market, which can be broadly divided into wound-closure products, anti-infectives, basic wound care, advanced wound care, active wound care, and miscellaneous therapies, is expected to continue to grow at a CAGR of 6%. Notably, over 50% of wound care sales still originate from relatively mature markets such as wound-closure products, anti-infectives, and basic wound care. According to a study published in 2012 by Visiongain, the total advanced wound care market was worth \$6.7bn in 2011, and will reach \$16.3bn in 2023.¹⁷

Chronic, hard-to-heal wounds represent one of the largest and fastest growing segments of the wound care market (~\$5.3 billion advanced wound care (AWC) market worldwide). It is believed that the AWC market is underpenetrated due to lack of effective products. About ~800K and

¹³ Singh et al. 2005; Rogers et al. 2008;

¹⁴ Karen Stock et al (2004) ("Costs of Lower-Extremity Ulcers Among Patients With Diabetes", in: Diabetes Care. 2004 Sep;27(9):2129-34.

¹⁵ Evidence-based Diabetes Guidelines DDG – Diabetic Foot Ulcer, Update 2008

¹⁶ CAGR – Compound Annual Growth Rate.

¹⁷ <https://www.visiongain.com/Report/1420/Advanced-Wound-Care-Market-Forecast-2015-2025>

~1,300K patients each year (US, EU5, Japan) experience hard-to-heal DFUs and VLUs, respectively¹⁸.

- 25% of people with Diabetes will develop a foot ulcer in their lifetime
- ~15% of hard-to-heal wounds result in amputations
- 80% of all amputations in the US are result of non-healing DFUs
- ~\$25 billion burden on the US healthcare system”

DFU Market

The **first main indication for APOSCIENCE AG is the Diabetic Foot Ulcer**, DFU. An analysis of the DFU market has been performed. DFU is one of the most common and severe consequences of diabetes. Treatment of DFU represents a major healthcare expenditure and, consequently, **better treatment is a huge market opportunity**. In the US alone, each DFU patient costs the healthcare system up to \$40,000 in the first two years after diagnosis.¹⁹ The cost of DFU treatment has been estimated to exceed \$2 billion in the United States annually. The research group Global Data to increase to \$2.28 billion by 2017 has estimated the market for the treatment of diabetic foot ulcers. In the EU an amount of 40.6 million persons suffer from diabetes and an annual increase of patients of 811.200 persons getting DFU annually. Market size in the EU is about 1.1 billion Euro per year. The **potential world market is about 15.6 billion Euro** per year.

Main competitors and competitive solutions

1) 1st generation products: single factors

These therapeutic products are based on recombinant human growth factors. But all of these single substance products do not have the relevant efficacy to heal chronic wounds.

Product	Company	status
Regranex	Smith & Nephew	Approved for DFU in US, EU, CAN, South Korea but with black box warning label of the FDA because of potential cancer risk. Revenues are therefore declining.
Fiblast	Olympos Biotech	Approved for DFU in Japan, South Korea
Heberprot-P	Heber Biotech	Approved for DFU in Cuba, South Korea, Belgium, Turkey
DSC127	Derma Sciences	Failed in phase III clinical studies for DFU
2 more candidates	Human Genome Sciences; RegenRx	Failed both in phase II clinical studies

2) skin equivalents

Some approaches are based on using cell-based skin substitutes for wound healing. It turned out that the skin substitutes are not fully integrated but resorbed or even rejected by the body of the patient and therefore not very efficient.

3) products working based on paracrine factors

Product	Company	status
CureXcell	Macrocare	Failed in phase III clinical studies
HP808-101	Healthpoint, Smith&Nephew	Failed in phase III clinical studies
Epifix	Forticell Bioscience	Approved for DFU in Cuba, South Korea, Belgium

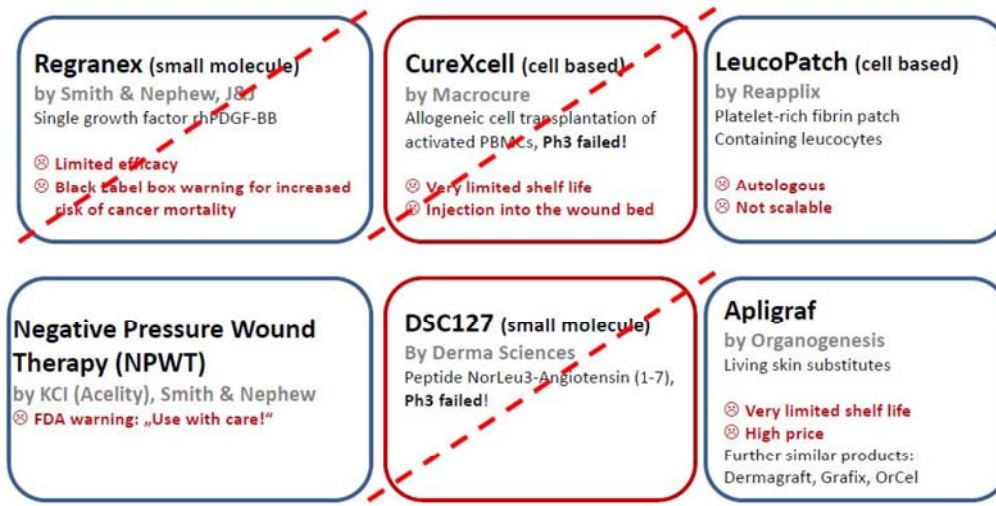
¹⁸ Macrocare Analyst day, Feb 2, 2015 (estimates by competitor Macrocare)

¹⁹ Edison Investment Research Limited (12 Feb 2015)

Grafix	Osiris Therapeutics	Under clinical development in the US.
LeucoPatch	Reaplix	Approved because autologous product, currently in a phase IV clinical trial with about 250 patients.

Analysing the mode of action, the cell based product CureXcell of the competitor from Israel, Macrocare, failed in a phase III study for DFU. The company told that within this study they were not able to proof wound closing after 16 weeks and sustainable wound closing after 4 weeks.²⁰ In comparison APOSCIENCE is based on a secretome based therapy approach.

Competitors of APO-2



The diagram above gives an overview of the competing products that are near to the mode of action of APOSEC™. Within the last two years, two competing products, Regranex and DSC127, disappeared due to failing within the phase III of clinical trials.

Important market barriers

Main challenges are seen in the successful **completion of the targeted clinical development plan**. Only if the different clinical trial phases (phase II, phase III and market authorisation in the case of DFU) are successfully completed the APO-2 product can be introduced by APOSCIENCE AG to the market. Clinical trials are **highly regulated** due to the fact that patients are involved and give their consent to the trial goals. Such a clinical development and further development of the company requires high investments before the product can be sold on the market. A mixture of private investments and public funding (H2020) is needed to leverage and bring APOSEC™ onto the market. Beside these financial obstacles it always can be the case to fail within the different phases of clinical trials due to adverse events, low efficacy, safety goals not fully met, and any other problems that does prohibit the commercialization of the product. Any delays in clinical trials may cause a delayed market uptake and may also cause delays in reimbursement discussions with national health authorities. There are also potential technical barriers to be taken into account. The production partner (Blood Bank Linz, Austria) needs to scale up the production of APO-2 product to an amount that is needed to serve the market in Europe. Currently, the GMP certified production process is able to produce enough APO-2 to serve the clinical trials phase II DFU and the systemic PHASE I study with APO-1 (with healthy probands as a prerequisite for further studies on AMI, stroke, spinal cord injury and myocarditis). However, for the phase III and market introduction a **higher production capacity is needed**. Therefore, this project is of high relevance to scale up the process and prepare for the future needs. Upscaling also includes relevant technical, logistics and

²⁰ <http://investor.macrocare.com/releasedetail.cfm?releaseid=938787>

process optimisations in order to reduce production costs. Now, the APOSEC™ production process is mainly based on hand work and most of the production steps have to be done in a clean room class B. These problems may be solved by a semi-automatic closed bag system. Therefore, the company concentrates on automatization in the first production steps as this way of posing a problem is more difficult. A potential concept that increases APOSEC™ production can be depicted in Fig. 5.

Upscaling of APOSEC™ production – automatization – in a closed system in bags

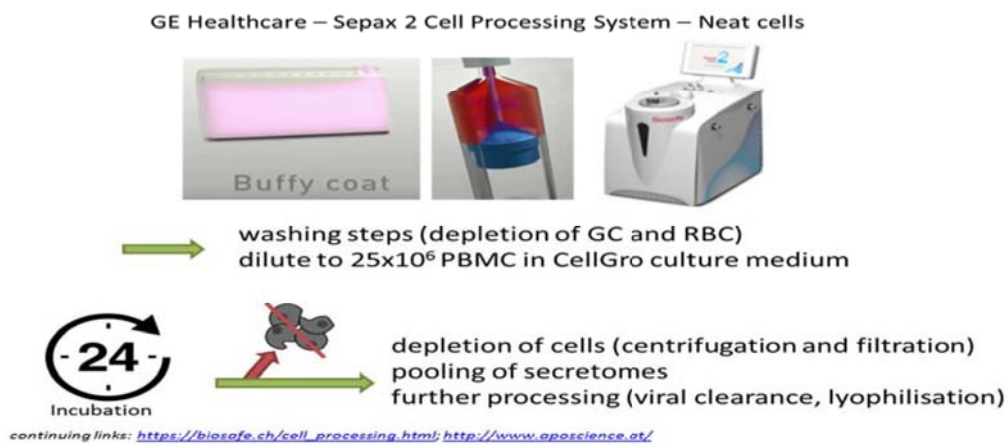


Fig.5: Possible method for upscaling the APOSEC production process

b) Company

Relevance, rationale and alignment with APOSCIENCE AG business strategy

Business Angels founded APOSCIENCE AG in Vienna in 2008 with the objective of developing the APOSEC™ technology towards market admission. Since then APOSCIENCE AG has been a pure research company, without any operative business. The current capitalization of the company is EUR [REDACTED] (one share equalling 1 EURO). Between 2009 and 2015 the preclinical work for APOSEC™ was concluded in a partnership between the Medical University and APOSCIENCE AG: efficacy of the drug substance in various indications was proved in small and large animal models; the data were published – all open access – in scientific high-impact journals; the patents were defended with the help of these preclinical data. In 2013, APOSCIENCE AG has started the product development process of APOSEC™ by working on such topics as the establishment of a GMP (Good Manufacturing Practice)-process including in-process-controls for APOSEC™ in order to be able to guarantee standardized production quality of the drug substance; the performance of stability assays and toxicology assays, and the development of potency assays. All these measures are taken in order to fulfil regulatory requirements. A recent scientific advice (April 2017) with the Austrian regulatory agency AGES reassured APOSCIENCE AG of the soundness and correctness of its development program for APOSEC™. A further scientific advice will be done with the Paul-Ehrlich Institute in Germany (Dec. 2017). From its beginning 2008 till now total costs of the APOSEC project sum up to approximately EUR [REDACTED]. Of these funds EUR [REDACTED] were provided by the shareholders of the company, approximately EUR [REDACTED] were granted by the Christian Doppler Forschungsgesellschaft, and EUR [REDACTED] - are granted right now by the Austrian Research Promotion Agency (FFG). The main strategy of APOSCIENCE AG is to **bring the therapy product APOSEC™ onto the market** in order to be used as treatment and therapy to heal DFU, ulcers, burns and to license out other indications like myocardial infarct. While the APOSEC™ product platform addresses a number of high-value indications, the company will focus on its most advanced program in **chronic wounds**. The mission of APOSCIENCE AG is to improve the health of patients in need of regenerative medicine by commercially exploiting the therapeutic potential of secretomes of white blood cells (PBMCs) isolated from peripheral blood. The activities within this proposed SME instrument fit well into the overall clinical development

plan but also the product development plan of APOSEC™. (see also figure concept and structure, p. 8) APOSEC™ is planned to be a first-line therapy for DFU. If the APOSEC™ product finishes the clinical development program and market authorization successfully, the granted *data exclusivity for medicinal products* (given by the European Medicines Agency) will ensure protection even **10 years after market entry**. In order to adjust the risk, APOSCIENCE AG calculated by an benchmarking approach the standard probability of technical and regulatory success (PTRS)²¹ which resulted in an overall PTRS for APO-2 from entry into phase I to approval/market authorisation of about 42% - 10% higher than benchmark.

Growth potential of the APOSEC™ solution

Costs of Good/Need for Upscaling: Based on the assumption that it is possible to pool 7 batches (in order to gain a significant reduction of vials that have to be retained for pharmacological testing and as retain samples) we have calculated costs of good between [REDACTED] [REDACTED] for one treatment cycle (12 treatments) for DFU depending on testing costs. These numbers do not reflect any automatization and/or upscaling yet. If we aim for a market price of [REDACTED] (our basis for the turnover calculation) the costs of good need to be reduced significantly. Automatization alone (automatization of the blood separation process and the implementation of a closed bag system resulting in reduced cleanroom costs) could reduce costs of good 20-40%.

Turnover: Based on the pricing assumption of [REDACTED] per treatment cycle (DFU) a turnover of about **390 million Euro** can be reached. If the price is higher, e.g. [REDACTED] Euro per treatment cycle a turnover of **510 million Euro** can be calculated.

Market share and Sales: Assumption of 980.000 DFU patients in EU with a **30%** market share by APO-2. The pricing strategy of APOSCIENCE AG foresees reimbursement and ensures fast ramp-up of sales. Peak sales will be reached within 5 years with a market share of 30%.

Employment creation: After a positive finalisation of phase II and phase III trials DFU a massive increase of personnel is to be expected. Depending on the further strategies implemented this might vary between 50 to 100 employees more in the APOSCIENCE AG company.

Return on investment (ROI): Two scenarios have been calculated.

First, an exit is modelled on positive phase II data of APO-2 in DFU in four years and shall be based on an IPO or trade sale. As a benchmark for an IPO the valuation of competitor [REDACTED] that went public with phase II data in 2014 with a market cap of [REDACTED] can serve. Therefore, APOSCIENCE AG foresees a similar approach to finance the phase III clinical trials and market authorisation / introduction by an IPO. An exit is foreseen after 4 years after market introduction. Calculations result in an ROI of 685%. (company valuation 137 million) Second, a partnering approach has been planned where APOSCIENCE AG will partner with a multinational player to perform phase III clinical trials and gain market admission for APOSEC™. ROI is difficult to calculate as it depends on the scenarios if the product will be funded by APOSCIENCE AG through all clinical phases until market authorisation or if a partner is coming in already after e.g. phase II clinical trial. The timing to an ROI is between 5 years and 9 years depending on the scenario.

Profit: APO-2 has the potential to **become best-in-class product** in the advanced wound care market, provided that the efficacy seen in preclinical animal experiments and compassionate use experiments in humans is corroborated in controlled clinical studies (phase II, III). APO-2 represents an opportunity for a turnover of more than one billion Euro worldwide depending on reimbursed pricing. Based on an assumed gross margin between [REDACTED] Euro per patient **profits can reach up to** [REDACTED] Taking into account that APO-2 will not be a first-

²¹ DiMasi et al., R&D cost study briefing, Boston, Nov 18, 2014

line treatment but only be used after standard-of-care product failed then the profits are less but up to [REDACTED]

Coaching services for SME Instrument beneficiaries: Coaching services will be mainly used for support in IPR issues but also in getting in contact with investors, financing bodies and other partners.

Estimated funding requirements to reach commercialisation stage: APOSCIENCE AG calculated a need of [REDACTED] to finalise the phase II clinical trial. This is based on [REDACTED] to start the company's operations and to complete preclinical product development and phase I, and a second investment of [REDACTED] to complete the clinical phase II study. There is a financial mix of investments of founders and investors, as well as national funding grants. Up to now a total investment of about € [REDACTED] has been achieved which means that another € [REDACTED] are needed. The funding mix is based currently on the following: Private funding from founders and investors: 45%, National funding sources: 20%, SME Instrument funding: about 35%. Further funding will be generated through an IPO after a successful phase II clinical trial results, but other options are regularly assessed and calculated in order to identify the best solution for APOSEC's successful commercialisation.

2.2 Measures to maximise impact

a) Dissemination and exploitation of results

Key stakeholders

Key stakeholders are those who play an important role for making a successful commercialisation of the APOSEC™ products. The following table gives an overview of the relevant stakeholder and its role during commercialisation of APOSEC™ products.

Type of Stakeholder	Role within the commercialisation
Patients (very important)	Patients are the key stakeholders of clinical trials and pharmaceutical companies producing healthcare products for human use. Patients need to understand their role as a “subject of research” in the relevant clinical trial. Information is provided and agreed via the so-called informed consent process.
End-user: Physicians (diabetologists, dermatologists, surgeons) nurses, hospitals in general (very important)	These are key stakeholders in using and applying APOSEC™ when approved by authorities. They are also very important during the performance of clinical studies. Doctors for example decide on the treatment for specific patients.
National health authorities, European health authorities (very important)	These national authorisation authorities rely on the results of clinical trials carried out by pharmaceutical companies to reach its opinion on the authorisation of medicines. The European authority, EMA, plays a key role in ensuring good clinical practise and also manages a clinical trials database carried out in the EU. The Committee for Medicinal Products for Human Use (CHMP) is responsible for conducting the assessment of a human medicine for which and EU-wide marketing authorisation has been sought.
Technology & production partners (very important)	APOSCIENCE AG has already a signed framework agreement with the Blood Centre in Linz, Austria, where the current GMP certified production process is installed and where the APOSEC™ product is produced. The blood donor centre is also a main partner within this SME Instrument project in order to implement upscaling and process optimisation. APOSCIENCE AG is also in contact with the company called

	biosafe (a subsidiary of GE) in order to further developing the production process of APOSEC™. APOSCIENCE AG is also in relation with a company called [REDACTED] in Austria that shall produce the Reconstitution and delivery device for APOSCIENCE AG which is also a part in this proposed project to reach a CE marked device and ready to be used within phase III studies. APOSCIENCE AG is also in relation with a company called [REDACTED] providing the NU-GEL as substance to be mixed with APOSEC™ within the reconstitution and delivery device and delivered to the patients.
Investors, financing institutions, funding institutions (important)	The whole clinical development plan needs multiple arms of investment: funding sources from public and private sources are important to ensure a stable and sustainable financing of the APOSCIENCE AG company.
Academia and science community	Are of great importance since APOSEC™ as idea was born in a research laboratory of the Medical University of Vienna. When APOSEC™ is further developed, multiple European clinic sites will be involved within the clinical Phase II-III trials (anticipated are POL, HUN, Czech Republic, Germany and Austria).

Further steps needed: Market authorization for the treatment of diabetic foot ulcers is aimed with only one pivotal phase III study. The results of the planned phase II study will provide the required data for planning the Phase III study. APOSCIENCE AG is aiming to fulfil 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 this strategy to plan for a single pivotal trial only. Otherwise two **phase III clinical studies** for indication DFU (with up to 250 patients involved) and will be planned for the assessment of the market authorisation by EMA. This will be done with a partner (pharma) or based on own funds. A **market introduction** is planned to be between the **years 2022 – 2024**. In regulatory terms, APO-2 will require Biologics License Application (BLA) in the US, and in EU the Market Authorisation Application (MAA) will be obtained via the centralised procedure. The “centralised procedure” for authorising medicinal products is laid down in Regulation (EC) No 726/2004. In a base case planning scenario, market authorization will require two independent confirmatory phase III studies. For global licensure, one phase III study could be conducted as a European study, and the other one as an US study. A number of activities will be conducted in parallel to phase III clinical studies and review of the MAA/BLA by the competent authorities: process development, further characterization of the product, mode-of-action studies, assay development, production of conformance lots, stability studies, development of the reconstitution & delivery device for large scale manufacturing, upscaling of manufacturing capacities, preparation of marketing collaterals, market access and reimbursement.

Strategy plan for commercialisation

The technology platform APOSEC™ is the basis for two products (based on one patent family):

- APO-1 → APOSEC™ formulation for the treatment of systemic inflammation illnesses caused by hypoxia like acute myocardial infarct, myocarditis, stroke and spinal cord injury.
- APO-2 → APOSEC™ formulation within a hydrogel (NUGEL) for the topic treatment and healing of acute or chronic wounds, especially of DFU.

APO-2 is the **most advanced product and lead product** for APOSCIENCE AG. The company has the goal to **finalise the phase II trial** within this project and to **start phase III clinical trials** as well as to go for commercialisation of the product. It is targeted to reach market authorization for APO-2 for the indication of DFU. Further indications like VFU, burns, etc. will be targeted later in order to reach a broad authorisation for chronic wounds. The efficacy of APO-1 has been proven in pre-clinical trials. **APO-1** will be tested in a **phase I trial (first-in-human)** with healthy volunteers to assess safety and tolerability on AMI, stroke, spinal cord injury and myocarditis before going into further clinical studies. Relevant ethical documents are in development and will be submitted in Q2/2018. An **upscaling of the GMP certified APOSEC™ production process** will be necessary in order to ensure the needed capacities for the market introduction. Further technological developments have to be implemented regarding the APOSEC™ reconstitution and delivery device to reach a CE mark. Prototypes of the reconstitution and delivery device have already been manufactured. Such a device is needed to reconstitute APOSEC™ with NaCl solution and mixed with the carrier gel (NU-GEL™) before delivering onto the affected skin area.

b) Intellectual Property, knowledge protection and regulatory issues

Outline the strategy for knowledge management and protection as well as current IP Status

APOSCIENCE AG is owner of several patents where two patent families are related to APOSEC™:

- **WO 2010/079086 A1 – PHARMACEUTICAL PREPARATION COMPRISING SUPERNATANT OF BLOOD MONONUCLEAR CELL CULTURE**

APO-2 patent family: The present invention relates to a topical pharmaceutical preparation for treating an inflammatory skin condition, preferably a condition associated with ischemia, comprising a supernatant of a physiological solution obtainable by cultivating peripheral blood mononuclear cells (PBMCs) or a subset thereof in a physiological solution free of PBMC-proliferating and PBMC-activating substances for at least 1 h.

Priority : 18/12/2008 (international protection : AU, BR, CA, CN, EP, JP, NZ, RU, US, ZA)

- **WO 2010/070105 A1 – PHARMACEUTICAL PREPARATION**

APO-1 patent family: 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.

Priority : 18/12/2008 (international protection : AU, BR, CA, CN, EP, JP, NZ, RU, US, ZU, AT, CH, DE, ES, FR, GB, HU, IT, NL, PL, SE, TR)

Both patents have been submitted in 2008 and have been already approved. Thus, the patent protection is running until 2028. In addition, data exclusivity ensures protection even 10 years after market entry. Furthermore, APOSCIENCE AG has registered the name APOSEC™ as a word mark in Nice classes 5 and 9. In an additional Annex, a list of currently valid patents per country is given.

Ensure commercial exploitation – FTO & Strategy for knowledge management and protection

Two Freedom-to-operate analyses have been conducted. Two well-known patent attorney agencies (Kliment & Henhapel, Vienna, and Isenbruck/Bösl/Hörschler, Munich) **proofed that the APOSEC™ patents do not infringe any other protecting rights and that a freedom to operate is given.** (both FTO documents are attached in other annexes) The «Kliment» FTO report assessed whether or not the APOSEC™ technology falls within the scope of protection of other patents, and if there exist patents and patent applications filed in the name of Macrocare Ltd, Hemostemix Inc, and Reaplix ApS which cover the aforementioned APOSEC™ technology in part or entirely. The expert opinion is based on patents and applications identified in the course of a keyword and assignee/applicant search. The APOSEC™ technology does not fall under the wording of claims of the patents and patent applications identified herein (a relevant list of assessed

patents and applications can be found in the attachment/annex). The «Isenbruck» FTO report assessed the validity of EP applications and EP patents resulting from PCT applications WO2010/100570, WO2012/032418, WO2013/136182, WO2013/136191 filed by the competing company Macrocare, inquiring whether the claimed subject-matter can be regarded as patentable invention or not. The analysis of all relevant documents resulted in questioning novelty and inventive step of the inventions claimed. In conclusion, the report estimates lack of novelty and / or inventiveness in the most prominent claims of the competing companies. **Data exclusivity** in Europe is for 10 (8+2), potentially even 11 (8+2+1) years: Data exclusivity will offer protection **from the date of first market authorisation of the APOSEC™ in Europe**. Since first market authorization for APO-2 is planned for 2023, data exclusivity will protect APO-2 against a generic version of the medicinal product using the same drug product **until 2033**. Data exclusivity refers to a set period of time after the marketing approval, during which no one else may rely on or use the innovator's data to obtain a marketing authorization for a particular product. It constitutes an important incentive to the research and development of new medicines. Data exclusivity is not an extension of patent rights, and it does not prevent the introduction of generic versions of the innovative drug during the data exclusivity period, as long as the marketing approval of the generic version does not use or rely upon the innovator's test data.²²

Explain the regulatory and/or standard requirements to be fulfilled for the exploitation of the technology/product/solution or concept: how they are to be met

According to APOSCIENCE AG, APOSEC™ is a biological medicinal product as defined in Directive 2001/83/EC on the Community code relating to medicinal products for human use. APOSCIENCE AG already managed to successfully reach certain milestones on the way to a market authorisation of the APOSEC™ products. These milestones are steps within the life-cycle of medicinal products that need to be fulfilled and certified by the Health Authorities. (AGES in Austria, EMA in EU)

1. Good Manufacturing Practice (GMP) production

The Austrian Authority has issued a manufacturing authorisation for the production of APOSEC™. The validated GMP production facility is located in Linz, Austria, at the manufacturing partner "Blood Center Linz". The products have to meet international standards (e.g. Ph.Eur.) and fulfil requirements by the authorities because only good quality ensures proven safety and efficacy, as well as protection of public health and patients. A CMC (Chemicals, Manufacturing & Controls) Document has been prepared. This CMC is a very important part of any clinical trial in order to ensure a high-quality product and manufacturing process.

2. Quality assurance approach for APOSEC™

Specific requirement and control strategy are based on Directive 2001/83/EC and are implemented on a Failure Mode-Effect-Analysis (FMEA). This includes a control of the starting material (blood donations), a tight control of the manufacturing process and critical process parameters (isolation of the PBMCs and cell culture conditions), tight control of in-process controls, batch release via selected proteins, an in-vitro potency assessment and stability checks.

3. Clinical trials for efficacy and safety & regulatory issues within clinical development

Clinical trials are well regulated and followed by national / EU authorities. APOSCIENCE AG will apply the centralised procedure for the marketing authorisation upon completion of the development process. National laws and also European directives and regulations regulate the clinical trials. A clinical trials application has been prepared and sent in to the Austrian Agency for Health, AGES, based on the law "Arzneimittelgesetz" (AMG) and to the relevant ethics committees. From 2018 on an EU regulation (Clinical trials regulation EU No. 536/2014) harmonises the assessment and supervision processes for clinical trials throughout Europe via an EU portal and database. This will

²² <http://www.ifpma.org/innovation/ip-rights/data-exclusivity.html>

harmonise the electronic submission and assessment process for clinical trials, increase transparency of information and ensure highest standards of safety for all participants in EU clinical trials. The scientific advice has been issued on 17th of April 2017 and it was agreed that the overall design of the phase II study DFU is accepted in terms of study population and run in period. Relevant ethical approvals are needed for each clinical trial from each site selected based on national rules. For phase II DFU ethical applications are in preparation and submitted in early 2018.

4. Market authorisation procedure

APOSCIENCE AG considers to apply for the centralized procedure which is regulated in Regulation EC No. 726/2004. An increasing number of new medicinal products is nowadays centrally authorized at one stroke throughout the EU and not handled by every single member state, as it is the case for e.g. national procedures. The Committee for Medicinal Products for Human Use (CHMP) and the Committee for Medicinal Products for Veterinary Use (CVMP) hold in this regard a central function in this procedure. Both committees consist of representatives of each member state and represent the scientific committee of the Commission. In addition, an obligation for batch release needs to be fulfilled.

c) Communication

Communication measures for promoting the project and its findings during the period of the grant

APOSECTM has defined a specific communication strategy to promote the results. The following target groups and objectives have been identified: Wound care specialists, Surgeons, Dermatologist, Podiatrists, Payors in the hospital, Patients and families. In order to promote APOSECTM the following communication measures are foreseen: product design, logo: a logo resp. project CI will be defined, to be used in all dissemination materials, website, press work: technological articles in relevant magazines, journals; a press conference at the end of the project, flyers, folders and brochures, training material: web based and training courses, audio and video material, workshops with stakeholders, users, social insurance. The aim is to communicate the benefits of the new products (in terms of cost effectiveness, production costs, easy-of-use concept, clinical trials results), to facilitate the diffusion of these innovations. Journalists/media are targeted to increase their interest in the new technology. They should help to increase awareness about the products and the benefits of the new solutions. The described communication measures will be used to reach these goals via different communication channels, like a project website, flyers, folders, videos and press articles. Special workshops and training materials will be organised and produced to inform and train installers and technicians about the new products/technology and to raise awareness.

EMA clinical trial portal and database (Clinical Trial Regulation EU No. 536/2014)

From 2018 on the EMA portal will be the single entry point for submitting clinical trial information in the EU, which will be stored in the database. EMA will make information stored in the database publicly available subject to transparency rules. The clinical trial application form and supporting dossier will cover all regulatory and ethics assessments from the Member States concerned. It will also include the public registration of the clinical trial and any subsequent updates. Through the public website, detailed information on all clinical trials conducted in the EU, in all official EU languages, can be accessed. The website will provide features like overview of clinical trial statistics, advanced search, download data and reports, site updates and announcements. The Clinical Trial Regulation requires all information stored in the database to be publicly available, unless exempted under the Regulation to protect personal data, commercially confidential information, in particular the marketing-authorisation status of the medicine, unless there is an overriding public interest.

3. Implementation

3.1 Work plan – Work packages, deliverables and milestones

Overall structure of the work plan

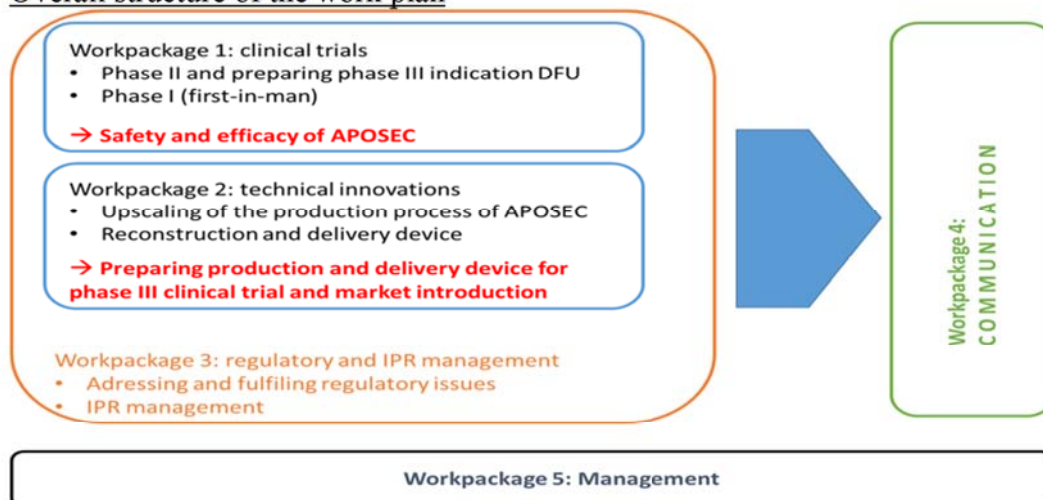
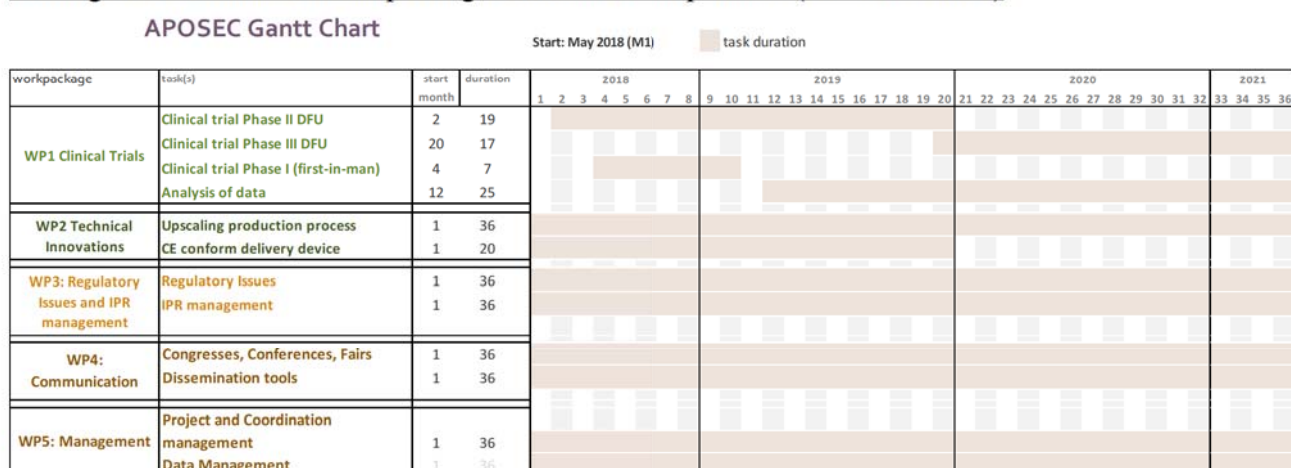


Fig.6: Structure of the workplan

Timing of the different work packages and their components (GANTT Chart)



Detailed work description

Description of each work package (table 3.1a)

Description of each work package (table 3.1a)			
Work package number	1	Start Date or Starting Event	1
Work package title	Clinical trials		
Participant number	1		
Short name of participant	APO		
Person/months per participant:	41,6		
Objectives			
• Conduct a phase II randomized, double blind prospective study utilizing APOSEC™ as topical treatment for Diabetic foot ulcer, DFU. • Conduct a phase I study (first-in-man) utilizing intravenous APOSEC™ as prerequisite for phase II studies in the treatment for acute myocardial infarction, AMI, spinal cord injury, stroke, and myocarditis			
Description of work			
The preparation of all relevant regulatory documents (protocol, ethics, informed consent, etc.) regarding the conducting of the following clinical trials will be established in the beginning of 2018.			

Task 1.1: Clinical trial Phase II Indication DFU (M2-M20)
This will be a prospective randomized double-blind multicentre phase II trial to investigate the efficacy, safety and feasibility of repetitive topical administration of human allogenic APOSEC™ in patients with DFU in a 12 week (84 day) trial. APOSEC™ will be applied topically 3x a week for 4 weeks. At day 84 the study will be terminated. The primary endpoint will assess wound area reduction at 4 weeks and the secondary endpoint to check the wound closure during the 12 week study period. The goal is to enrol 120 study objects, patients.
Task 1.2: Preparation of Phase III clinical trials indication DFU (M20-M36)
All relevant documents and planning will be done within this project in order to launch the phase III trials for indication DFU as a basis for market introduction and authorisation.
Task 1.3: Clinical trial Phase I to prove that systemic application of APOSEC™ in healthy young men is safe and well tolerated (M4-M10)
This will be a prospective non-randomized First-in-Man Phase I trial to investigate the safety and tolerability of single intravenous administration of human allogenic APOSEC™. No formal sample size calculation is made as this is a hypothesis generating pilot study and includes healthy volunteers.
Task 1.4: Analysis of data from Phase II trial and phase I trial (M12-M36)
The Medical University of Vienna will perform data management and statistical analysis for phase I. Descriptive statistics and comparisons between treatment groups with respect to demographic, efficacy, and safety parameters will be applied. All recruited probands will be included in the primary safety analysis.
Deliverables
D1.1: Study results of Phase II trial – DFU: (M24): findings will be summarised and described within a manuscript, circulated to all investigators before the finalization of a clinical study report and submission to a scientific journal.
D1.2: Study results of phase I trial of systemic application of APOSEC™. (M16) compiled in a clinical study report.

Work package number	2	Start Date or Starting Event	3
Work package title	Technical innovations		
Participant number	1		
Short name of participant	APO		
Person/months per participant:	100		
Objectives	• Optimisation of the production process in order to reach capacities of APOSEC™ product for market introduction • Technical optimisation and reduction of production costs • Determine logistical and transporting needs		
Description of work	Task 2.1: Upscaling and optimisation of APOSEC™ production process (M1-M36) The upscaling of the production process includes the assessment of a technical optimisation, the assessment of relevant human resources and limitation, the assessment of available blood and raw material for APOSEC™ production. Currently clean room conditions are needed. Technological methods and devices are available in the field of bone marrow donation and umbilical cord treatment. These technologies will be tested and assessed to produce APOSEC™. As these systems are closed systems it might be the case that a clean room is not needed. These are also automatized methods which require much less human resources. In addition, a standard has to be defined for suppliers of raw material (coming from blood banks) and how it needs to be transported to the production unit. The current capacity of the GMP certified production process is sufficient for the treatment of 500 patients with APOSEC™ per year.		

<u>Task 2.2: Production of CE conform Reconstitution and delivery device (M1-M19)</u>
Cooperation partner Goller Systems, Austria, has produced prototypes of the Reconstitution and delivery device. Goller is capable of manufacturing the device on commercial scale. The relevant production process for commercial production of this device will be prepared.
Deliverables
D2.1: Report on the automatization / upscaling strategy of APOSEC™ for market introduction (M24)
D2.2: Report on the reconstitution and application device (M20) – production manual

Work package number	3	Start Date or Starting Event	1
Work package title	Regulatory and IPR management		
Participant number	1		
Short name of participant	APO		
Person/months per participant:	69		
Objectives - Ethical approvals are given for phase II and phase I trials - Close communication and cooperation with national and EU regulatory bodies - Management of IPR and assesment of potential new exploitation measures			
Description of work <u>Task 3.1: regulatory and ethics issues (M1-M36)</u> APOSCIENCE AG is in close contact with relevant national and EU regulatory bodies (AGES, Austria, EMA, UK). Ethical approvals will be managed in time before the launch of the relevant study, trial. APOSCIENE AG and partners will apply current legislative procedures and regulations to conduct the clinical trials and market authorisation. A CE mark is needed for the reconstitution and delivery device (Goller Systems). <u>Task 3.2: IPR management (M1-M36)</u> Results will be evaluated during the whole project duration and beyond in order to identify intellectual property and define a strategy to exploit.			
Deliverables D3.1: Report on regulatory issues (M36) D3.2: further developed IPR strategy and report (M36)			

Work package number	4	Start Date or Starting Event	1
Work package title	Communication		
Participant number	1		
Short name of participant	APO		
Person/months per participant:	18,6		
Objectives • Implement a communication strategy with relevant stakeholders and users • Inform the scientific and medical community about results on APOSEC™			
Description of work			
<u>Task 4.1: Congresses, Conference and fairs (M1-M36)</u>			
During the project life-cycle the team of APOSICIENCE AG will regularly visit and participate in international congresses and conference to exchange know-how and results within the scientific community. Fairs will be used to get in contact with the pharmaceutical industry. This includes also relevant investors' fora, or partnering events and platforms.			
<u>Task 4.2: Dissemination tools and channels (M1-M36)</u>			
Dissemination tools will be designed based on a product and project identity being website, flyers,			

folders, posters and any other printable tool to be used. Any documentation needed within the clinical trials to inform patients, families, and professionals, it will be designed in APOSCIENCE AG identity. A specific marketing plan and strategy will be developed and formulated.
Deliverables
D4.1: Report on events where APOSCIENCE AG was presented (M15)
D4.2: Report on communication efforts for APOSCIENCE AG products (M15)

Work package number	5	Start Date or Starting Event	1
Work package title	Management		
Participant number	1		
Short name of participant	APO		
Person/months per participant:	18		

Objectives
• Project management, Data management • Communication, reporting with the EC

Description of work
Task 5.1: Project and Coordination Management (M1-M36)
• Set up and maintenance of the communication system between the project partners and third-parties • Organising and moderating of project partner meetings • Coordination of the technical activities of the project • Overseeing the overall legal, contractual, ethical, financial and administrative aspects in the project • Coordination of knowledge management and other innovation-related activities • Promotion of the gender equality in the project, Overseeing of science and society issues related to the research activities,
Task 5.2: Data management (M1-M36)
Investigators must maintain information in the patient's medical needs, which corroborate data collected on the case report forms according to ICH, "Good Clinical Practice". The regulatory requirements list a minimum of information that needs to be collected. Data collected at all visits are entered into the electronic individual Case Report Forms (CRF) for a later transfer into a database for statistical analysis.
Deliverables
D5.1: Reports

List of work packages (table 3.1b)

Work package No	Work Package Title	Lead Participant No	Lead Participant Short Name	Person-Months	Start Month	End month
1	Clinical trials	1	APO	41,6	1	36
2	Technical innovations	1	APO	100	3	36
3	Regulatory and IPR management	1	APO	69	1	36
4	Communication	1	APO	18,6	1	36
5	Management	1	APO	18	1	36
				247,2		

List of major deliverables (table 3.1c);

Deliverable (number)	Deliverable name	Work package number	Short name of lead participant	Type	Dissemination level	Delivery date
D5.2	Data management plan	5	APO	R	RE	M6
D1.1	Study results of phase II DFU	1	APO	R	PU	M24
D1.2	Study results of phase I. (FIH systemic APOSEC™)	1	APO	R	RE	M12
D2.1	Report on the upscaling strategy of APOSEC™ for market introduction	2	APO	R	RE	M24
D2.2	Report on the device (production manual)	2	APO	R	RE	M20
D3.1	Report on regulatory issues	3	APO	R	RE	M36
D3.2	further developed IPR strategy and report	3	APO	R	RE	M36
D4.1	Report on events where APOSCIEN CE AG was presented	4	APO	R	PU	M15
D4.2	Report on communication efforts for APOSCIEN CE AG products	4	APO	R	PU	M15
D5.1	reports	5	APO	R	RE	M18, M36

Graphical presentation of the components showing how they inter-relate (Pert chart or similar)
See graphic on page 10, Concept.

3.2 Management structure and procedures

Organisational structure and the decision-making (including a list of milestones (table 3.2a));

Structures are based on the company's management decision-making and management team.

Univ.-Prof. Dr med. Hendrik Jan Ankersmit MBA, (COO) is the scientific founder of APOSCIENCE AG. He is a cardiac and thoracic surgeon working at the Medical University of Vienna at the Vienna General Hospital. He was laboratory head of the Christian Doppler Laboratory for Diagnosis & Regeneration of Cardiac and Thoracic Diseases (funding period: 2009 – 15), organizing the preclinical studies for APOSEC™. Currently, he is heading the FFG-project "APOSEC" (project-nos.: 852748 and 862068, runtime: 2015-2018) organizing the product development work for APOSEC™

██████████ is responsible for finances and market strategy of APOSCIENCE AG since 2016. In his former career, he covered national and international management positions in various pharmaceutical companies for more than 30 years. Most recently, he served as General Manager for Baxter Healthcare Österreich GmbH and Actelion Pharmaceuticals Austria GmbH, a Janssen Company of Johnson & Johnson.

██████████ (Assistant to the Board of Directors) is responsible for project management, budget planning, controlling, HR, purchase, management of funding projects, reporting to funding agencies and other administrative issues. He has been involved within the APOSEC project from 2011 on.

██████████ takes leadership for the **clinical development** for APOSCIENCE AG. She is certified in Internal Medicine, Cardiology and Clinical Pharmacology, MD, and awarded Associate Professor in Internal Medicine, with more than 18 years of clinical and research experience in academia as well as for pharmaceutical companies.

██████████ is in charge of **quality management** and supports the product development of APOSEC™ on an experimental level. He has gained several years of experience in the research on bio-surgery in the pharmaceutical industry. As a biologist, he has a strong background in skin tissue regeneration, vascularization, and cutaneous wound healing.

██████████ is in Charge of **Research supervision** and Quality Management and supports the FFG-Project "APOSEC". As a chemist and scientist he is the leading expert in the development of APOSEC™.

Involved PhD students:

- ██████████ (female)
- ██████████ (male)
- A further PhD researcher will be recruited.

Table 3.2 a: List of milestones

Milestone number	Milestone name	Related work package(s)	Estimated date	Means of verification
1	Clinical trial phase II DFU completed	1	M20	Proven safety and efficacy in about 120 patients
2	Clinical trials phase III DFU launched	1	M24	Phase III trials have been prepared and launched
3	Clinical trial phase I (FIH systemic APOSEC™)	1	M10	Proven safety with healthy persons in study population
4	Upscaling production process concept finalised	2	M24	An upscaling concept has been designed and is ready to be implemented.
5	Reconstitution and	2	M20	CE marked device available

	delivery device with CE mark			
6	Regulatory issues have been fulfilled	3	M30	Close relationship with authorities (national and EU)

Effective innovation management

The management team and the cooperating patent attorneys will evaluate relevant innovations and inventions regularly. Any new inventions that have a potential for a protection via a patent, trademark, utility model, industrial design or trade secret will be discussed in detail and a relevant application issued. IPR will be managed as a dedicated task and will accumulate in development of further steadily developing business plans. If results are classified as being not potentially commercial these material is free to disseminate to the various stakeholders.

Critical risks, relating to project implementation (Table 3.2b: Critical risks for implementation)

Description of risk	WP(s) involved	Proposed risk-mitigation measures
Emerging disruptive technologies	4	Continuous and close market watch
Reimbursement and treaters budget constraints may limit use and penetration	3	Adapt pricing strategy to macro- and microeconomic environment
Delayed clinical study progress	1	Site number and selection and robust recruitment plan
Study stop due to safety issues	1	Phase 1 data from the MARSYAS I study and the compassionate use cases have demonstrated no safety issue with APO-2 even at the highest concentration tested. This said, safety issues, which only can be observed when a larger exposure will be achieved in phase 2 and 3 studies, cannot be ruled out. The quality systems should ensure that wound care staff will be trained on the safe and appropriate use of the product.
Study does not show adequate efficacy in range of effect sizes observed for CureXcell, DSC127	1	Comparing effectiveness in animal studies prior to clinical where possible
Development of reconstitution and delivery device delayed by the manufacturer	2	Manual formulation of product by clinical pharmacy
Today's sole APOSEC™ provider, [REDACTED] goes out of business	2	Close contact will be established to other blood banks during the project or setup of an own production line will be taken into account.
Infringement of APOSCIENCE AG patents by a third party	3	Continuous market watch, selection of inventions to further strengthen the patent portfolio and prolong patent life beyond 2018.
Regulatory issues are complicated to be fulfilled	2, 3	Ensure batch to batch consistency in the manufacturing process by quantifying select lead cytokines. This approach has already been approved by the Austrian health agency AGES.

3.3 Consortium as a whole (if applicable) *n.a.*

3.4 Resources to be committed

Costs are estimated based on the following budget. Main costs are personnel costs for employing experts when implementing the clinical development program, the technical optimisations and upscaling plan. Further costs will occur for material and other goods and services needed for all development steps within the project. A Clinical Research Organisation within the clinical development program and the development of the reconstitution and delivery device foresees to sub-contracts for services. The H2020 funding is not foreseen to finance the completely development of APOSCIENCE AG, the clinical development program, technological developments but to partially support the implementation of these.

SME	MM w/o OH	Funding rate	O/Head rate	WP1	WP2	WP3	WP4	WP5	Totals
APOSCIENCE	in Euros	100%	25	clinical trials	techn. innovations	regulat. IPR mgmt	Comunic.	Management	
		100							
Man months			Man months						
Personnel costs			Personnel co						
Travel			Travel						
Consumables			Consumables						
Other direct costs			Other direct co						
Total non-person.			Total non-per						
Indirect costs			Indirect costs						
Subtotal			Subtotal						
Audit cert			Audit cert						
Sub-contract			Sub-contract						
Total budget			Total budget						

Fig. 6: Total budget for the duration of the APOSEC SME Instrument project

The total budget to needed for the implementation of all activities during the time when the SME Instrument will be implemented and furtheron is definitely higher than the requested EU funding. A mix of investors, public funding and further sources will finance the activities in these three years of EU project duration. The APOSCIENCE AG requests **an EU funding of** [REDACTED] in order to co-fund these activities.

	WP1	WP2	WP3	WP4	WP5	Total Person Months per Participant
APOSCIENCE AG						

Participant 1 / APO	Cost (€)	Justification
Travel		Travel budget for meetings with cooperation partners, clinical sites, production partners, communication, dissemination, congresses, fairs, events.
Consumables, material costs		Material costs for clinical trials, automation and upscaling material, reconstitution and application device material, laboratory goods
Other goods and services		Insurances, printing cost, wound measurement tool, data safety managing board, machine(s) for automatisisation-upscaling, fees for fairs, presentation flyers, electronic storage of clinical data, fees for regulatory authorities, IPR costs
Total		

List of optional annexe: (uploaded separately under “optional annex 4: other supporting documents”

GMP Certificate: Certificate of GMP compliance of a manufacturer (production of APOSECTM at [REDACTED]) ; Scientific advice: meeting minutes BASG / AGES Austrian Medicines and Medical Device Agency, Austria; Patents: List of patents issues per country and current status; Freedom to operate reports: two reports by patent attorneys on freedom to operate issues and letter from patent attorney.

Section 4: Members of the consortium

Coordinator: APOSCIENCE AG (www.aposcience.at)

Description of the legal entity

APOSCIENCE AG is a biopharmaceutical company established in 2008 and headquartered in Vienna.

The company is developing innovative therapeutics for regenerative medicine that is based on the secretome of white blood cells isolated from peripheral blood. This approach sets APOSCIENCE AG apart from the significant number of competitors working on stem cell based approaches. It is in tune with the so called “Paracrine Hypothesis” which ascribes the beneficial effects of stem cells to paracrine signalling, and not to their capacity of rebuilding tissue per se. In contrast to competitors in the field, the company utilizes for APOSEC™ production easily obtainable peripheral blood mononuclear cells as compared to stem cells or stem cell-derived secretomes from bone marrow.

A priority for management and shareholders is preclinical product development for its advanced therapeutic products in order to provide the regulatory agencies with all relevant data and documents and a subsequent clinical proof of concept trial in wound healing.

APOSCIENCE AG is currently funded with seed investments from private Austrian sources. In addition, APOSCIENCE AG receives grant funds from the Austrian Research Promotion Agency (FFG). Research within the framework of the FFG-project “APOSEC” is performed by APOSCIENCE AG at the [REDACTED] on the basis of a collaboration agreement with this aforementioned medical school.

An explanation whiteboard video is available online: <https://youtu.be/LaSzczGvxnk>

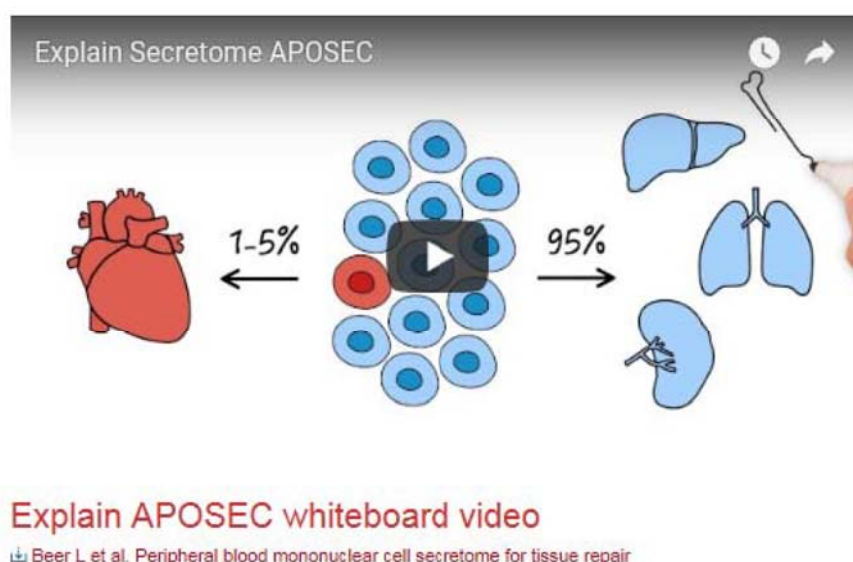


Figure: Screenshot of the Explain APOSEC™ whiteboard video

Products:

The drug substance APOSEC™ denotes the lyophilized secretome of apoptotic allogeneic PBMCs. It is manufactured from a waste fraction of blood banking which results in low costs of goods. It comes as a white powder.

The technology platform APOSEC™ is the basis for two products (based on two patent families):

- APO-1 → APOSEC™ formulation for the treatment of systemic inflammation illnesses caused by hypoxia like acute myocardial infarction, myocarditis, stroke, and spinal cord injury.
- APO-2 → APOSEC™ formulation within a hydrogel (NUGEL) for the treatment of acute or chronic wounds, especially of diabetic foot ulcers (DFU).

APOSCIENCE AG has found that the mixture of active components secreted from cultured apoptotic peripheral mononuclear blood cells (PBMCs) has superior efficacy in promoting wound healing and skin regeneration. The product APO-2 exerts this effect by stimulating migration of keratinocytes and fibroblasts into the wounded area, as well as by promoting neovascularization of the wound and improving blood and oxygen supply.

The company expects that APO-2 will have a significant impact in the care for millions of patients who are afflicted by poorly healing wounds (diabetic foot ulcers, ischemic ulcerations, pressure ulcers) and therefore present a very important market opportunity.

APO-1 is superbly efficacious in reducing infarct size and maintaining left ventricular function in animal models of myocardial infarction (MI).

Description of the profile of the persons

Univ.-Prof. Dr med. Hendrik Jan Ankersmit MBA, (COO) is the scientific founder of APOSCIENCE AG. He is a cardiac and thoracic surgeon working at the Medical University of Vienna at the Vienna General Hospital. He was laboratory head of the Christian Doppler Laboratory for Diagnosis & Regeneration of Cardiac and Thoracic Diseases (funding period: 2009 – 15), organizing the preclinical studies for APOSEC™. Currently, he is heading the FFG-project "APOSEC" (project-nos.: 852748 and 862068, runtime: 2015-2018) organizing the product development work for APOSEC™.

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██████████ (**Assistant to the Board of Directors**) is responsible for project management, budget planning, controlling, HR, purchase, management of funding projects, reporting to funding agencies and other administrative issues. He has been involved within the APOSEC project since 2011.

██████████ (**clinical studies**) takes leadership for the clinical development for APOSCIENCE AG. She is certified in Internal Medicine, Cardiology and Clinical Pharmacology, MD, and awarded Associate Professor in Internal Medicine, with more than 18 years of clinical and research experience in academia as well as for pharmaceutical companies.

██████████ (**Post-doc**) is in charge of quality management and supports the product development of APOSEC™ on an experimental level. He has gained several years of experience in the research on bio-surgery in the pharmaceutical industry. As a biologist, he has a strong background in skin tissue regeneration, vascularization, and cutaneous wound healing.

██████████ is in Charge of **Research supervision** and Quality Management and supports the FFG-Project "APOSEC". As a chemist and scientist he is the leading scientific expert in the development of APOSEC™.

Involved PhD students:

- ██████████ (female)
- ██████████ (male)
- A further PhD researcher will be recruited.

List of up to 5 relevant publications, and/or products, services

Relevant Publications:

Safety and tolerability of topically administered apoptotic PBMC secretome (APOSECT™) in healthy men with artificial dermal wounds: a randomized clinical phase 1 trial

Simader E, Traxler D, Kasiri MM, Hofbauer H, Wolzt M, Glogner C, Storka S, Mildner M, Gouya G, Geusau A, Fuchs C, Eder C, Graf A, Schaden S, Golabi B, Aretin M-B, Suessner S, Gabriel C, Klepetko W, Tschachler E, Ankersmit HJ. Sci Rep. 2017 Jul 24;7(1):6216. doi: 10.1038/s41598-017-06223-x.

Peripheral blood mononuclear cell secretome for tissue repair. Beer L, Mildner M, Gyöngyösi M, Ankersmit HJ. Apoptosis. 2016 Dec;21(12):1336-1353. (REVIEW)

Dying blood mononuclear cell secretome exerts antimicrobial activity. Kasiri MM, Beer L, Nemec L, Gruber F, Pietkiewicz S, Haider T, Simader EM, Traxler D, Schweiger T, Janik S, Taghavi S, Gabriel C, Mildner M, Ankersmit HJ. Eur J Clin Invest. 2016 Oct;46(10):853-63. doi: 10.1111/eci.12667.

Paracrine Factors from Irradiated Peripheral Blood Mononuclear Cells Improve Skin Regeneration and Angiogenesis in a Porcine Burn Model. Hacker S, Mittermayr R, Nickl S, Haider T, Leberherz-Eichinger D, Beer L, Mitterbauer A, Leiss H, Zimmermann M, Schweiger T, Keibl C, Hofbauer H, Gabriel C, Pavone-Gyöngyösi M, Redl H, Tschachler E, Mildner M, Ankersmit HJ. Sci Rep. 2016 Apr 29;6:25168. doi: 10.1038/srep25168.

Analysis of the Secretome of Apoptotic Peripheral Blood Mononuclear Cells: Impact of Released Proteins and Exosomes for Tissue Regeneration. Beer L, Zimmermann M, Mitterbauer A, Ellinger A, Gruber F, Narzt MS, Zellner M, Gyöngyösi M, Madlener S, Simader E, Gabriel C, Mildner M, Ankersmit HJ. Sci Rep. 2015 Nov 16;5:16662. doi: 10.1038/srep16662.

Patents of APOSCIENCE AG:

- **WO 2010/079086 A1 – PHARMACEUTICAL PREPARATION COMPRISING SUPERNATANT OF BLOOD MONONUCLEAR CELL CULTURE**
Patent family of APO-2; abstract: The present invention relates to a topical pharmaceutical preparation for treating an inflammatory skin condition, preferably a condition associated with ischemia, comprising a supernatant of a physiological solution obtainable by cultivating peripheral blood mononuclear cells (PBMCs) or a subset thereof in a physiological solution free of PBMC-proliferating and PBMC-activating substances for at least 1 h.
Priority: 18/12/2008 (international protection: AU, BR, CA, CN, EP, JP, NZ, RU, US, ZA)
- **WO 2010/070105 A1 – PHARMACEUTICAL PREPARATION**
Patent family of APO-1; 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 (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.
Priority : 18/12/2008 (international protection : AU, BR, CA, CN, EP, JP, NZ, RU, US, ZU, AT, CH, DE, ES, FR, GB, HU, IT, NL, PL, SE, TR)

List of up to 5 relevant previous projects or activities

FFG Project: a nationally funded project is currently running for two years (start in 2016) in order to perform stability studies, develop potency assays and implement toxicology studies for APO-2

and prepare for the phase II studies by setting up the whole quality assurance program and the APOSEC™ production process.

MARSYAS I: was a phase I (healthy volunteering human males) trial to determine safety and tolerability of the autologous APOSEC™ product. The study was successful and showed no intolerance, allergic reaction or other adverse events. On the basis these results a First in man/phase II trial with allogeneic APOSEC™ can be started by 2018.

Christian Doppler Laboratory for Cardiac & Thoracic Diagnosis and Regeneration (2009-15): Preclinical development of APOSEC™, proof of effectivity in various indications in small and large animal models, laboratory in vitro experiments to defend patent claims, clarification of the modes of action (MoA) of APOSEC™.

Description of any significant infrastructure

- GMP Production process, [REDACTED] in Austria:

APOSCIENCE AG has a framework contract with the [REDACTED] for the production of APOSEC™. There the only GMP certified production plant is in place. The [REDACTED] possesses a GMP certificate as well as an AGES certificate for the production of APOSEC™ for the use in clinical studies. This production plant has the capacity to produce enough APOSEC™ for the clinical trials but an upscaling process is needed to prepare for market authorisation and product launch. This production process is working under clean room conditions.

APOSCIENCE AG owns an industrial lyophiliser [REDACTED] and a Methylen-Blue-Virus-Inactivation device ([REDACTED]).

- [REDACTED] Framework Agreement

The relevant infrastructure to perform research for the development of a quality control and assessment program has been prepared at the [REDACTED], Austria, a long-lasting partner of APOSCIENCE AG. This includes the performance of non-GLP stability tests the development of GLP potency assays together with a renowned GLP-laboratory partner and further tests systems for the quality assurance of the APOSEC™ GMP-production.

Office and laboratories rooms including technical equipment are available for APOSCIENCE AG use ruled by the framework programme. This includes standard laboratory equipment, ELISA, FACS, and cell culture experiments.

Description of any third parties that are not represented as project partners

- [REDACTED] Austria: GMP production line to produce APOSEC™
- [REDACTED] Switzerland: development of GLP potency assays for APO-2, evaluation of the comparability of different batches of APO-2.
- [REDACTED] Germany: supports in questions and strategies of regulatory affairs of pharma products, takes lead of the CMC (Chemicals, Manufacturing & Controls)-project to assure quality and comparability of GMP-produced APO-2.
- [REDACTED], Austria: provides office and laboratory space; supplies APOSCIENCE AG with additional laboratory and research methods through its so called Core Facilities.
- [REDACTED] Austria: provides viral clearance of APOSEC™ by gamma irradiation.

- [REDACTED], Austria: will be the supplier of the reconstitution and application device for APO-2 (for wound healing) if the device fulfils the necessary standards and a status of CE mark can be attained.



Figure: Organogram of the APOSEC™-Project

4.1. Third parties involved in the project (including use of third party resources)

Does the participant plan to subcontract certain tasks	Y
<i>CRO, Contract Research Organisation: for the professional management and implementation of the clinical development programme (phase II DFU) a professional contract research organisation, CRO, will be contracted. The selection process is described below this table.</i> <i>A subcontracting budget of [REDACTED] has been planned and calculated related to work-package 1 “clinical trials”.</i> <i>Further sub-contracting is foreseen within the further development of the automatization and upscaling and the reconstitution and application device. Here costs for architects, GMP engineering offices for any adaptation of the production process facilities are needed.</i> <i>Development costs (3D modelling, simulation, part drawing, tool design, medical device registration), biocompatibility studies and cytological tests according to ISO 10993, stability studies, clinical evaluation, validation of sterility, and transport validation are needed for the reconstitution and delivery device, as well as costs for regulatory bodies for the attainment of a CE certification.</i> <i>A subcontracting budget of [REDACTED] has been planned and calculated related to work-package 2 “technical innovations”.</i>	
Does the participant envisage that part of its work is performed by linked third parties	N
Does the participant envisage the use of contributions in kind provided by third parties (Articles 10 and 11 of the Model Grant Agreement)	N

CRO selection process for clinical phase 2-study in DFU (Marsyas II)

The Clinical Research Organization for the Marsyas II-Study (clinical phase 2-study in diabetic foot ulcers) was selected by the APOSCIENCE AG team in the following way:

1. Identification and selection of suitable CROs (Feb-March 2017)

- Approximately 20 suitable CROs were identified by the APOSCIENCE AG team; 16 were contacted; 13 expressed interest and capability to cooperate.
- A mutual confidentiality agreement was submitted to 13 CROs and signed by 11 of them.
- A Request for Proposal (RFP) and a Synopsis of the Clinical Study Plan were sent to the CROs by [REDACTED]. The CROs were asked to provide various documents (among others: study budget, feasibility assessment, confirmation of number of sites, project execution plan, risk plan, project team structure, experience of the team involved, randomization, IMP management etc.)

2. Invitation for a bid-defense meeting (April 2017)

- 9 proposals for the phase 2-study were received by APOSCIENCE AG; 4 CROs were selected for the bid-defense meeting on their experience in diabetic foot ulcer, the performed feasibility and the proposed budget.
- The bid-defense meetings took place at the premises of APOSCIENCE AG, Mariannengasse 14/9, 1090 Vienna, on 24, 26, 27 and 28 April 2017. Prof. Hendrik Ankersmit, [REDACTED]
[REDACTED]
[REDACTED] (=APOSCIENCE AG team) participated on the side of APOSCIENCE AG.
- A second bid-defense meeting with the two favoured CROs of the first bid-defense round took place at the premises of APOSCIENCE AG on 2 May 2017.

3. Feasibility studies and audits (May-September 2017)

- The two remaining CROs were ordered to perform detailed feasibility studies to evaluate study sites and their capability to recruit and treat a sufficient number of DFU patients for the Maryas II-study.
- Professional audits were performed with these two CROs by [REDACTED]
[REDACTED] former head of AGES inspection, accompanied by [REDACTED]
on 30 August and 13 September 2017.
- Site visits were performed (on invitation of one of the CROs) at the [REDACTED]
Vienna [REDACTED] and [REDACTED]
[REDACTED]

4. Decision for [REDACTED] (26 September 2017)

- The decision to entrust [REDACTED] was taken by the same APOSCIENCE AG -team mentioned above on the basis of the reports of the feasibility studies and the audit reports by [REDACTED] had been able to show the possibility of sufficient patient recruitment in the identified sites; the audit found stable business processes and low risk of failure in the case of cooperating with this [REDACTED]

Section 5: Ethics and security

5.1 Ethics

- national legal and ethical requirements of the country or countries where the tasks raising ethical issues are to be carried out;

Explanation to point 2. Human beings, point 3. Human cells / tissues of the ethics table:

All clinical studies will be monitored by an independent Clinical research organisation, CRO, and the study protocol will be submitted to the local ethics committees in the different countries. Approvals of each ethical committee must be obtained before the launch of the study. A Data Safety Monitoring Board will be established. Patient information and consent will be translated into relevant European languages. The permission to conduct the studies will be requested by the relevant hospitals and legal authorities. The clinical trials shall be performed in full compliance with the legal regulations according to the laws of the relevant countries. Each study will be registered with the European Clinical Trials Database through EMA. APOSCIENCE AG and related partners, clinical sites will comply with the Declaration of Helsinki and with the principles laid down in Oviedo Bioethics Convention and the EU Regulation No 536/2014 on clinical trials on medicinal products for human use.

A scientific advice from the Austrian Health Authority (AGES) has confirmed that a First in Man/phase II trial on Diabetic Foot Ulcer, DFU, can be prepared and launched in 2018.

Ethical advice is and will be given by the Ethics Department of the Medical University of Medicine Vienna.

Informed consent of subjects:

The study patients' written informed consent will use an IRB/EC approved form and the study will be explained to the patients in local language. The investigator will be available to answer any questions. Study patients will be assured that they may withdraw from the study at any time for any reason and receive alternative conventional therapy as indicated.

APOSECTM is produced at the site of the production partner Blood Center Linz, Austria. It is produced from a waste fraction of blood banking. It is prepared by a proprietary process from whole blood drawn from healthy donors. A GMP-conforming manufacturing process has been developed and has been approved by the Austrian Ministry of Health, and its authority AGES. Any samples taken from the involved patients will be confirmed and explained via informed consent.

Copies of the ethics approvals will be provided at the start of the SME project.

- explains in detail how you intend to address the issues in the ethical issues table, in particular as regards:
 - research objectives & methodology

PHASE II trial – indication DFU:

Study population: (planned number – 120)

- wound healing problems >4 weeks
- diabetes I/II

Design:

- combined exploratory efficacy/dose-ranging phase II study
- Safety lead-In study prior to start of main study to evaluate for safety signals

APOSEC™:

- Lyophilisate to be shipped frozen
- Frozen storage -20°C

Comparator:

- Parallel induced cell-free control lyophilisate formulated in NU-GEL for topical administration

Dose groups:

- Low dose: 12.5 Units (U)/ml, middle dose: 25 U/ml, high dose: 50 U/ml and comparator (lyophilized CellGenix DC medium)
- Strata on wound size among groups

Endpoints:

- Primary endpoint: wound area reduction in % in 4 weeks
- Secondary endpoint: wound closure during a 12 week study period

First in Human / Phase II Study in DFU

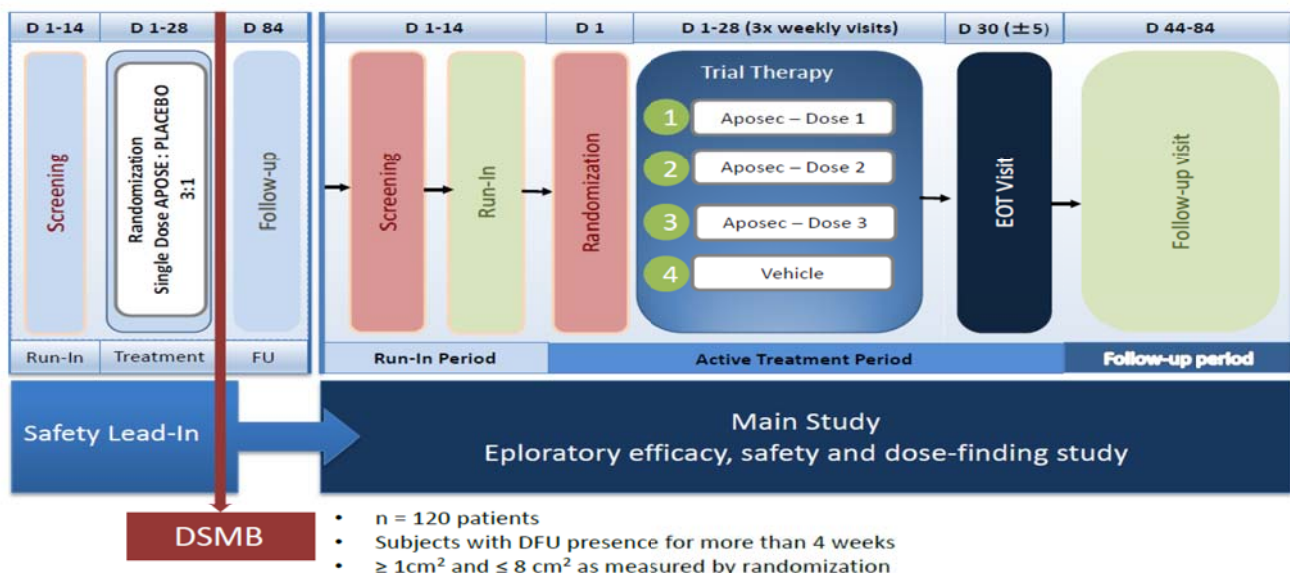


Fig: diagram showing phase II trial approach.

The relevant phase III trial on DFU will be prepared during this SME Instrument as results from phase II trials are the basis for the preparation of the study protocols for phase III.

First in Man PHASE I trial – intravenous application of allogeneic GMP APOSEC™ in healthy humans to evaluate safety and tolerability of APOSEC™ as a prerequisite for phase II studies in acute myocardial infarction, stroke and spinal cord injury

Study population: (planned number – 35)

- Healthy human males

Design:

- Prospective non-randomized First-in-Man phase I trial
- Safety and feasibility of single intravenous administration

APOSEC™:

- Single intravenous dose of allogenic human APOSEC™

Endpoints:

- Primary endpoint: safety and feasibility of the single intravenous application of allogenic APOSEC™. The clinical study will be performed at the Dept. of Clinical Pharmacology, headed by Prof. Michael Wolzt, at the Medical University of Vienna. an ethics committee opinion;

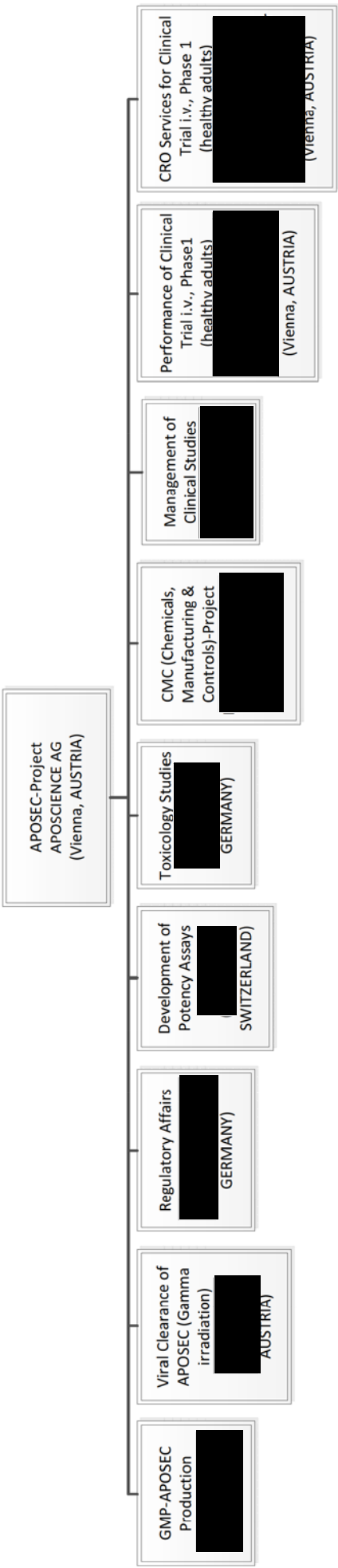
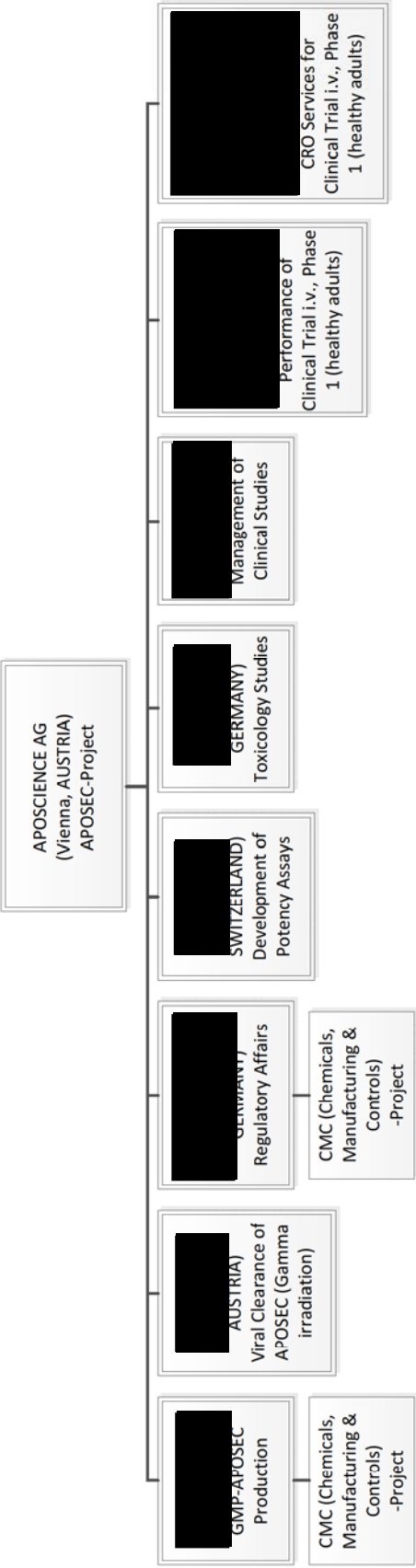
The relevant documents for ethical approval are currently under preparation. Also the relevant study protocol is under preparation.

5.2 Security¹

Please indicate if your project will involve:

- activities or results raising security issues: NO
- 'EU-classified information' as background or results: NO

¹ See Article 37 of [Model Grant Agreement](#)





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