Please check our wiki for help on navigating the form.

Horizon 2020

Call: H2020-EIC-SMEInst-2018-2020

(SME Instrument)

Topic: EIC-SMEInst-2018-2020

Type of action: SME-2

Proposal number: 850251

Proposal acronym: APO-2

Deadline Id: H2020-SMEInst-2018-2020-2

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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 steps in the submission wizard.

This proposal version was submitted by [redacted] on **10/10/2018 16:57:13** Brussels Local Time. Issued by the Participant Portal Submission Service.

1 - General information

Topic	EIC-SMEInst-2018-2020	Type of Action	SME-2
Call Identifier	H2020-EIC-SMEInst-2018-2020	Deadline Id	H2020-SMEInst-2018-2020-2

Acronym: APO-2

Proposal title: 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: *24*

The first set of keywords (main keyword 1 and sub-keyword 1) will have the heaviest weight in matching the expert-evaluators who will evaluate the proposal, therefore it is crucial to ensure this first set of keywords reflects the area of your proposal as accurately as possible.
In order to ensure your proposal is matched to evaluators with the best expertise, we highly recommend that you choose at least one main keyword and one sub-keyword.

Main Keyword 1: Health

Sub Keyword 1: Dermatology and venereal diseases

It is highly recommended to select the highest number of relevant keywords that correspond to your proposal with a maximum of three main keywords and three sub-keywords. The main keyword can be repeated up to three times, but a different sub-keyword should be chosen if possible each time.

Main Keyword 2: Health

Sub Keyword 2: Cardiac and Cardiovascular systems

Main Keyword 3: Health

Sub Keyword 3: Immunology

Free keywords: *Secretome Based Therapy, Regenerative Medicine, Biological, Pharmaceutical Development*

This proposal version was submitted by [redacted] on **10/10/2018 16:57:13** Brussels Local Time. Issued by the Participant Portal Submission Service.

Abstract

The Austrian SME APOSCIENCE AG develops innovative cell free therapeutics for regenerative medicine which have disruptive potential. The company is poised to commence clinical development in several indications to enter a large global market for regenerative medicine. The intellectual property of ten years innovative research has been protected by a patent portfolio providing extensive freedom to operate in a wide variety of applications. A licensed production process of secretomes of apoptotic white blood cells has been approved by the Austrian regulator and the therapeutic is safe for use in clinical trials.
Chronic wounds are an unmet medical need with a global market worth 3 Bn €. The advanced wound care market is set to grow due to demographic changes and the rising incidence of diabetes at 5.7% annually. APOSCIENCE has identified diabetic foot ulcer (DFU) as a priority indication, which limits the quality of life in up to 6% of diabetics. In the absence of curative therapy DFU progresses in 15% of patients with severe sequelae, accounting for up to 75% of all amputations in developed nations. The product APOSEC will be tested for its safety and efficacy within a phase II clinical trial. Upon marketing authorisation this treatment has the potential to become the first advanced wound care treatment becoming standard of care in DFU. A stepwise expansion to other ulcers and wounds is an integral part of the strategy for sustained growth of APOSCIENCE. Within the global market APOSCIENCE anticipates to market this treatment with a strategic partner already engaged in therapeutic blood products to generate significant revenues by 2025.
Together with a committed investor this revenue will make APOSCIENCE a global leader in regenerative medicine, exploiting secretomes to harness the intrinsic regenerative potential of damaged tissues. The company currently advances a pipeline of more complex indications including heart attack, stroke and spinal cord injury.

Remaining characters 7

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

Please give the proposal reference or contract number.	
806344	

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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 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.

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2 - Participants & contacts

#	Participant Legal Name	Country	Action
1	Aposcience AG	Austria	

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2 - Administrative data of participating organisations

PIC	***Legal name***
911933279	*Aposcience AG*

Short name: APO

Address of the organisation

Street Dresdner Straße 87/A 21

Town Vienna

Postcode 1200

Country Austria

Webpage www.aposcience.com

Specific Legal Statuses

Research and Innovation legal statuses

Public body .....no
Non-profit .....no
International organisation .....no
International organisation of European interest .....no
Secondary or Higher education establishment .....no
Research organisation .....no

Legal person .....yes

Industry (private for profit).....yes

Enterprise Data

SME self-declared status.....31/12/2016 - yes

SME self-assessment .....31/12/2016 - 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.

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Department(s) carrying out the proposed work

No department involved

Department name: *Name of the department/institute carrying out the work.* ☒ not applicable

☐ Same as proposing organisation's address

Street: *Please enter street name and number.*

Town: *Please enter the name of the town.*

Postcode: *Area code.*

Country: *Please select a country*

This proposal version was submitted by [redacted] on **10/10/2018 16:57:13** Brussels Local Time. Issued by the Participant Portal Submission Service.

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: Prof. Sex: (•) Male ( ) Female

First name: **Hendrik Jan Leonard** Last name: **Ankersmit**

E-Mail: **hendrik.ankersmit@aposcience.com**

Position in org.: Scientific founder, member of managing board and Chief Operational Officer

Department: Aposcience AG ☒ Same as organisation name

☒ Same as proposing organisation's address

Street: Dresdner Straße 87/A 21

Town: Vienna Post code: 1200

Country: Austria

Website: http://www.aposcience.com/

Phone: [redacted] Phone 2: +xxx xxxxxxxxx Fax: +xxx xxxxxxxxx

Other contact persons

First Name	*Last Name*	*E-mail*	*Phone*
[redacted]			[redacted]

This proposal version was submitted by [redacted] on **10/10/2018 16:57:13** Brussels Local Time. Issued by the Participant Portal Submission Service.

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	[redacted]										
	Total												

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

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4 - Ethics

1. HUMAN EMBRYOS/FOETUSES		Page
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	20-22
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	20.22
Are they healthy volunteers for medical studies?	○ Yes ◉ No	
Does your research involve physical interventions on the study participants?	◉ Yes ○ No	20-22
Does it involve invasive techniques?	◉ Yes ○ No	20-22
Does it involve collection of biological samples?	◉ Yes ○ No	20-22
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	20-23
Are they available commercially?	○ Yes ◉ No	
Are they obtained within this project?	◉ Yes ○ No	20-22
Are they obtained from another project, laboratory or institution?	○ Yes ◉ No	
Are they obtained from biobank?	○ Yes ◉ No	
4. PERSONAL DATA		**Page**

This proposal version was submitted by [redacted] on **10/10/2018 16:57:13** Brussels Local Time. Issued by the Participant Portal Submission Service.

Does your research involve personal data collection and/or processing?	◉ Yes ○ No	20-22
Does it involve the collection and/or processing of sensitive personal data (e.g: health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)?	◉ Yes ○ No	20-22
Does it involve processing of genetic information?	○ Yes ◉ No	
Does it involve tracking or observation of participants?	○ 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	22-23
Are they vertebrates?	◉ Yes ○ No	22-23
Are they non-human primates?	○ Yes ◉ No	
Are they genetically modified?	○ Yes ◉ No	
Are they cloned farm animals?	○ Yes ◉ No	
Are they endangered species?	○ Yes ◉ No	

Please indicate the species involved (Maximum number of characters allowed: 1000).

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	

This proposal version was submitted by [redacted] on **10/10/2018 16:57:13** Brussels Local Time. Issued by the Participant Portal Submission Service.

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	
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

This proposal version was submitted by [redacted] on **10/10/2018 16:57:13** Brussels Local Time. Issued by the Participant Portal Submission Service.

5 - 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.

First Name	
Last Name	
Institution	
Town	
Country	
Webpage	

Extended Open Research Data Pilot in Horizon 2020

If selected, applicants will by default participate in the Pilot on Open Research Data in Horizon 2020[1] , 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.

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We wish to opt out of the Pilot on Open Research Data in Horizon 2020.	(•) Yes	( ) No

If opting out please indicate the reason(s) for not being able to participate in the Pilot:

- the project does not generate any data	☐
- to allow the protection of results (e.g. patenting)	☒
- incompatibility with the need for confidentiality linked to security	☐
- incompatibility with privacy/data protection	☐
- achievement of the project's main aim would be jeopardised	☐
- other legitimate reasons	☐

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.*

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Title of Proposal: APO-2 – Secretome Based Regenerative Therapy

List of participants:

Participant number	Organisation name	Country
(Coordinator)	APOSCIENCE AG	Austria

TABLE OF CONTENTS

Executive Summary
The Austrian SME APOSCIENCE AG develops innovative cell free therapeutics for regenerative medicine which have disruptive potential. The company is poised to commence clinical development in several indications to enter a large global market for regenerative medicine. The intellectual property of ten years innovative research has been protected by a patent portfolio providing extensive freedom to operate in a wide variety of applications. A licensed production process of secretomes of apoptotic white blood cells has been approved by the Austrian regulator and the therapeutic is safe for use in clinical trials.
Chronic wounds are an unmet medical need with a global market worth 3 Bn €. The advanced wound care market is set to grow due to demographic changes and the rising incidence of diabetes at 5.7% annually. APOSCIENCE has identified diabetic foot ulcer (DFU) as a priority indication, which limits the quality of life in up to 6% of diabetics. In the absence of curative therapy DFU progresses in 15% of patients with severe sequelae, accounting for up to 75% of all amputations in developed nations.
The disruptive approach is driven by

- Strong preclinical and clinical evidence
- Certified production
- Strong patenting position and freedomto operate
- Regulatory approval for clinical study
- Committed investor

The product APOSEC will be tested for its safety and efficacy within a phase II clinical trial. Upon marketing authorisation this treatment has the potential to become the first advanced wound care treatment becoming standard of care in DFU driving fast market penetration at least in Europe. A stepwise expansion to other ulcers and wounds is an integral part of the strategy for sustained growth of APOSCIENCE. This treatment will be marketed with a strategic partner already engaged in therapeutic blood products to generate revenues for APOSCIENCE by 2025 exceeding 15 M€ annually. Market penetration of 30% in Europe will be driven by the adoption of APOSEC as standard of care, if efficacy can beachieved as anticipated.
Together with a committed investor this revenue will make APOSCIENCE a global leader in regenerative medicine research, exploiting secretomes to harness the intrinsic repair mechanisms of damaged tissues. The company currently advances a pipeline of more complex indications including heart attack, stroke and spinal cord injury.

1 EXCELLENCE

1.1 Challenge and solution

Organisms have evolved astounding capabilities to restore and renew themselves through internal regenerative processes. The molecular mechanisms which adult organisms use to reactivate developmental programs to regrow a functional, properly proportioned organ inspires the modern branch of regenerative medicine. Through stem cell-based therapies regenerative medicine aims to restore tissues and organs damaged beyond the potential of natural repair processes by age, disease or trauma[12]. **It is widely accepted in the field that regenerative approaches resulting in advanced therapy medicinal products (ATMPs) have the potential to disrupt health care effectively wherever they may enter clinical routine[3].**

Today, isolated indications benefit from available approaches, including heterologous bone marrow transplants and autologous immune cells, chondrocytes and keratinocytes. But other areas of research remain an unresolved challenge despite initially promising data, raising sometimes excessive expectations. With the advent of induced pluripotent stem cell (iPSC)-technologies enhancing the intrinsic regenerative capacity of the host with stem cell injections received widespread attention for many tissues, including myocardium, central nervous system and skin. The transplantation of stem cells should support regeneration in the patient's own body. In the last decade encouraging pre-clinical and clinical data over a wide array of organ systems and contexts have been reported, including dermal wounds, cardiovascular diseases and traumas[4,5]. **In 2017 the market for regenerative medicine was estimated to be worth 16.4 Bn EUR and predicted to reach 46.11 Bn EUR by 2021, with stem cell-based therapies anticipated to provide a major driver for growth within the next years**[6].

iPSCs are currently widely used in developing healthy and disease-state tissue models for both basic research and drug screening, tissue replacement therapies suffer from the complexities of organs, high production costs and technical safety issues[7]. Moreover, the concept that stem cells transplantation into harmed organs transform themselves into new organ cells to repair tissue has become under scrutiny. Several reports show transplanted stem cell preparations contain paracrine factors that enhance the capacity for endogenous regeneration[8,9] including the induction of angiogenesis, the inhibition of immune cells[10] and the activation of internal stem cells[11,12]. It has therefore now become commonly accepted that internal regenerative processes can be triggered by secretomes.

APOSCIENCE has developed an innovative technology to harness the intrinsic regenerative potential with an innovative medicinal product, which is based on the purified secretome of apoptotic peripheral blood mononucleated cells (PBMC). This technology is protected by a strong patent portfolio providing extensive freedom to operate[13,14].

PBMC-derived secretomes

APOSCIENCE AG has pioneered PBMC-derived secretomes as an exclusive proprietary technology, which represents a **potential game-changer** in regenerative medicine. Apoptotic cells have long been known to release a complex mixture of materials, including vesicles, proteins and lipids. APOSCIENCE AG has shown that the secretome of stressed and apoptotic cells enhances angiogenesis and wound healing in vivo[15].

The secretome from cultured apoptotic PBMC has been extensively tested in pre-clinical experiments employing faithful animal models of disease for their potential to guide regenerative processes, with proven efficacy in promoting wound healing, myocardial infarction, stroke, spinal cord injury and myocarditis.

These secretome preparations have therefore the potential to transform the therapeutic approaches of regenerative medicine in a wide spectrum of indications; secretome-based therapies could be applied where

[1] Srivastava, Ahlawat, and Srivastava, 'Amniotic Fluid Stem Cells'.
[2] Mao and Mooney, 'Regenerative Medicine'.
[3] Hildreth, '2017 Marks the 1st Year That Regenerative Medicine Disrupted Healthcare'.
[4] Srivastava, Ahlawat, and Srivastava, 'Amniotic Fluid Stem Cells'.
[5] Mao and Mooney, 'Regenerative Medicine'.
[6] Globe Newswire, 'Global $53 Billion Regenerative Medicine Market Analysis & Forecast Report 2017-2021'.
[7] Globe Newswire.
[8] Beer et al., 'Analysis of the Secretome of Apoptotic Peripheral Blood Mononuclear Cells'.
[9] Gnecchi et al., 'Paracrine Action Accounts for Marked Protection of Ischemic Heart by Akt-Modified Mesenchymal Stem Cells'.
[10] Hoetzenecker et al., 'Mononuclear Cell Secretome Protects from Experimental Autoimmune Myocarditis'.
[11] Hill, Wernig, and Goldspink, 'Muscle Satellite (Stem) Cell Activation during Local Tissue Injury and Repair'.
[12] Lichtenauer et al., 'Secretome of Apoptotic Peripheral Blood Cells (APOSEC) Confers Cytoprotection to Cardiomyocytes and Inhibits Tissue Remodelling after Acute Myocardial Infarction'.
[13] Agentur Kliment, 'Freedom to Operate Analysis "Kliment"'.
[14] Agentur Isenbruck, 'Freedom to Operate Analysis "Isenbruck"'.
[15] Mildner et al., 'Secretome of Peripheral Blood Mononuclear Cells Enhances Wound Healing'.

initially stem cell-based therapies had been considered. In an attempt to identify the active components within the secretome, we have come to the conclusion that no single fraction provides the complex regenerative function of the secretome. Rather, the regenerative capacity resides mainly in exosomes, proteins and lipids as the major biologically active components. Based on this analysis a robust production

process has been developed in cooperation with the [redacted] which is now licensed by APOSCIENCE to produce material approved by the Austrian regulatory agency AGES for the use in clinical trials.

Therefore, this proposal aims to commercialize the clinical application of a new therapeutic approach to harness the enormous potential regenerative medicine applications provide to tackle some of the most pressing unmet clinical needs. APOSCIENCE is convinced PBMC derived secretome based therapeutics have a **disruptive market potential** in clinical areas, where curative therapies are currently lacking. We have therefore prioritized diabetic foot ulcer (DFU) and other chronic wounds as our initial clinical application. In addition to this topical approach with active wound dressing we will aim to advance a systemic application to restore regenerative potential of internal organs.

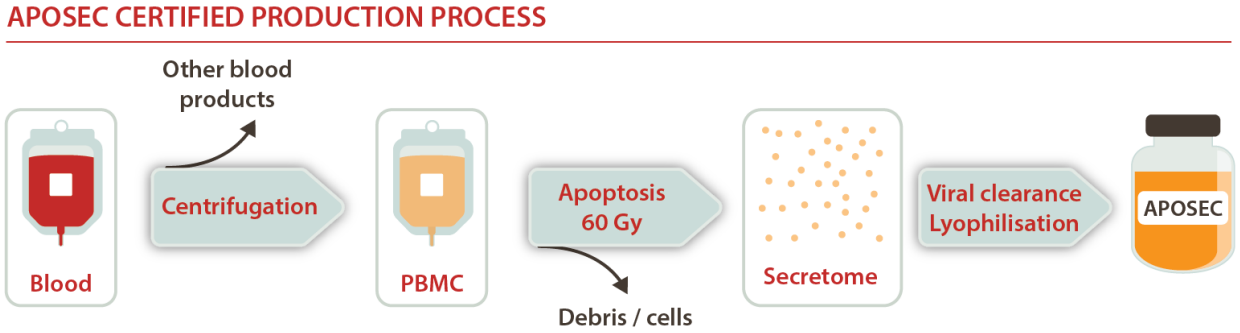

Figure 1: Production of APOSECTM – the lyophilized secretome of apoptotic PBMC.

Diabetic foot ulcer as priority indication within chronic wounds

Chronic wounds are defined as not healing within 12 weeks[16,17]. They are thus characterized as an unmet clinical need, which is mainly treated with moist wound dressings. If closure of the wound is delayed, extended hospitalization, decreased quality of life and sequelae including infections of the bone, amputations or even death are the consequence. Ulcers are an unmet challenge to wound care professionals, consuming an increasing share of healthcare resources around the globe with severe impact on quality of life of patients. Due to increasing incidence of diabetes and demographic changes patient numbers are expected to rise. In developed countries, the prevalence rate for chronic nonhealing wounds is 1% to 2% of the general population[18] and a curative treatment has been estimated to reduce public health care costs per patient by 20.000 €. As such they are an enormous threat to the sustainability of public health care systems in Europe with expenditures of more than 2.5 Bn € annually[19]. Efficient treatments with the consequence of lowered hospitalization rates have the potential to reduce the burden chronic wounds pose to patients and health care systems.

DFU are a leading cause of hospitalization. They have a severe impact on the quality of life (QoL) of patients as they fail to heal over extensive time periods and frequently become infected. Up to 75% of allamputations in developed nations are aconsequence of DFU. Thus, The clinical challenge is to provide a therapy that ensures wound closure within 4 weeks[20]. APOSCIENCE chose DFU as a suitable first indication for its intense medical need, market size and lack of therapeutic strategy. No active wound care product has become standard of care, which provides an enormous opportunity for a treatment with APOSEC-2, which is a novel and affordable therapeutic approach to restore the internal regenerative capacity. Importantly topical application of APOSEC conforms well with the current standard of care. Moreover, the therapeutic

[16] Kyaw et al., 'Need for Improved Definition of "Chronic Wounds" in Clinical Studies'.
[17] Dubhashi and Sindwani, 'A Comparative Study of Honey and Phenytoin Dressings for Chronic Wounds'.
[18] Nussbaum et al., 'An Economic Evaluation of the Impact, Cost, and Medicare Policy Implications of Chronic Nonhealing Wounds'.
[19] Markets and Markets, 'Advanced Wound Care Market by Product, Wound, End User- 2022'.
[20] Hingorani et al., 'The Management of Diabetic Foot'.

endpoints are well established and can be evaluated within relatively short observation periods with simple and inexpensive diagnostic measures.

Diabetic foot ulcer provides a priority indication for development of a novel secretome-based regenerative therapy under the guidelines set by the regulatory bodies: (i) unmet medical need; (ii) simple topical administration; (iii) European market worth 1 Bn [21]€

Innovation

Cell based therapies have revolutionized several aspects of modern medicine, including wound care of contact dermatitis[22]. But the enormous costs associated with their production pose a dilemma for public health care systems. Therefore, affordable alternatives to realize the potential of these therapies with innovative approaches are an important focus of biomedical research efforts. Within this area of research APOSCIENCE has established a unique proprietary technology poised to revolutionize regenerative medicine by harnessing the intrinsic potential for self-repair of damaged tissue with an off-the-shelf heterologous therapeutic product. APOSCIENCE have pioneered apoptotic secretomes as the source of regenerative potential in stem cell preparations. Based on this finding the company developed the secretome of irradiated PBMC as an innovative medication with the potential to support regenerative processes in situ in a wide variety of tissues. APOSEC mimics the intrinsic trigger of regeneration in vivo upon tissue damage and reliably promotes a complex biological response in several in vitro assays and animal models[23,24,25]. In animal models of cutaneous wound healing, the product stimulates migration of keratinocytes and fibroblasts, as well as neoangiogenesis – thereby contributing to accelerated wound closure, and increased epidermal thickness. A phase I clinical trial confirmed safety and tolerability of APOSEC[26]. Moreover, in 2014 a compassionate trial with 10 patients suffering from DFU provided initial evidence that the proposed therapeutic concept is highly effective. In preclinical models of myocardial infarction, protection of cardiomyocytes, platelet inhibition and induction of the growth of new blood vessels were observed, contributing to a reduction of infarct size and attenuated remodelling of the left ventricle.

APOSEC promises to restore damaged tissues by coordinating the intrinsic regenerative processes upon injury and thus provides a unique and highly innovative approach to regenerative medicine. As the production of APOSEC is affordable compared to cell-based therapies the treatment under development is compatible with the requirements of public health care systems and thus may constitute a disruptive approach to regenerative medicine available to large numbers of patients in many indications (Figure 2).

Certified Regulatory Compliant Production of PBMC Secretomes

Within the secretome of PBMCs no individual or separable activity was able to elicit the complex therapeutic response. APOSCIENCE has therefore developed a robust and affordable procedure to generate the complex biological mixture referred to as the secretome of PBMCs from donated blood samples. This proprietary procedure supports sufficient production capacity of a complex biological mixture of cytokines, anti-inflammatory and pro-angiogenic proteins, lipids, exosomes, and anti-microbial peptides. The production process of APOSECTM as a human investigational medicinal product for the use in clinical studies in a GMP facility is approved by the Austrian Health Authority (AGES) and subjected to mandatory double viral clearance. APOSECTM is a novel cell free product approved for use in human patients with a regulatory-compliant and cost-effective production. GMP production, including batch testing and filling within the requirements of a medicinal product, are established with the subcontractor [redacted]. Stability data for APOSECTM is currently generated for the clinical study and available in early 2019. The promising safety profile of the Marsyas I study allows for a combined clinical study phase I/II in the indication DFU. A study protocol for a combined phase I/II clinical trial has been confirmed and ethical approval obtained [27].

[21] Markets and Markets, 'Advanced Wound Care Market by Product, Wound, End User- 2022'.
[22] Li and Maitz, 'Cell Therapy for Severe Burn Wound Healing'.
[23] Mildner et al., 'Secretome of Peripheral Blood Mononuclear Cells Enhances Wound Healing'.
[24] Hacker et al., 'Paracrine Factors from Irradiated Peripheral Blood Mononuclear Cells Improve Skin Regeneration and Angiogenesis in a Porcine Burn Model'.
[25] Beer et al., 'Peripheral Blood Mononuclear Cell Secretome for Tissue Repair'.
[26] Simader et al., 'Safety and Tolerability of Topically Administered Autologous, Apoptotic PBMC Secretome (APOSEC) in Dermal Wounds'.
[27] ApoScience, 'Clinical Study Protocol A Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Safety and Dose Dependent Clinical Efficacy of APOSECTM at Three Different Doses in Patients with Diabetic Foot Ulcer (MARSYAS II)'.

Thus, APOSCIENCE has developed an investigational new drug (IND) in regenerative medicine ready to be clinically evaluated for its efficacy in human patients. We will implement a phase II clinical trial on diabetic foot ulcer (DFU). In addition, we will advance clinical development of intravenous application for patients with internal tissue damage. With completion of the MARSYAS I trial the topical application has a technological readiness level (TRL) of 6, which will be corroborated further by the beginning of the project with the phase I part of the clinical trial of MARSYAS II.

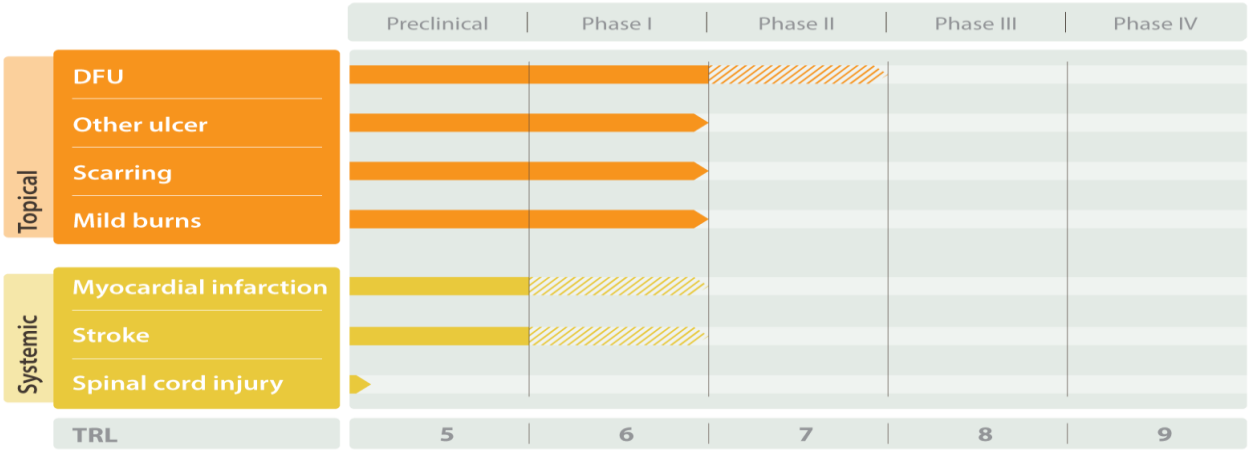

Figure 2: Pipeline of APOSCIENCE APOSEC and its modes of action and treatment opportunities

Market for DFU

DFU patients are treated according to local practice with moist wound dressings, either in-patient or out-patient settings. Owing to the scale of the problem, several European countries have specialized wound care centers dealing with chronic wounds, while others provide care through the relevant endocrinology units in hospitals. It is estimated that 60% of all DFU patients in developed nations receive treatment in hospitals, while more immobile and elderly patients may also receive treatment in nursing homes. However, in developed nations care for DFU is administered generally by highly trained personnel in specialised units according to standard of care set out by international guidelines of high level working groups[28]. This provides an excellent framework to penetrate a market without effective therapy quickly with an innovative new therapeutic therapeutic, as it remains an ambition of these working groups to ensure the best possible treatment for as many patients as possible. In the absence of any other effective treatment this working group needs to be made aware of the relevant treatment option with APOSEC and its efficacy upon obtaining marketing permission.

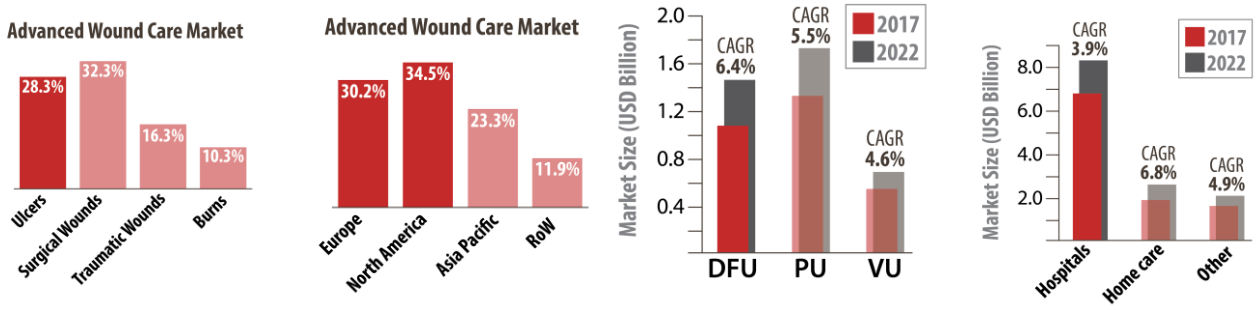

FIGURE 3: advanced wound care market 2017: The advanced wound care market is dominated by Europe and North America (left) with ulcers exceeding a quarter of the market. Diabetic foot ulcer (DFU) exceeded 0.9 Bn EUR showing the highest annual growth rate compared to pressure and venous ulcers (left). Main users within the advanced wound care market are hospitals (right)[29].

In general the highly regulated market of health care in developed nations offers an enormous business opportunity for innovative approaches, which provide a first curative therapy. **A novel therapeutic for advanced wound care might thus penetrate the current market quickly, as patients have a right for**

[28] Armstrong, 'Best Practice Guidelines Wound Management in Diabetic Foot Ulcers'.
[29] Markets and Markets, 'Advanced Wound Care Market by Product, Wound, End User- 2022'.

appropriate treatment once it becomes available and enters recommendations. As IPR protection bars competitors from imitation products and the extensive investments required for novel therapies might discourage companies to develop alternative approaches, APOSEC-2 might become the standard of care for DFU for many years. Expanded production permitting APOSCIENCE is expected to also obtain approval for pressure ulcers and other wounds which would provide an opportunity for the company to grow fast and become a market dominating force in wound healing.

1.2 Approach

Currently standard of care for DFU are moist wound dressings, which are insufficient to control the disease and prevent progression, frequently resulting in eventual amputation. Despite some therapeutics obtaining marketing approval (see Table 3), no company has obtained a significant market share with an active wound care product. Thus currently there is an intense medical need for a curative therapy which APOSCIENCE aims to meet with the first effective reatment based on APOSEC-2.

APOSCIENCE aims to raise the potential of regenerative medicine with a unique, proprietary and affordable therapy, which is compliant with the limited resources of public health care systems. The innovative approach to elicit a regenerative response with a cell free preparation has the potential to become standard of care and APOSCIENCE a fast-growing leader in the European biotech sector. This ambition is underpinned by a research and development program for the next two years to reach the necessary stage for the company to realise the enormous growth perspectives its disruptive product offers in a wide number of indications. We have therefore identified the following objectives:

1) **Proof of concept:** a phase II clinical trial for efficacy of topical administration of APOSEC™ in DFU
2) **Expand pipeline:** Explore additional indications for topical and systemic application of APOSEC™
3) **Intravenous application:** a phase I clinical trial to explore safety and tolerability for intravenous application of APOSEC
4) **Expand Production**: explore partners with extensive blood product program for scaleable production
5) **Marketing**: support market penetration with a global distribution network
6) **Investments:** Disseminating the success story of APOSCIENCE we aim to raise sufficient funds from our current investors to initiate a phase III clinical trial for efficacy of APOSEC™ in DFU

APOSCIENCE after some 10 years of research and development has reached the critical point, where it may provide a disruptive approach in regenerative medicine. The company has already established the necessary preclinical evidence, freedom to operate by comprehensive protection of the intellectual property underlying the technology, regulatory approval for a first-in-human clinical trial and a production process in line with the highly regulated environment in which innovative therapeutics are introduced into clinical application. Moreover, the company is backed by a committed investor, who has the necessary financial means to support financially the chosen development path and shows strong support for the current leadership. The concept to promote the clinical development of APOSEC therefore rests on these essential pillars, which in combination place APOSCIENCE in an exclusive position to bring an effective first line therapy for the large patient population suffering from DFU, an indication without efficacious treatment.

APOSCIENCE follows thus an ambitious approach to develop an innovative therapeutic based on an exclusive and proprietary technology with the potential to have an enormous impact on chronic diseases, to revolutionise regenerative medicine and to realise an expansion of APOSCIENCE to become a global leader in regenerative medicine.

Milestones

The approach conforms to a **well-planned clinical development strategy** providing sufficient evidence for APOSEC™ to be an innovative therapeutic targeting failing wound healing. The anticipated funding should provide the necessary non-dilutive investment to generate technological readiness to convince the current investor to support the necessary steps for further clinical development and attract a global pharmaceutical company for production and marketing of the product in cooperation. To achieve this goal the approach rests on five important milestones already attained:

1) **Preclinical evidence:** The „Dying Stem Cell“ hypothesis explained initial positive results of the transplantation of stem cells which could not be confirmed in the clinic. Gnecchi et al. showed that secreted components of the injected stem cells supported heart regeneration upon infarction.[30]

[30] Gnecchi et al., ‘Evidence Supporting Paracrine Hypothesis for Akt-Modified Mesenchymal Stem Cell-Mediated Cardiac Protection and Functional Improvement’, 1 April 2006.

APOSCIENCE obtained essential funding to advance the preclinical evidence with the Christian Doppler Society from 2009-2015. Today an extensive body of evidence shows that secretomes constitute a complex and inseparable mix of proteins, lipids and vesicles with the ability to coordinate regenerative processes in damaged tissue in a variety of small and large animal disease models.[31,32,33] In addition, APOSEC™ did have no adverse effects in GLP toxicology studies and a clinical phase I (first in man - FIM) showed it is safe and tolerable for topical administration in humans[34].

2) **Freedom to operate:** APOSCIENCE owns exclusive and extensive rights to exploit the commercial use of secretomes for regenerative medicine. Two patent law firms have conducted Freedom to Operate (FTO) searches (Isenbruck/Bösl/Hörschler, Munich, Dec. 2014 and Kliment & Henhapel, Vienna, May 2015), which both confirmed that APOSEC patent applications do not infringe the registered property rights of third parties (see also section 2.3).
3) **Production of a unique innovative medicinal product:** APOSCIENCE has developed a production method to generate secretomes from PBMC, a fraction generated during the processing of blood donations without other use (Figure 1). The Austrian Authority (AGES) has provided extensive scientific advice on a compliant production process and issued a manufacturing authorisation for the production of APOSECTM under INS-480102-0013-006 on 25.4.2014 for clinical studies. In April 2017 APOSCIENCE AG and the [redacted] obtained regulatory approval for APOSEC as an innovative medicine product for use in humans. The [redacted] produces in license APOSEC within a GMP certified production site. APOSCIENCE AG has a framework agreement with the [redacted], and the [redacted] where the drug product APOSECTM is manufactured with the necessary regulatory approval as an innovative medicine product for use in humans. The current GMP certified production process is able to deliver sufficient material for treatment of 505 patients with middle dose (as projected in the clinical study in DFU), and thus sufficient for all the activities described within this proposal and a subsequent phase III clinical trial. GMP production of APOSEC at [redacted] with current infrastructure could be upscaled to to treat up to 1,500 patients. Thus, to prepare for market entry a large scale production process will need to be certified in cooperation with a strategic partner (see Table 1).

Based on the current pre-clinical pharmacology and preclinical GLP toxicology results, data from the MARSYAS I study, and clinical experience with compassionate use of APOSEC™, no safety concerns have been raised that contradict the envisioned development program.

4) **Regulatory approval:** Together with external advisors APOSCIENCE has implemented in recent years an effective strategy to obtain regulatory approval for the clinical testing of APOSEC-2 based also on toxicology and stability testing. APOSCIENCE has initiated the generation of a proof of concept for APOSEC as topical medication for DFU, by obtaining regulatory and ethical approval to conduct a combined phase I/IIa clinical trial to explore the efficacy of APOSEC in a randomized placebo controlled clinical trial according to national / EU regulations . This is based in part on the successful completion of a compassionate use of 10 DFU patients, which have been treated successfully in (2014) with APOSEC. Based on this success a clinical trials application has been approved by the Austrian Agency for Health, AGES, according to the Austrian law "Arzneimittelgesetz" (AMG) and the positive decisions of relevant ethics committees. Thus, the multicentric clinical trial will be initiated as soon as the Data Safety and Monitoring Board provides the necessary permission.[35]
5) **Investments:** APOSCIENCE has a proven track record to raise funds for an ambitious development program and effectively partnered with [redacted] to ensure a production process compliant with applicable regulations was initiated. If this funding Proposal is successful the [redacted] has currently signaled interest to provide sufficient funds for completing the phase III clinical trial of APOSEC in DFU.

[31] Mildner et al., 'Secretome of Peripheral Blood Mononuclear Cells Enhances Wound Healing'.
[32] Hacker et al., 'Paracrine Factors from Irradiated Peripheral Blood Mononuclear Cells Improve Skin Regeneration and Angiogenesis in a Porcine Burn Model'.
[33] Lichtenauer et al., 'Secretome of Apoptotic Peripheral Blood Cells (APOSEC) Confers Cytoprotection to Cardiomyocytes and Inhibits Tissue Remodelling after Acute Myocardial Infarction'.
[34] Simader et al., 'Safety and Tolerability of Topically Administered Autologous, Apoptotic PBMC Secretome (APOSEC) in Dermal Wounds'.
[35] ApoScience, 'Clinical Study Protocol A Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Safety and Dose Dependent Clinical Efficacy of APOSECTM at Three Different Doses in Patients with Diabetic Foot Ulcer (MARSYAS II)'.

In 2016 the [redacted] [redacted] decided as private investor to financially support the

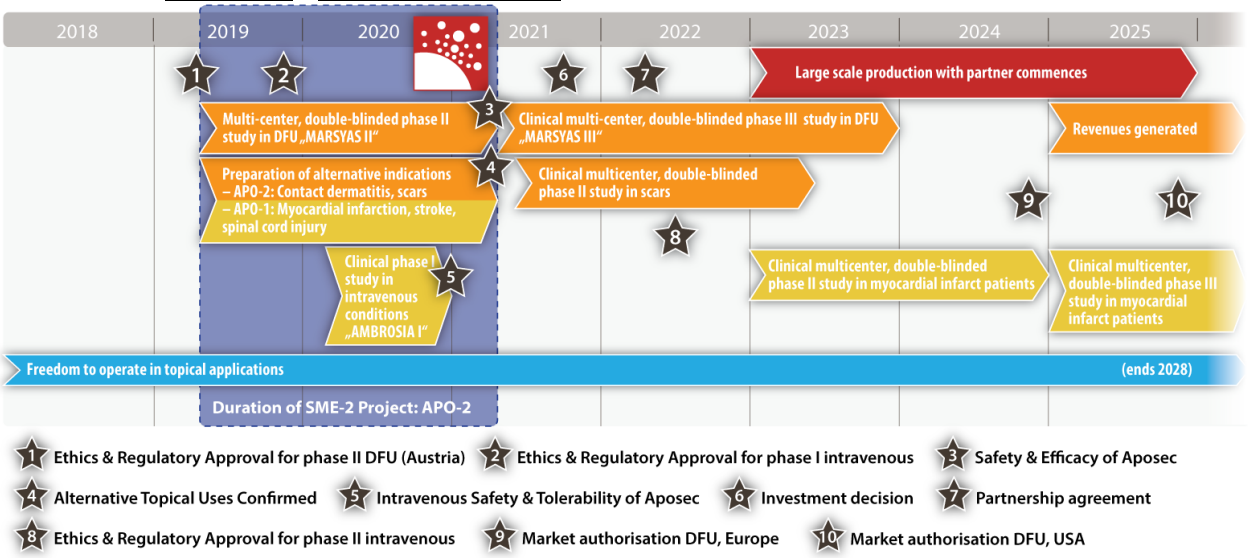

Figure 4: Exploitation strategy: APO-2 forms an integral part of the business strategy of APOSCIENCE and will be a crucial investment to advance the clinical development independently of a large pharma company. Relevant milestones serve as success criter

development of APOSEC. These funds were leveraged with national funds from the Austrian Science Promotion Agency. Currently approval for funding of the Austrian Business Agency for complementary product development activities is pending.

Expected Outcomes of this Phase-2 project and the related success criteria

Considering the extensive costs anticipated for cell-based therapies currently favoured by many competitors in regenerative medicine, APOSCIENCE provides an affordable product compatible with the requirements of European public health care systems. Therefore, APOSCIENCE has established a highly innovative medicinal product with enormous market potential and is poised to provide a proof of concept for the lead indication DFU to attract private investors to achieve market access and substantial revenues by 2024 (see Table 2). This cell-free and affordable off-the-shelf preparation of APOSEC will be tested for efficacy in treating DFU within MARSYAS II. If successful APOSCIENCE aims to raise funds from current investors to complete a phase III clinical trial and obtain subsequent regulatory approval with a new drug application at EMA. Thus, APOSCIENCE aims to attain a strong negotiating position supported by phase III clinical trial data to enter into a contractual arrangement with a strategic partner with blood product manufacturing (Table 1). In addition, we will develop further applications for our unique therapeutic with a stepwise expansion of the pipeline into related indications in wound healing including pressure and venous ulcers, but also scarring and contact dermatitis. This will support growth into a global market currently worth 2.7 Bn € with a CAGR of 5.9% exceeding the current revenue predictions.

In parallel APOSCIENCE aims to develop a systemic treatment with APOSEC for internal tissue damage, including heart infarction, reperfusion injury and stroke. This development is expected to be advanced within the project into phase I clinical testing to test safety and tolerability. If successful such a therapy is expected to generate unprecedented revenues compared to the topical products. To support the fast growth of the company strategic partnerships will be sought already during the project to identify a partner with the potential to implement a large scale production of APOSEC.

Launching a new medicinal product for an indication with a global market exceeding 2.5 billion € will be a major achievement for a European SME. Attaining a 30% market share within Europe and expanding into other developed nations should provide a significant basis for rapid growth. Generating an independent income by 2025 will provide the necessary financial independence to the company to expand its pipeline rapidly for a wide variety of indications supporting the vision of the company to become a global leader in regenerative medicine (see Figure 4).

2 IMPACT

2.1 Entering the market

Unique selling point
DFU treated with moist wound care dressing provides wound closure after 6 weeks only in 40% of patients, while some active wound care products may support up to 60% but failed to become standard of care. APO-2 is anticipated as a highly innovative topical wound care product which has demonstrated safety and efficacy in compassionate use cases: DFUs refractory to healing under standard of care healed within 20 to 28 days. APO-2 offers efficacy second to none, is easy to use, and has the clear potential to become best-in-class for the advanced wound care market. The pricing will be compatible with European public health care systems and is expected to become recommended within the relevant guidelines as standard of care[36].

Type of market – Diabetic foot ulcer
Currently more than 1% of the total population (EU 5.12M patients, US: 3.28 M patients) suffer from DFUwhich generally limit the quality of life of patients. In developed nations therefore more than 6 M patients suffer from these chronic wounds, which progress towards amputation in 15% of all cases[37]. The incidence of amputations in the diabetic population ranged from 78 to 704 per 100,000 person-years, depending on the level of care. In Germany alone 20.000 amputations were performed on diabetics in 2001[38]. Amputations severely limit the quality of life, result in enormous direct as well as indirect costs and eventually may even be fatal due to complications.

- 6% of people with Diabetes will develop a foot ulcer in their lifetime
- 6.4% annual growth DFU is the fastest growing chronic wound (REF: awc market global forecast)
- 30% of DFU fail to heal
- 15% of hard-to-heal wounds result in amputations
- 70% (80%) of all amputations in Germany (US) are result of non-healing DFUs

The clinical trial protocol for Marsyas II foresees therapy of DFU of grade 2, without infection and a surface area < 8 cm2. While there are no reliable numbers of how many DFU patients might fall into this category, we estimate this may be 30% of all patients. Therefore, APOSCIENCE aims to develop a curative therapy for a significant proportion of a large patient population of approximately 2 M individuals. At the moment treatment for a newly diagnosed DFU patient costs an estimated 35.000 € in the first two years. Moreover, as most patients progress towards amputation and may even eventually die of complications costs for treatments increase substantially with more frequent hospitalisations. A curative treatment has been estimated to reduce public health care costs per patient by 20.000 €.
APOSCIENCE has decided to develop APOSEC initially for diabetic foot ulcer (DFU), a disease of high prevalence and growing number of patients. Currently the market for DFU is more than 1 Bn and characterized by a growth rate of 5.7 %[39].

Market for advanced wound care
Chronic wounds (ulcers) constitute an unmet clinical challenge relevant for a large number of patients and therefore an attractive global market worth >2.5 Bn € annually and expected to rise to 3.3 Bn € by 2022. Moreover, chronic wounds display the highest annual growth within the wound care market with a growth rate of 5.7% p. a. driven mainly by demographic changes and the higher prevalence of diabetes with the improving economic situation of many countries in Asia providing an additional stimulus. In Europe and the US there are approximately 6 M patients suffering from DFU which has a prevalence of 6% amongst diabetics. Currently the market in North America and Europe make up more than 60%, with ulcers exceeding a quarter of the revenue (see Figure 3).
In Europe reimbursement will be through public health care, if the anticipated efficacy can be reached in the trials. Thus in principal all patients will be able to afford therapy with APOSEC independent of their social status. In the US health care insurance is more heterogeneous, currently under reform and it is difficult to

[36] Gnecchi et al., 'Evidence Supporting Paracrine Hypothesis for Akt-Modified Mesenchymal Stem Cell-Mediated Cardiac Protection and Functional Improvement', 1 April 2006.
[37] Narres, Kvitkina, and Claessen, 'Incidence of Lower Extremity Amputations in the Diabetic Compared with the Non-Diabetic Population: A Systematic Review'.
[38] Heller, Günster, and Schellschmidt, '[How frequent are diabetes-related amputations of the lower limbs in Germany?'
[39] Gnecchi et al., 'Evidence Supporting Paracrine Hypothesis for Akt-Modified Mesenchymal Stem Cell-Mediated Cardiac Protection and Functional Improvement', 1 April 2006.

predict how the environment will be regulated in five years from now. Nevertheless many patients are expected to receive reimbursement through public health care, while others will have to pay individually, which may make market penetration more slow.

Standard of care

The global advanced wound care market is 9 Bn € and expected to grow to 11 Bn € by 2022. The advanced wound care market is separated into three segments, with moist wound dressings (61%), devices (24%) and active wound dressing (15%). However, while active therapies for severe burns and traumatic wounds have successfully entered the market, for chronic wounds effective active therapies have not become standard of care. Chronic wounds represent the fastest growing segment of the wound care market, mainly driven by Asian countries, the increasing prevalence of diabetes and demographic changes.

Currently the market is dominated by several moist wound dressings as standard of care, which contain gels preventing the wound to dry up, but no active ingredient. Several active wound care therapeutics have obtained marketing approval, however none have become standard of care and thus they have no significant market share (see table 4). While standard of care yields wound closure in approximately 40% of cases, current active treatments do not exceed 60% of wound closure. This is anticipated to be significantly exceeded by APOSEC-2 treatment, which should provide a convincing basis for becoming standard of care in particular if the pricing is compatible with public health care budgets. With APOSEC aiming to become the first efficacious active wound care therapeutic for chronic wounds, market penetration is expected to be fast and for several years meaningful competition remains unlikely. **The market share for APOSEC is therefore expected to reach 30% in those markets addressed and remain or exceed level for the foreseeable future.**

User needs identified

Chronic wounds are defined as failing to progress towards closure within 30 days. Diabetic foot ulcers often start as small scratches or bruises which patients with diabetes fail to notice due to nerve damage and limited sensitivity. These initially benign wounds due to a compromised immune system, infections and damaged capillaries develop into chronic wounds, of which up to 30% fail to heal completely. These patients experience a progressive disease with decreasing quality of life and even life threatening complications. **There is an intense medical need for therapies that accelerate the sustainable closure of these cutaneous ulcers to reduce costly hospitalisations due to sequelae.** Thus diabetic foot ulcer (DFU) remains a major unmet clinical need for millions of patients globally and is the most frequent cause of hospitalisation in Europe (811,000 patients in the EU per year with a growth rate of 6.4%). In the US, each DFU patient costs the healthcare system up to 34,000 € in the first two years after diagnosis with hospitalisation and amputation being the most significant cost drivers. A curative therapy will reduce hospitalisation and the extensive financial burden chronic wounds pose to public health care in Europe.

Reportedly >60% of all ulcers in Europe are taken care of in hospital environments, either in in-patient or out-patient settings. The main users of the APOSECTM therapy products are employees of hospitals and wound care centers. **These include, wound care specialists, endocrinologists dermatologists and podologists making the therapeutic decisions for APOSEC, while mainly nurses and podiatrists will apply the treatment.** As the anticipated product will be very similar to a moist wound dressing, we expect no barriers to enter the market characterised by highly trained wound care specialists.

Marketing partner:

To support distribution and fast market penetration APOSEC seeks a strategic partner with experience and products in the global advanced wound care market to support market entry with an efficient distribution network. Prime candidates will be global companies already active in producing blood products. These companies would therefore have the expertise to implement the production process, possess the relevant infrastructure and have access to blood donations as raw material. Some of the prime candidates are globally active companies like Biotest (see table 1). These companies might conceive APOSEC as an important opportunity to expand their portfolio of blood products, as PBMCs are usually a waste product of processing blood donations. The existing distributional network, packaging and marketing expertise will be an essential boon to entering the market with an innovative product. This strategy is expected to overcome any hurdles in generating sufficient product within the anticipated time frame and decrease any potential resistance to introducing APOSEC and support the anticipated rapid market penetration.

company	origin	revenue	employees
Takeda Pharmaceuticals	Japan	10.6 Bn EUR (2017)	31,000
Octapharma	CH	1.3 Bn EUR (2016)	7,000
Biotest	DE	0.3 Bn EUR (2017)	1,600
Grifols	ES	3.9 Bn EUR (2015)	14,700
CSL Behring	AUS	4,7 Bn EUR (2015)	14,000

Table 1: potential strategic partners

Market entry

After completing the clinical studies **market authorisation with one pivotal study according to EMA guidance**[40] **at the authorities and introduction** can be planned the earliest in 2024. Once successful similar market authorisation will be sought for the US from the FDA in 2025. Once marketing approval has been obtained by the EMA in Europe market entry will commence organised independently by the strategic production and marketing partner.

Based on the clinical study centers, which will act as early adopters and an extensive network of established leading clinicians in wound management APOSCIENCE will aim to achieve an adoption by the European Wound Management Association (EWMA) as standard of care [41]. In cooperation with the leading clinicians in DFU we will aim at clear diagnostic criteria for patients with delayed healing as measured by slow wound area reduction within 4 weeks, which should result in a recommendation to use APOSEC as an adjunctive therapeutic. If the guidelines are adapted by the end of 2024 this would meaningfully support a market introduction across Europe backed by a reimbursement through public health care providers.

Therefore, we expect minimal resistance in the market to change to moist wound dressings fortified with APOSEC as active ingredient as it will not only be easy to use, but virtually indistinguishable to current therapies. Importantly very minimal training will be required to use the APOSEC product for those medical staff who have already used mmoist wound dressings.

Based on the severe consequences patients face and the enormous costs of hospitalisation we expect APOSEC to become a **cost-effective product**. More importantly it has the potential to become **best-in-class for the advanced wound care as it will be the first efficacious active wound care therapy for chronic wounds.**

Market entry will be stepwise in developed nations, starting with Europe, folloed by the US, Japan/australia and eventually the urban population in China and India (10% of the total population in these countries). In Europe, where we expect a market share of 30% of all DFU grade 2 patients. In the US, Japan and Australia we aim at 15%, while in the middle class of China and India we anticipate 10% market penetration (see Table 2).

region	citizens (M)	Dm prevalence	Dm patients (M)	DFU patients (M)	DFU grade 2	market share	treatments
Europe	741	8,3%	61,5	1,23	370.000	30%	110.000
North Ameri	460	10,8%	49,7	0,99	280.000	15%	40.000
Australia Jap	150	7,7%	11,6	0,23	70.000	15%	10.500
China/India	250	9,7%	24,3	0,49	145.000	10%	15.000
Total							175.500

Table 2: Market size for DFU based on the prevalence of diabetes in the general populations, an estimate of 5-6% of DFU patients and 30% of these being grade 2

If the market introduction in ulcers is successful and meets our conservative expectations, we aim to conduct clinical trials in additional wound care indications, which include contact dermatitits and scarring. To expand the pipeline preclinical activities for these indications are anticipated.

Listing therapeutic products and allowing reimbursement by the European public health insurers is only possible when efficacy and ease-of-use are guaranteed. This project is an important step to achieve both within the foreseeable future to ensure a successful market entry and a sizeable market share of 30% the grade 2 DFU in Europe.

[40] COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS, 'Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study'.

[41] European Wound Management Assosciation, 'Home - Wounds International'.

Business Model:
Currently no appropriate therapeutic is available and APOSEC promises to be a first in man therapeutic with the potential to achieve a significant market share, as it is designed as a curative therapeutic. Based on active wound care product currently on the market APOSEC is expected to be marketed at 5,000 € per treatment for 2 weeks.
Commercial exploitation of the therapeutic rests on an efficient and large production of APOSEC. The cost of good currently is approximately 50,000 €/2.5 l batch. This is anticipated to be sufficient to treat up to 35 patients at the middle dose, ie costs of good is 1,400 €/patient. Anticipating packaging and marketing costs we presume the per costs per treatment would be below 2,000 €, in particular if cost savings in an automated production process on a larger scale become implemented. Therefore we anticipate a price of 5,000 €/treatment to be a commercially viable option, which may be attainable on the market as competitors with less efficacy have similar or even higher prices. We anticipate a licensing arrangement sharing revenues 20/80 between the strategic partner and APOSCIENDe, thus we calculate with 1,000 € revenue per patient for the company.
APOSCIENCE has been pursuing since its foundation the research and development of secretomes preparations as a therapeutic in regenerative medicine. The market introduction of APOSEC as a treatment for DFU and the anticipated revenues are the cornerstone of the companies business strategy (see table 3). A viable income from this product would provide the necessary financial flexibility to pursue alternative indications. This would not only include other topical applications, but importantly regenerative therapy of internal organs, like the mycordium upon heart attack, the brain upon stroke and the spinal cord upon injury. To expand our pipeline a Phase I first-in-man study for systemic (i.v.) application is anticipated. This study is the prerequisite for phase II trials in AMI, stroke, spinal cord injury and myocarditis. These activities, which are supported by extensive pre-clinical evidence, constitute an important part of the future growth perspective of the company, which is aiming to become a global brand in research and development of regenerative medicine.

2024	2025	2026	2027	2028	2029	2030	
	15.000	42.000	80.000	132.000	149.000	175.500	Total patients
	15.000.000 €	42.000.000 €	80.000.000 €	132.000.000 €	149.000.000 €	175.500.000 €	Revenue
	5%	10%	20%	30%	30%	30%	Market share
MA Europe	15.000	35.000	70.000	110.000	110.000	110.000	Treated patients
	MA North America	2.5%	5%	7.5%	12.5%	15%	Market share
		7.000	10.000	15.000	25.000	40.000	Treated patients
				5%	10%	15%	Market share
			MA Asia/Pac	7.000	14.000	25.500	Treated patients

Table 3: Projected revenue from DFU therapeutic

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. The AGES had no general objections against this strategy to plan for a single pivotal trial only. A **market introduction** is planned for **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. 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[42].

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 800 Million Euro worldwide. Based on 5,000 € per treatment and 2,000 € expenses profit would be 3000 €. If a licensing arrangement of 20/80 can be negotiated, APOSCIENCE would earn 1,000 €/treatment. In 2025 we anticipate thus revenues of 15 M€, increasing stepwise with antering new markets and increasing the market share to 175 M€ (see Table 3).
Business development: APOSCIENCE has partnered with a powerful investor who is currently committed to finance the development of APOSEC as treatment of DFU until market entry, pending the achievement of

[42] COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS, 'Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study'.

specific milestones. This will provide a strong negotiating position for APOSCIENCE to enter into a contractuual arrangement with a strategic partner for production (see table 1) and marketing of APOSEC. We are currently anticipating a licensing agreement splitting the revenues 20/80 with 20% for APOSCIENCE (see table 3).
If the current investor should decide that further development will not be fiannced, APOSCIENCE wills seek alterantive sources of income to fund the clinical development of APOSEC until market entry. These alternatives may include other corporate investors or a licensing agreement with the strategic partner (see table 1) before clinical development is completed. This should decrease the contribution APOSCIENCE may achieve out of the licensing agreement once market authorisation is attained. If no investor/strategic partner will enter into a licensing agreement with APOSCIENCE within acceptable conditions, the management will explore alternative sources of financing, including a public offering.

Potential 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. A mixture of private investments and public funding (H2020) is needed to leverage and bring APOSEC™ onto 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. Decisive is the provision of clear evidence that APOSEC-2 is an efficacious and cost effective treatment of DFU. This will not only support marketing permission, but also recognition of the treatment as standard of care within international guidelines of managing DFU. If APOSEC has the expected efficacy we expect thus no significant barriers in Europe from users following the strategy as outlined above. Moreover, in Europe public health care providers are expected to very quickly approve reimbursement of the therapeutic supporting a very fast penetration in the entire patient population.
Despite the fact that health care practitioners are a highly skilled and trained profession, who are contiuously faced with implementing new and improved methods, also health care markets frequently resist the introduction of new products. However, APOSEC delivery will be very similar in its application to moist wound dressing currently the standard of care in chronic wounds. While the final formulation needs to be determined after the clinical trials are completed, we are clinically testing a combination of the therapeutic with NU-GEL alginate. Therefore, we expect no significant resistance to using the new product amongst users.
In the US less patients may be able to afford the treatment, as not all patients may possess a health insurance. Therefore we expect a lower market share as potentially a significant number of patient will not be able to afford the treatment.
A significant barrier may lie in the necessary expansion of the production capacity. Therefore APOSCIENCE has decided to seek an experienced globally active pharma company, which is already engaged in the productiuion of blood products. It is anticipated that the successful company will be able to ramp up production very quickly due to the availability of the necessary raw material and infrastructure. .

Main benefits for the patients
DFU is a major complication of diabetes mellitus with significant impact on quality of life. Todate DFU remains a chronic condition without cure which causes the hospitalisation of 800.000 patients annually in Europe alone. Patients face repeated hospitalisations and the risk of amputations. They are frequently hindered to participate in everyday activities with a severe impact on their professional and social life. Moreover, repeated sick leave reduces their productivity and threatens their employability. Even more so once an amputation becomes necessary, which may constitute a severe impact on the patients private and professional life, including rehabilitation and change of job due to the diability.
APOSEC promises to be a curative therapy and thus DFU will become a manageable disease, which can be treated successfully within 4 weeks. While a new lesion may appear regularly, as the underlying cause will not be altered, the curative therapy should prevent the initial lesion from developing into a chronic wound. Patients therefore will have a higher quality of life, will be better integrated into their daily life including the work place and most importantly will not have to face the risk of amputations. Moreover, families and their social environment will benefit from the release of immediate psychological and economical strain.

Main benefits for the health care providers

DFU patients require continuous wound care by professionals and face repeated and increasingly long hospitalisation periods with up to 800,00 patients hospitalised annually. While standard wound care might be administered by local carers in an out-patient setting, this might be reduced once the condition has worsened, with increasing hospitalisations as the disease progresses in the absence of a curative therapy. The calculated costs are 11,000 € per treatment period in average in DFU patients[43], but hospitalisation costs may be up to **17,000 € per stay**[44,45] and constitutes the main cost driver. Moreover, the costs of an amputation are very diverse depending on the specifics and might even include next to surgery costs also rehabilitation costs. Long-term costs after amputation are estimated to be 36,000 € and more.

Similar reasonings are true for any chronic wound, for which APOSEC will attempt to obtain marketing approval in a second step. With up to 2.5 M hospitalisations in Europe and 4.5 M in the US due to chronic wounds a market penetration of 30% we might estimate that up to 50% of the hosptialisations could be avoided, as we anticipate the therapy being more often applied in the the more severe cases. We therefore estimate that 3.5 M hospitalisations could be saved every year in these two markets alone.

Contribution to important benefits to society

Chronic wounds represent a significant burden for the public health care systems in Europe. In Europe alone chronic wounds affect 5.7 million patients and advanced wound care therapeutics cost an estimated 2,5 B € annually. Moreover up to 75% of all amputations are due to severe cases of DFU, which due to disability, unemployability, loss of productivity and rehabilitation are associated with enormous indirect costs. Turning a chronic condition without treatment into a manageable disease will produce a significant reduction in the burden of indirect costs associated with chronic wounds.

The most tangible and direct benefit will be the burden of 2.5 M hospitalisations annually due to chronic wounds, which may be significantly reduced with an effective therapy. We anticipate a significant higher share in the more severe cases and thus estimate we might reduce the hospitalisations of patients with chronic wounds effectively by 50%. In the European public health care systems, 2.5 M hospitalisations costing 17.000 € each would correspond to a cost saving of more than 21 B € annually.

Main competitors and competitive solutions

Therapeutic	company	Marketing approval	Active ingredient	Therapeutic success
Regranex (Beclapermin)	Janssen-Cilag International	USA/EU	Growth factor from platelets	Within 20 weeks 50% of wounds heal compared to 36% in control
Apligra	Organogenesis Inc	USA/CH	Skin transplant from neonatal keratinocytes	Within 12 weeks 56% of wounds heal compared to 39% in control
Epifix	Forticell Bioscience	Cuba, South Korea, Belgium	Membrane preparation from human placenta	
LeucoPatch	Reapplix ApS	Trial ongoing	Preparation from patients own blood	Within 20 weeks 55% of wounds heal
Grafix	Osiris Therpeutics	Under clinical development in the US	mesodermal stem cells	
CureXcell	Macrocure	Failed in phase III clinical studies		
HP808-101	Healthpoint, Smith&Nephew	Failed in phase III clinical studies		

Table 4: Examples of approved active wound care therapeutics without any significant market share

Currently several active treatments of ulcers have received approval, but nevertheless they have failed to successfully enter the market due to their limited efficacy (see Table X). Standard of care with moist wound dressing provides closure in 40% of patients and an alternative therapy would need to exceed at least 60% to become recommended. This appears within the scope of APOSEC within two weeks treatments according to current projections. Some approaches are based on paracrine factors isolated from blood, others are using cell-based skin substitutes for wound healing. Therefore, there is an intense medical need for a curative

[43] Stockl et al., 'Costs of Lower-Extremity Ulcers Among Patients With Diabetes'.
[44] Singh, Armstrong, and Lipsky, 'Preventing Foot Ulcers in Patients with Diabetes'.
[45] Rogers, Bevilacqua, and Armstrong, 'The Use of Marrow-Derived Stem Cells to Accelerate Healing in Chronic Wounds'.

therapy of DFU, as standard of care administerd with moist wounddressing. Thus APOSEC has the potential to replace current standard of care with ab affordable and efficacious therapy. Such a therapy would disrupt the current market and provide an important progress for this larger patient population.

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
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.
Global producers of blood products as production and marketing 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 for APOSEC™ is installed. APOSCIENCE AG is also in contact with other global companies processing blood products in order to identify partners for large scale production in preparation for market entry.
End-user: Physicians, diabetologists, dermatologists, endocrinologists, surgeons, nurses (very important)	These are key stakeholders in conducting the anticipated clinical trials, 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.
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 before providing informd consent. Information is provided and agreed via the so-called informed consent process.
National health authorities, European health authorities; FDA (very important)	These national authorities approve the production process and provide market access relying on the results of clinical trials carried out be pharmaceutical companies to reach an 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.
Academia and science community (important)	APOSCIENCE is conceived as a research intensive SME applying cutting edge research results into clinical application. As such it is embedded into the scientific community, benefits from highly trained personnel and their concepts.

Table 5: List of stake holders

Data from Phase II clinical trial: EMA first published guidance documents in March 2016 on reporting on clinical trials. APOSCIENCE is committed to make the relevant data available on the EMA clinical trial portal and database (Clinical Trial Regulation EU No. 536/2014) irrespective of the outcomes as soon as feasibly possible. As SME APOSCIENCE will draw on the free redaction tool license and consider the opinion of the Committee for Medicinal Products for Human Use (CHMP). 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.
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.
Investigational Medicinal Product Dossier (IMPD) on APOSEC™: The IMPD is continuously updated according to the relevant guidelines within the legal framework of the EU Regulation No 536/2014 on Clinical Trials on Medicinal Products for Human Use to support an application for mareting authorisation. It will include summaries of information related to the quality, manufacture and control of any IMP (including reference product and placebo), and data from non-clinical and clinical studies.

Patient data: APOSCIENCE will ensure full data protection of any patient data.
Research Data: APOSCIENCE supports the widest possible recognition of research results, which is supported by open access publications. Therefore, any relevant project results will be published in scientific

journals providing open access and under strict adherence to the requirements of attributing the funding by the EU through H2020.
Commercialization: Information on market, patient population and competitors will be continuously collected as important and relevant information for determining the worth of a possible licensing agreement. These data will provide important information on the potential revenue of a future therapeutic, its cost effectiveness and compliance with reimbursement through public health care systems. These data will be collated and made available exclusively to potential investors and partners.

2.2 Financing

Company's ownership and capital structure
Since its foundation APOSCIENCE AG has been a pure research company, without any operative business. The current capitalisation of the company is [redacted] (one share equalling 1 EURO). The APOSEC project has been financed so far with [redacted], including [redacted] by the shareholders, EUR [redacted] by the Christian Doppler Forschungsgesellschaft, and [redacted] by the Austrian Research Promotion Agency (FFG). SME instrument are therefore corresponding to the core of the technological development APOSCIENCE has been following since its foundation by Business Angels in 2008.

Turnover based on the pricing assumption of 5,000 Euro per treatment cycle (DFU) and a licence rate of 20% (=1,000 Euro per treatment cycle for APOSCIENCE AG) from our industry partner, a turnover of about 122 million Euro can be reached in 2029, this represents a market share of 30% in Europe and 15% in the USA (see table in the annex).
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.

2.3 Intellectual Property Right (IPR) and legal framework

Regulatory and standard requirements to be fulfilled for exploitation
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

Strategy for knowledge management and protection
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-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)

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 1h. Priority: 18/12/2008 (international protection: AU, BR, CA, CN, EP, JP, NZ, RU, US, ZA) WO 2010/070105 A1 – PHARMACEUTICAL PREPARATION
Both patents were submitted in 2008 and 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
APOSCIENCE has an excellent track record of protecting its IPR and it will continue to professionally screen its newly generated knowledge and knowhow in the project for any other commercially valuable IP

requiring protection. Two Freedom-to-operate analyses have been conducted by well-known patent attorney agencies (Kliment & Henhapel, Vienna, and Isenbruck/Bösl/Hörschler, Munich**). Their analyses showed that the APOSEC™ patents do not infringe any other protecting rights and that full freedom to operate is provided**. (both FTO documents are attached in other annexes). The report also estimates lack of novelty and / or inventiveness in the most prominent claims of 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 2024, data exclusivity will protect APO-2 against a generic version of the medicinal product using the same drug product **until 2035**[46].. Data exclusivity constitutes an important incentive to the research and development of new medicines.

2.4 Communication and access to research data

Communication measures for promoting the project

All research data will be subjected to intense scrutiny of potential IPR of commercial value to ensure its protection prior to publication. APOSCIENCE has an excellent track record of publicising its research findings and will continue to make its data publicly available through open access publications, once IPR is protected. APOSEC™ will define a specific communication strategy to promote commercialization of the results and project outcomes, which will be stipulated in the dissemination and exploitation plan. The aim of this strategy is to communicate progress towards the clinical application of the product and its benefits (in terms of cost effectiveness, production costs, easy-of-use concept, clinical trials results). To facilitate the diffusion of these innovations suitable communication measures will be used via different communication channels, like a project website, flyers, folders, videos and press articles.

Moreover specific dissemination by the management to potential partners, funders, investors and regulatory bodies will be supported with specific communication material based on the investigational medicinal product dossier.

The following target groups have been identified:

- Clinicians and scientific societies: Wound care specialists, Surgeons, Dermatologist, Podiatrists
- Patients and patient organisations: Diabetics, patient organisations, DFU, Patients and families
- Health care providers and insurers: Hospitals, national health insurers,
- Regulatory bodies: EMA, FDA, AGES
- Pharma companies: moist wound care producers and blood product producers
- Investors and Funders: investment funds, FFG, AWS, EU

3 IMPLEMENTATION

3.1 Team

Team	Position	Expertise	WP leader
Univ.-Prof. Dr. med. Hendrik Ankersmit MBA	CSO, COO	Inventor of APOSEC Thoracic surgeon; regenerative medicine; clinical research	Strategic planning and operative coordination (WP 6)
[redacted]	CFO	Pharmaceutical product devel-opment & regulatory issues.	Financial & legal issues, strategic development, partnering. (WP 5)
[redacted]	Assistant (B. of Directors)	Head of administration, project and grant management.	Coordinates tasks internally and keeps them in evidence (WP 4)
[redacted]	Head of clinical dev.	Stem cells; tissue regeneration	Management of product development on the regulatory level (WP 1)
[redacted]	Quality Manager	Quality control and management	Quality Management (WP 3)
[redacted]	Researcher, Post-Doc	Clinical research focus on burns medicine, burn wound infections and wound healing	Experimental work (participating inWP 3)

[46] IFPMA, 'Data Exclusivity'.

[redacted]	Consultant explorative studies	Deepest understanding of the scientific background of APOSEC (~20 publications)	Scientific support (participating in WP 3)
[redacted]	Consultant of clinical studies	Clinical research in Internal medicine, Cardiology, Clincal pharmacology	Management of the clinical phase I/II (WP 2)

Strengths of the team

- interdisciplinarity brings stability and a considerable knowledge basis
- well rehearsed for many years supports complemetarity and reciprocal support
- social cohesion avoids disruptions and friction in the workflow.
- procativity and initiative carries the project through high pressure periods
- learning from experienced external advisors supports extensive knowledge base about specifics of APOSEC as an investigational medicinal product, its development and regulatory issues

Weaknesses of the team

- Although the team has accumulated extensive knowledge, they do not possess the pharmaceutical development competence of a large pharmaceutical company. This weakness is balanced by a group of excellent advisors (such as Dr. Regenold GmbH in regulatory affairs, toxicology consultants, GLP laboratories as development partners and consultants in GMP and quality issues) whose advice is taken seriously by the team.
- The team has not yet established a fully functional infrastructure as it is required for a pharmaceutical company and sponsor of clinical studies. However, the team has identified this problem and is working on it by further developing its SOP- and quality management system, better defining roles and functions of the team members and training them on defined company structures and processes.

Role of the company's owners

The company's owners are its shareholders. Aposcience AG has currently 25 shareholders, of which 20 are natural persons and 5 corporate entities. The largest shareholder is [redacted], the investment of the [redacted], representing 50% of all shares. The other shareholders (natural persons and corporate entities) represent mainly, with few exceptions the business angels who made the APOSEC project possible from its start in 2008. In the shareholder structure these business angels are represented in the family members and corporate entities of [redacted] and [redacted]. Dr Ankersmit, as founding member of Aposcience AG, is also a shareholder of the company.

The main shareholders are members of the supervisory board. The board of directors reports quarterly to the supervisory board. The supervisory board is informed on all short and long-term plans of the board of directors and approves the general course of development of the APOSEC project.

3.2 Work packages, deliverables, milestones, risks

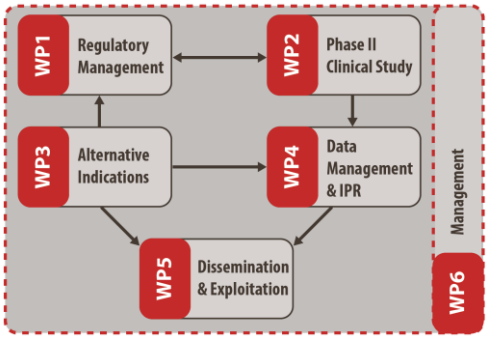

Figure 5: PERT chart

In WP 1 *Regulatory Management* comprises all activities aimed at the preparation and continuous updating of documents for Regulatory Agencies in preparation for and during the implementation of clinical studies. In WP2 *Conduct of a phase II clinical study assessing safety and efficacy of APOSEC™ in diabetic foot ulcer ("Marsyas II")* a randomized double-blind multicenter phase II trial will assess the efficacy, safety and feasibility of repetitive topical administration of human allogenic APOSEC™. In WP3 *Preparation of alternative indication* it is intended to gather scientific data concerning further possible therapeutic indications for APO-2 and describes the production pipeline and quality control of APOSEC™. In WP4 *Data Management and IPR* data collection and further processing in full keeping with the applicable regulations and will be continuously screened taking all IPR measures in consideration. The market for chronic wounds and clinical trials conducted within regenerative medicine will be continuously monitored for new developments to get updated information on the current state of best practice in wound care. In WP5 *Dissemination and Exploitation* describes how to engage relevant stakeholder groups with the project and to establish trust in the project goals and results. In WP6 *Management* the research and dissemination activities will be supported with an efficient management structure and all project activities will be supervised and reviewed.

Figure 6: GANT chart

Table 3.a: List of work packages

WP No	Work Package Title	Lead Participant No	Lead Participant	Person Months	Start Month	End month
1	Regulatory management	1	APO	9,24	1	24
2	phase II clincal study	1	APO	16,72	1	24
3	Alternative indications	1	APO	45,12	1	24
4	Data management and IPR	1	APO	4,48	1	18
5	Dissemination & Exploitation	1	APO	9,60	1	24
6	Management	1	APO	14,08	1	24
			Total months:	99,24		

Table 3.b.: Work package description

Work package number	1	Lead	APO	
Work package title	Regulatory management			
Participant number	1			
Short name of participant	APO			
Person months per participant	13,04			
Start month	1		End month	24

Objectives

- Preparation of study documents for Ambrosia I
- Collection of patient and scientific data and preparation of Product Dossier on APO-2 (APOSEC for topical application)
- Collection of scientific data and preparation of Product Dossier on APO-1 (APOSEC for internal application)

Work package Leader: [redacted];

Participants: [redacted], H. Ankersmit,

Description of work

Background information:

WP1 comprises all activities aimed at the preparation of documents for Regulatory Agencies. Some of the documents are prepared to achieve immediate goals (such as the approval to conduct a clinical study), others, like the preparation of Product Dossiers, are aimed at the all-encompassing aim of the pharmaceutical development process, market admission (MA).

The study phase I/II in DFU, MARSYAS II, was submitted to EudraCT-system, No.: 2018-001653-27. CSP and other relevant documents, such as Investigator Brochure (IB) and the Investigational Medicinal Product Dossier (IMPD) were submitted for approval by local Ethics Committees and regulatory agencies. Regulatory approval to commence with MARSYAS II based on a safety board decision after the safety lead-in is expected shortly before the project is anticipated to commence. For the Ambrosia I preclinical data will be collected in WP3 to complement existing data to support the development of a CSP to be submitted by the end of this project.

Tasks:

Task 1.1: Collection of scientific data and preparation of Investigational Medicinal Product Dossier (IMPD) on APO-2 (APOSEC for wound healing) (M1_M24, TL: [redacted])

The IMPD (2017), containing all experimental data on APOSEC, will be updated continuously with clinical data from the phase I/II study in DFU Marsyas II as well as new experimental data revealing new insights into composition and mode of action and modifications of the GMP-production process of APOSEC.

Task 1.2: Collection of scientific data and preparation of Investigational Medicinal Product Dossier on APO-1 (APOSEC for internal conditions) M1_M24, TL: [redacted])

Based on the IMPD for APO-2, an IMPD for APO-1 will be established and specified for the use of APOSEC at internal conditions.

Task 1.3: Preparation of study documents for clinical study phase I for APO-1 at internal conditions Ambrosia I" (M1_M 12, TL: [redacted])

The task consists in the preparation of the Clinical Study Protocol (CSP) and further documents required for the conduct of the clinical study "Ambrosia I", such as Investigator Brochure (IB), Study Synopsis, Informed Consent Form (ICF), and Test Schedule.

Task 1.4: Preparation of study documents for clinical phase 2 study for APO-1 ("Ambrosia II") with the indication acute myocardial infarction (M12_M24, TL: [redacted])

The task consists in the preparation of the Clinical Study Protocol (CSP) and further documents required for the conduct of the clinical study "Ambrosia I", such as Investigator Brochure (IB), Study Synopsis, Informed Consent Form (ICF), and Test Schedule.

Work package number	2	Lead beneficiary	APO
Work package title	phase II clinical study of APOSEC™ in DFU ("Marsyas II")		
Participant number	1		
Short name of participant	APO		
Person months per participant	15,72		
Start month	1	End month	24

Objectives

- Conduct of a phase II randomized, placebo-controlled, double blind, prospective study utilizing APOSEC as topical treatment (APO-2) for diabetic foot ulcer ("Marsyas II")
- Quality assurance
- Publication of study results of clinical study Marsyas II

Work package leader: [redacted]; participants: [redacted]

Description of work

Background information

MARSYAS II, a randomized, placebo-controlled, double-blind study to evaluate safety and dose dependent clinical efficacy of APO-2 at three different doses in patients with diabetic foot ulcer. 120 DFU patients will be recruited in compliance with the inclusion and exclusion criteria to treat with APO-2.

Tasks:

Task 2.1: Study conduct for clinical study phase II in DFU "MARSYAS II" (M1-M24; TL [redacted])

The randomized double-blind multicenter phase II trial will assess the efficacy, safety and feasibility of repetitive topical administration of human allogenic APOSEC™ in a total of 120 patients with DFU in a12 weeks (84 day) treatment and follow-up period. This study is preceded by a safety lead-in period evaluating multiple dose safety of APO-2 in patients with DFU in a cohort of 12 subjects. Subject population and trial design in the safety Lead-In will be identical as the Phase II study. After completion of a 4 weeks treatment period, safety and wound measurement data will be provided to a data safety monitoring board for evaluation of safety to proceed to phase II study.

Study coduct will be guided and followed by the CRO [redacted] in close collaboration by the clinical project manager [redacted] of APOSCIENCE. This is meant to support sites and applies to all aspects of the study (e.g. clarification of in-/exclusion criteria, sample storage, question to storage/use of study of APOSEC™). Study visits (foreseen: 17 in person visits are defined in the protocol and will be done accordingly. A Data safety monitoring board will decide after a safety Lead-In study of 12 subjects performed at the Austrian sites for continuation of the study to the main study (Phase II, proof of concept dose finding study).Wound imaging and wound size measurement will be assessed using the eKARE inSight® wound imaging solution at site level and centrally adjudicated by a blinded evaluator. Data for the primary efficacy endpoint will be collected/ will derive from the central adjudication assessment.

Task 2.2: IMP storage and distribution (M1-M24; TL [redacted])

The company [redacted]) will support APOSCIENCE AG in the area of storage and distribution of the Investigational Medicinal Drug (IMP), placebo and other materials for the study (such as wound dressing materials). Any deviations from the recommended storage conditions will be reported immediately to the sponsor. Use of affected IMP will be suspended until authorization for its continued use has been received from the sponsor.

Task 2.3: Quality assurance (M1-M24; TL [redacted])
Quality assurance for the CRO activities are provided by sponsor and delegates in reviewing all documents that are submitted to external partners. QA measures start by training the study personnel in all aspects required for study conduct according to GCP. Regular monitoring visits will ensure 100% source data verification. Audits of sites will complete quality control measures, which, in aggregate, will contribute to study integrity. An eCRF will be designed and validated for the study by the CRO and completed for each patient by trained and authorized personnel at site. Data review process will be performed collaborately between the CRO and APOSCIENCE, Data management will be performed by the CRO. Photos of the diabetic food wounds will be taken by the investigators utilizing 3D-cameras after surgical debridement before every treatment with the Investigational Medicinal Product (IMP). These images will be uploaded to the cloud via internet and checked by APOSCIENCE AG staff for quality. Inspections by regulatory bodies may be performed at any time of the study with the aim to ensure performance is ensuring subject's safety and study integrity based on adherence to the ICH-GCP, local regulatory and ethical standards.
Task 2.4: Sponsor responsibility for clinical study Marsyas II (M1-M24; TL [redacted])
Sponsor responsibility for the phase I/II clinicals study Marsyas II will include, among others, SUSAR management and reporting of clinical study results to authorities. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported by APOSCIENCE to the authorities; clinical study results will be posted according to EMA regulations on the EMA clinical trial portal and database (Clinical Trial Regulation EU No. 536/2014).
Task 2.5: Publication of study results of the clinical study Marsyas II (M22-24. TL [redacted])
Clinical trial findings will be summarized and described within a manuscript, circulated to all investigators before the publication in an open-access scientific journal.
Task 2.6: Internal trainings at APOSCIENCE(M1-M24; TL [redacted])
APOSCIENCE AG will organize internal trainings for APOSCIENCE staff on the topic of Standard Operational Procedures (SOPs), compliance issues and data privacy.

Work package number	3	Lead beneficiary	APO
Work package title	Preparation of alternative indications		
Participant number	1		
Short name of participant	APO		
Person months per participant	44,12		
Start month	1	End month	24

Objectives

- Production and quality control of APOSEC ™ and placebo
- Exploratory research for further treatment indications

WP Leader: [redacted]; Participants: [redacted]

Description of work
Background information
In WP3 it is intended to gather scientific data concerning further possible therapeutic indications for APO-2 and describes the production and quality control of APOSEC™ for MARSYAS II and Ambrosia I. Via its immune-modulatory capacity, APOSEC™ is effective in various indications beside skin wounds, such as acute myocardial infarction, latent myocardial infarction, stroke, and spinal cord injury. This therapeutic effectivity has been proven in small animal models (stroke, spinal cord injury) and large animal models (skin wounds, acute and latent myocardial infarction).
Task 3.1: Production and quality control measures of APOSEC ™ (M1-M9; TL: [redacted])
Production and release testing will be performed at the [redacted], at [redacted] and [redacted]

- At [redacted], apart from sterility testing, cytokine values of IL-8, EGF and TGFβ will be performed. These cytokines serve as proxies to guarantee continual quality, within certain ranges, of the production process.
- [redacted] will test residual moisture, uniformity of mass and reconstitution time of the lyophilisate, and appearance, color, clarity, pH value, osmolality and visible particles of the lyophilisate reconstituted in NaCl according to the European Pharmacopoeia.

- [redacted] will test biological activity of APOSEC and placebo utilizing the potency assays which were developed for that purpose in collaboration with APOSCIENCE AG.

Task 3.2: Development of APO-2 in contact dermatitis for providing efficacy of topical application (M1-24; TL [redacted])

Acute and chronic contact hypersensitivity will be evaluated in a DNFB-mouse model to determine potential beneficial immunomodulatory actions of APOSEC. Special emphasis will be laid on investigating effects of APOSEC on recruitment and activation status of distinct T cell subpopulations reportedly involved in contact hypersensitivity, such as regulatory T cells, CD4+ and CD8+ T cells, and tissue resident memory T-cells. Moreover, it will be investigated whether APOSEC affects mast cell degranulation and dendritic cell maturation and function in the context of contact hypersensitivity. Dendritic cells will furthermore be functionally evaluated by their (in-)ability to stimulate differentiation of CD4+ T cells towards TH1, TH2, TH9, and TH17 lineages.

Task 3.3: Analysis of the efficacy of APOSEC™ on scar formation and tissue remodelling after wounding (M1-24; TL V. Vorstandlechner)

In an *in vitro* approach, APOSEC™ will be studied regarding parameters of scar formation such as morphology, intracellular accumulated secretion of extracellular matrix and conversion into myofibroblasts. These parameters are also investigated in an *ex vivo* human skin model. Moreover, the effects of APOSEC™ on human skin cells will be determined on transcriptome level. The effect of the product on prevention and treatment of scar formation will be evaluated in full-thickness skin wound mouse model.

Work package number	4	Lead beneficiary	APOSCIENCE
Work package title	Data management and IPR		
Participant number	1		
Short name of participant	APO		
Person months per participant	10,28		
Start month	1	End month	24

Objectives

- Data management
- Market research and review of competition
- IPR screening, management and protection
- Defense and nationalization of patent for APOSEC potency assays

WP leader: [redacted]; participants: [redacted]

Description of work

Background information

In December 2017 a patent was requested at the European Patent Office (European Patent Application No. 17209165.4) to protect the IP of the potency assays which were developed in order to test biological activity and shelf life of APOSEC. These potency assays are an integral part of the Good Manufacturing Practice (GMP) APOSEC production process and will, by that function, renew the IP of the APOSEC patents filed in 2008. In WP 3, upon request experimental work will be performed in order to defend the claims of this patent application.

Task 4.1 Data management (M1-M24; TL [redacted]):

To support effective exploitation of any IPR, all relevant data will be collected centrally at APOSCIENCE and continuously reviewed for further processing by an external regulatory agency. The clinical data pertaining to the clinical trial described in WP 2 will be only externally managed by the CRO in full keeping with the applicable regulations. To support the exploitation of any know-how and knowledge generated within this project a data management plan will be established. APOSCIENCE maintains a safe and independent data repository. The data will be stored either within a pass word protected environment with version control and all user access being monitored.

Task 4.2 Market research and clinical environment (M1-M24; TL [redacted]):

APOSCIENCE continuously reviews the market for chronic wounds and clinical trials conducted within regenerative medicine. The scientific programs of international conferences on diabetes and on wound

healing will be screened for presentations of competitor's products. Wound care professionals and heads of wound care units of hospitals will be contacted in order to get updated information on the current state of best practice in wound care. The business plan of APOSCIENCE will be updated, including the most recent market research data as well as new prospective calculations on costs of good for GMP-APOSEC and revenue goals. A strategy for licensing of the APOSEC technology to partners outside of Europe will be designed. (Payments from such licenses will be used for APOSCIENCE's own business development in Europe.) Further appropriate GMP production facilities for APOSEC in European countries will be searched and evaluated. Possible business partners as well as early adopters of APOSEC will be approached at international diabetes and wound care conferences. To support a seamless initiation of a phase III clinical trial after this project the clinical trial sites and other potential early adopters of APOSEC will be kept informed about progress of the clinical development of APOSEC.

Task 4.3: IPR management (M1-M24; TL [redacted]):
In close collaboration with the Patent attorneys Schwarz & Partner H. Ankersmit (COO) will support the project with respect to all IPR measures, including IPR screening, patenting procedures and commercialization of project findings. This will also ensure effective protection of any novel results and support their effective exploitation.

Task 4.4: Defense and nationalization of patent for APOSEC potency assays (M1-M12; TL H. Ankersmit):
The patent for potency assays of APOSEC will be nationalized in the same countries as the original APOSEC patents for APO-1 and APO-2. Upon request by the European Patent Office or other national patent offices experiments will be performed in order to generate data to defend the claims of the European patent application No. 17209165.4.

Task 4.5: Novel patent applications (M1-M24; TL H. Ankersmit):
Composing of novel descriptions for APOSEC patent applications in additional treatment indications in case of suitable scientific findings.

Work package number	5	Lead beneficiary	APO
Work package title	Dissemination and Exploitation		
Participant number	1		
Short name of participant	APO		
Person months per participant	5,8		
Start month	1	End month	24

Objectives

The aim of this work package is to engage relevant stakeholder groups with the project and to establish trust in the project goals and results. To achieve this aim the following objectives were defined:

- The development of a communication strategy to transport key messages and consecutive performance of dissemination activities;
- The creation dissemination material based on appropriately processed information to suit the target groups and key messages identified
- To establish and maintain contact with relevant press and media channels;
- Development of an exploitation plan to ensure the possibility of commercial exploitation and effective translation of the generated know-how.

WP leader: [redacted]; participants: H. Ankersmit

Description of work

Background information

To maximise the impact of the project exploitation is supported by an efficient dissemination of the project results to the relevant stakeholder groups in the project. We have broadly divided the target audience in: the medical research community; clinicians, healthcare providers and patient groups; blood banks; and potential investors. These groups differ with respect to their background and their particular needs and interests possibly addressed by the project.

APOSCIENCE aims at advancing clinical development of APOSEC™ for DFU therapy for marketing approval in the EU and other developed nations.

The steps required for implementation of a phase III clinical trial and subsequent production and marketing of APOSEC™ will be dependent on successful partnering with further blood banks to increase production and a suitable pharma company with expertise in wound healing to support international distribution and fast

market penetration. An exploitation plan covering all steps from IP protection over clinical trial implementation to final market entry and distribution of application of treatment will be established in parallel by APOSCIENCE.
Task 5.1: Preparation of a dissemination plan (M1-M2, TL [redacted]):
A clearly structured plan for disseminating project outcomes to the relevant target audiences will be developed and continuously updated. This plan will: • Identify target audiences • Prepare distribution lists and target group databases • Define key messages • Select the appropriate measures and tools in specific areas of communication • Evaluate risk factors and counter measures. All disseminations will be strictly labelled with the project number and the appropriate acknowledgement of EU-funding through H2020 SME instrument. All dissemination tools will be developed according to an appealing corporate design.
Task 5.2: Website and social media presence (M1-M9; TL H. Ankersmit):
The APOSCIENCE company website will be relaunched to update on project outcomes in collaboration with a professional media agency. The website will be maintained and updated with input from the project. Regular updates through social media (Twitter, Linkedin, Youtube) will spread information beyond the project's website.
Task 5.3: Creating video and graphics for the project (M1-M8; TL H. Ankersmit):
Professional graphics and layouts for leaflets will be produced to target stakeholders accordingly. Flyers, folders, posters and any other print material for professional dissemination of the project outcomes will be developed and distributed at relevant events/occasions. Digital versions of the material will be made available on the website for download.
A video will be developed and made available on the website and on social media describing the therapeutic concept of APOSEC and its market potential. This video will support all communication activities with a professional storytelling to ensure the relevant key messages are reaching the target audience. Video and graphics will be developed in collaboration with a media agency.
Task 5.4: Disseminate progress and results on national and international meetings, through publications and collaboration with relevant scientific societies (M1-M24; TL H. Ankersmit):
During the project life-cycle the team of APOSCIENCE AG will regularly attend national and international congresses and conferences to exchange know-how and results within the biomedical and biotech community. Relevant personal contacts within pharmaceutical industry exist and will be deepened to support partnering. In addition, relevant investors fora, or partnering events and platforms will be attended to expand the existing network.Any research results will be published in open-access peer-reviewed journals after IPR screening.
-Selected events organized by the Alliance for Regenerative Medicine (https://alliancerm.org)
-Annual Meeting of the Austrian Diabetes Association (Österreichische Diabetes Gesellschaft (ÖDG))
-Annual Meeting of the Austrian Wound Association (Österreichische Gesellschaft für Wundbehandlung (AWA))
-Selected events announced by International Diabetes Foundation (https://www.idf.org/global-diabetes-calender.html)
-Annual conference of the European Wound Management Association (EWMA)
-Annual meeting of the Wound Healing Society (http://woundheal.org/Meeting)
-Annual meeting of the European Association for the Study of Diabetes (EASD)
-International Conference on Advances in Skin, Wound Care & Tissue Science (https://woundcare.conferenceseries.com/europe/)
-Europe Bio Partnering Forum (https://ebdgroup.knect365.com/bioeurope/)
-China Bio Partnering Forum (https://ebdgroup.knect365.com/chinabio-partnering/)

It is intended to participate annually two national, two European and one international conferences during project time presenting the APO-2 project.
Task 5.5: Disseminate progress and results via press and handling press enquiries (M1-M24; TL H. Ankersmit,): Press work will be done in cooperation with a public relations agency and relevant information for the press will be professionally prepared and distributed to the appropriate media channels (incl. radio/television by approaching editors of scientific broadcasts).
Task 5.6: Development of an exploitation plan (M1-M24; TL [redacted]): A plan for active and successful development and exploitation of APOSEC^{TM} will be developed based on a dossier on the therapeutic activity. The dossier will be established based on sound preclinical and clinical data package available at the time. The steps undertaken in the development of this plan will be the acquisition of further investors to advance APOSEC^{TM} for phase III in DFU, other indications as well as the development of partnering strategies with external partners to expand production and for fast product development and

market entry.

Work package number	6	Lead beneficiary	APO
Work package title	Management		
Participant number	1		
Short name of participant	APO		
Person months per participant	10,28		
Start month	1	End month	24

Objectives
Overall objective of this WP will be to support the research and dissemination activities of WP 1-6 with an efficient management structure:

- Implementation of various contractors, funders and investors
- Establish effective communication between the project lead and various contractors, funders and investors
- Implementing efficient monitoring and controlling procedures
- Prepare and submit the EU technical and financial reports
- Oversee legal, financial and administrative issues

WP leader: H. Ankersmit; participants members: [redacted]

Description of work APOSCIENCE is a small company working as an organizational hub coordinating the various contributions. The company will be responsible for steering the project and fulfilling the administrative tasks.

Task 6.1: Selection and implementation of third party vendors (M0-2; TL: H. Ankersmit)
In particular, the study will require collaboration with 3rd party vendors. These fall into two categories: general clinical trial methodology, study specific task. The former includes companies offering regulatory services or electronic data capture systems. The latter covers members of the independent data safety monitoring board (DSMB) and the CRO taking the function of the conduct of the trial. .Vendor selection follows general rules. The company providing the best offer (cost-performance ratio) and the essential certifications will get the task (see table 4 subcontracting). Specific role of the provider, responsibilities and costs will be defined in a contract.
Task 6.2: Communication & meetings (M1-24; [redacted]):
The multitude of involved parties such as clinical sites and subcontractors contributing to this project require an efficient communication structure. Modern online communication tools will be used wherever possible to be cost effective. Most of the stakeholders have been working with APOSCIENCE for several years and the professional relationship is rooted in mutual trust, with regular meetings held informally whenever necessary. Telephone conferences with all stakeholders are scheduled at regular intervals of 3 months. Teleconferences with the CRO will take place every 2nd week.
Task 6.3 Preparation and maintenance of legal documents and reports (M1-M24; [redacted]):
APOSCIENCE will be responsible for the maintenance of all legal project documents ensuring that all team members have access to the latest versions of the relevant documents. APOSCIENCE will prepare the mandatory EU technical and financial reports and submit the reports to the EU. Deliverable reports will be made available at the timepoints defined in the work plan. All reports will be centrally stored at APOSCIENCE.
Task 6.4 Monitoring and controlling of project progress (M1-M24; [redacted]):
APOSCIENCE will be in charge of monitoring and controlling project progress against the defined work plan and performance criteria. Work progress will be discussed at internal monthly project meetings and any corrective actions to the work plan will be defined if needed.

Table 3.c: List of Deliverables

Deliverable (number)	Deliverable name	Work package number	Short name of lead participant	Type	Dissemination level	Delivery date in months
D1.1	Updated version of product Dossier for APO-2, APO-1 for topical use available	1	1	R	CO	24
D1.2	Clinical Study Protocol for Ambrosia I submitted to the Austrian health agency AGES	1	1	R	CO	24
D1.3	Documents for the clinical study Ambrosia II completed	1	1	R	CO	24
D2.1	Final Study Report of Marsyas II study	2	2	R	CO	24
D2.2	Reports on clinical study results posted on the EMA clinical trial portal and database	2	2	R	CO	24
D2.3	Publication of the study results in a scientific open access journal	2	2	R	PU	24
D3.1	9 batches of APOSEC have been produced for all clinical and pre-clinical tasks	3	3	R	CO	9
D3.2	APOSEC as treatment for contact dermatitis preclinically evaluated analysis	3	3	R	CO	24
D3.3	APOSEC as treatment for scar formation and tissue remodelling preclinically evaluated analysis	3	3	R	CO	24
D4.1	Business plan updated on market research	4	4	R	CO	10
D4.2	Patent on APOSEC potency assays successfully defended and nationalized in 20 countries	4	4	R	CO	12
D4.3	Novel patent filed at European Patent office	4	4	R	CO	6
D5.1	Dissemination plan established	5	5	R	PU	2
D5.2	Commercial exploitation plan established	5	5	R	CO	24
D5.3	Dissemination of project results via print media, publications, meetings completed	5	5	DEC	PU	24
D5.4	Report on data sharing with potential partners/investors	5	5	R	CO	24
D6.1	Legal project documents continuously maintained	6	6	R	CO	24
D6.2	Minutes of monthly project meetings held	6	6	R	PU	24

Table 3.d: List of milestones

Milestone number	Milestone name	Related WP(s)	Due date (in month)	Means of verification
1	Study report of clinical Phase II "Marsyas II" publicly available on trial registry	1,2	M13	Internal and deliverable report
2	Study report of clinical Phase I "Ambrosia I" publicly available on trial registry	1,3	M19	Internal and deliverable report
3	All necessary contracts with 3rdparties in place	2	M2	Signed Contracts
4	Essential study documents available to all study centers	2	M5	Study start
5	Completion of clinical trial phase II DFU ("Marsyas II") with 120 patients	2,3	M14	Proven safety/ efficacy in 120 patients
6	7 batches of APOSEC have been approved for use in clinical trials	3,4	M10	application
7	Data management plan established	4	M5	Report
8	Kick-off press release published	5	M1	published
9	Project video available	5	M8	online
10	Website relaunched	5	M9	online
11	Implementationof third party vendors	6,5,2,	2	contracts

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.e: Critical risks for implementation

Description of risk	WP(s) involved	Proposed risk-mitigation measures
Emerging disruptive Technologies (low risk)	4	Due to the highly regulated market several years are required to achieve market authorization for a new treatment. Continuous survey of clinical trials for DFU and other chronic wounds, potential competing biotech companies and regular conference participations in the field will further mitigate this risk.
Reimbursement and treaters budget constraints may limit use and penetration (moderate risk)	3	In Europe and US pricing for therapeutics is highly regulated and will be negotiated with regulators resulting in an approved pricing strategy to the national environment. In Europe reimbursement by the
Patent infringement by a third party (low risk)	5	Continuous market watch, selection of inventions to further strengthen the patent portfolio and prolong patent life beyond 2018. According to the current analysis of the current patent situation APOSCIENCE enjoys full FTO and will aggressively protect any potential infringements.
Delayed clinical study progress (low risk)	1	If recruitment of patients is delayed within the study in individual centers, the large number of DFU patients will allow compensatory patient recruitment in other centers.
Study stop due to safety issues	1	With innovative treatments safety issues, which only can be observed when a larger exposure will be achieved in phase 2 and 3 studies, cannot be ruled out. However the risk is low due to extensive preparatory work including 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. The quality systems should ensure that wound care staff will be trained on the safe and appropriate use of the product.
Study fails to show adequate efficacy in range of effect sizes observed (moderate risk)	1	This inherent risk associated with innovative treatments is mitigated by alternative therapeutic options including scarring, moderate contact dermatitis and even systemic indications like myocardial infarction. Moreover, to rescue the lead indication DFU if the MARSYAS II study fails to show efficacy data will be analysed in detail to identify potential subgroups of patients who might benefit from the treatment more reliably in preparation for a second phase II study.
Today´s sole APOSEC™ provider, Blood bank Linz or Sanartis, goes out of business (low risk)	2	APOSCIENCE enjoys a close and trusting partnership with the bloodbank Linz, which is an extraordinarily well run operation. However, if problems should arise parnbering with alternative production to prepare for market entry in Europe and US in a large number will mitigate this risk. Close contact will be established to other blood banks during the project or setup of an own production line will be taken into account.
Regulatory issues with production cannot be fulfilled by new production partner (low risk)	2, 3	Initiating APOSEC production in a large scale production with an experienced global partner in producing blood products will require a lengthy regulatory process to attain the necessary standards and subsequent approval. Nevertheless a global company with extensive experience and expertise should complete this task within the available time frame without major set backs before marketing authorization is attained in 2025.

3.3 Resources

Costs are estimated based on the following budget. Main costs are personnel costs for employing experts when implementing the clinical development program and the preclinical research. Further costs will occur for material as well as other goods and services needed for all development steps within the project. The clinical trial requires subcontracting of tasks to a Clinical Research Organisation and other service providers. In addition production of APOSEC will be subcontracted to the [redacted]. 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.

	RTD	**Management**	**Other**	**Total**
Person months	[redacted]	[redacted]	[redacted]	[redacted]
	RTD	Management	Other	Total costs in €
Personnel	[redacted]	[redacted]	[redacted]	[redacted]
Travel	[redacted]	[redacted]	[redacted]	[redacted]
Consumables	[redacted]	[redacted]	[redacted]	[redacted]
Other goals + services	[redacted]	[redacted]	[redacted]	[redacted]
Indirect cost (25%)				[redacted]
Subtotal				[redacted]
Subcontracting	[redacted]	[redacted]	[redacted]	[redacted]
Total eligible cost	[redacted]	[redacted]	[redacted]	[redacted]
Max Eu contribution *	[redacted]	[redacted]	[redacted]	[redacted]
Requested EU contribution*	[redacted]	[redacted]	[redacted]	[redacted]

***Reimburesemnt rate 70%**

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

The total budget is needed for the implementation of all activities during the time when the SME-2 Instrument will be implemented and furtheron is definitely higher than available EU funding. A mix of investors, public funding and further sources will finance the activities in these two years of EU project duration. The APOSCIENCE AG requests **an EU funding of** [redacted] in order to co-fund these activities.
List of annexe: Clinical Study Report "Marsyas I", Clinical Study Prodocol "Marsyas II", Approval of APOSEC Production by Austrian Regulator AGES, Freedom to Operate Analysis "Isenbruck"
Freedom to Operate Analysis "Kliment", Market Analysis "advanced wound care market – global forecast to 20200

Table 3.f: Summary of staff effort

	WP1	WP2	WP3	WP4	WP5	WP6	Total Person Months per Participant
APOSCIENCE AG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3.g: 'Other direct cost' items (travel, equipment, infrastructure, goods and services)

Participant 1 / APO	**Cost (€)**	**Justification**
Travel	[redacted]	Travel budget for meetings with cooperation and production partners, dissemination, congresses, fairs, events.
Consumables, material costs	[redacted]	Material costs for clinical trials, reconstitution and application device material, laboratory goods
Other goods and services	[redacted]	Insurances, IPR costs, printing costs, dissemination material, Video development, Web design, PR,
Total	[redacted]	

4. Company (or, if applicable: members of the consortium)

4.1. Participants (applicants)
Description of legal entity

APOSCIENCE AG is a biopharmaceutical company headquartered in Vienna. The company is developing innovative therapeutics for regenerative medicine based on the secretome of stressed white blood cells isolated from peripheral blood. This platform technology is termed APOSEC (see explanation video: https://youtu.be/LaSzmzGvxnk). It is patented and benefits from a worldwide freedom to operate.

APOSCIENCE AG was founded in 2008 as a spin off of the Medical University of Vienna and represents a collaborative effort of scientists, product developers, and management in order to bring the patented APOSEC technology into the realm of patient care.
Advancing a novel therapy into clinics is a highly regulated affair that mandates a multidisciplinary approach including e.g. GMP-manufacturing facilities, toxicology, validated potency assays, release testing, and stability programs that lead to an Investigational Medicinal Product Dossier (IMPD) which eventually is approved by the regulatory agencies. In the years 2015-19, the management of APOSCIENCE AG was capable to master all these tasks pertaining to the pharmaceutical product development. The clinical trial phase II in diabetic foot ulcer, which commences in April 2019, will bring forward the proof of concept (PoC) that confirms the developmental work already completed in the recent years. The current team includes a strong management, clinical development team, quality control, and scientific core team. Furthermore, intellectual property management was highly successful in defending the proprietary platform technology.

APOSCIENCE AG is currently funded from private Austrian investors. In addition, the company received multiple grant funds, including from the Austrian Christian Doppler Society (www.cdg.ac.at), and the Austrian Research Promotion Agency (FFG). All research is performed by APOSCIENCE AG in conjunction with the Medical University of Vienna based on an agreement of mutual interest.

An explanation whiteboard video is available online: https://youtu.be/LaSzmzGvxnk

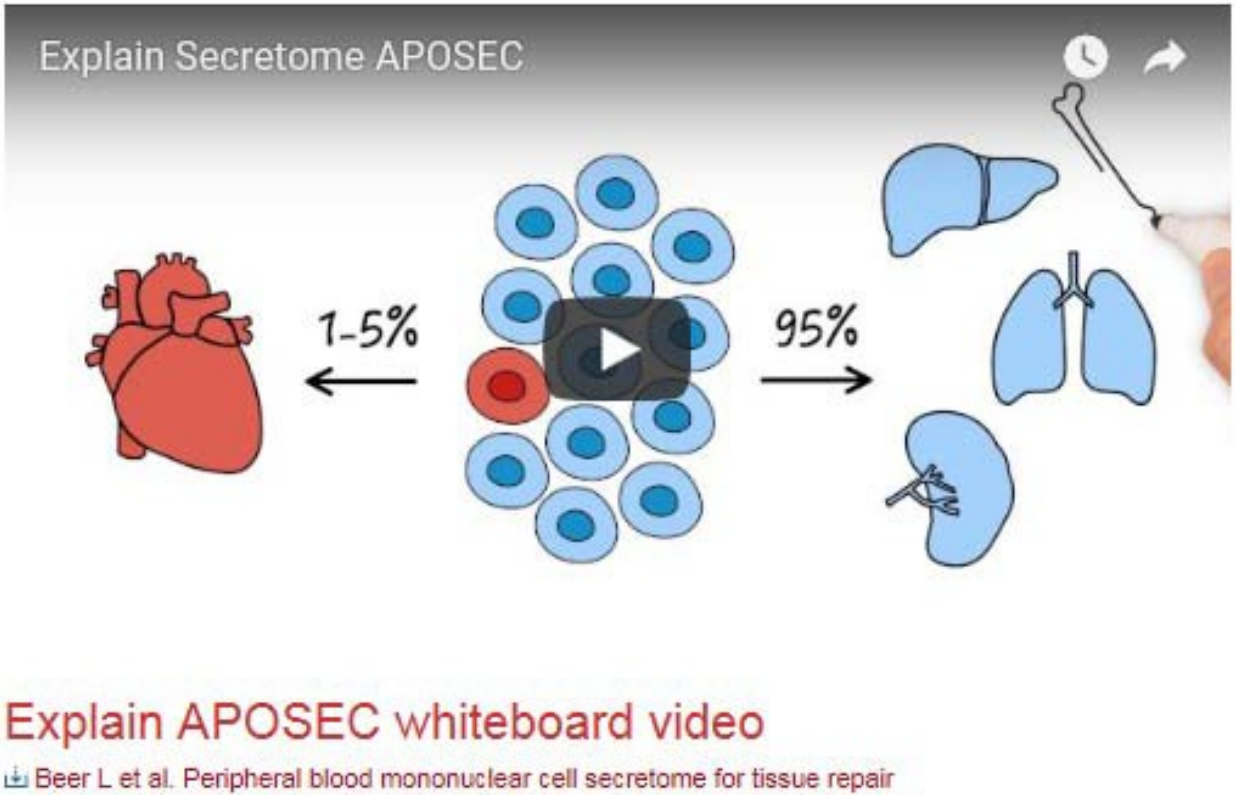

Figure 1: Screenshot of the Explain APOSEC^{TM} whiteboard video

Products

The drug substance APOSEC^{TM} 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^{TM} is the basis for two products (based on two patent families):

- APO-1 APOSEC^{TM} formulation for the treatment of systemic inflammation illnesses caused by hypoxia like acute myocardial infarction, myocarditis, stroke, and spinal cord injury.
- APO-2 APOSEC^{TM} 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).

Team

Univ.-Prof. Hendrik Jan Leonard Ankersmit (male)
Prof. Ankersmit is CSO and COO of Aposcience AG. He is the sole inventor of APOSEC, a novel cell-free, secretome-based therapeutic, and the author of the APOSEC patents. From 2009-15 he was head of the Christian Doppler Laboratory for Cardiac and Thoracic Diagnosis & Regeneration, a private-public partnership grant format of the Christian Doppler Forschungsgesellschaft providing [redacted] € for the latter time period. Together with his scientific collaborators Prof. Ankersmit evaluated the therapeutic effects of APOSEC in different experimental disease entities in small and large animal models and performed research on the contents and modes of action of the drug substance. Furthermore, a GMP production facility was established at the premises of the [redacted] to produce autologous and allogeneic APOSEC as investigational drug product. In 2015 the first secretome-based regenerative medicine trial was conducted under Dr. Ankersmit's supervision utilizing autologous APOSEC. APOSEC was evaluated to be safe and well tolerated by healthy humans in an acute wound model.

Main Tasks
Prof. Ankersmit assumes the ultimate project responsibility, oversees the project, integrates the team and takes initiative wherever it is most needed at the moment. The main task of Prof. Ankersmit will be (i) strategic planning (ii) operative coordination of the product development

Education

1988-1994	[redacted]
1999-2001	
2000-2001	
2002	
2002	
2003	
2003	
2004	
2005	

2006	[redacted]
2009	
2009-2012	

Employments

1994-1995	[redacted]
1995-1996	
1996	
1996-1998	
1999	
1999	
1999	
1999	
1999-2000	
2001	
2002	
2003	
2003	
Since 2008	
Since 2009	

[redacted] **(male)**

[redacted] is CFO of Aposcience. He is a professional of the pharmaceutical industry and brings more than 30 years of management experience in various pharmaceutical companies to Aposcience AG. He worked for companies like [redacted] and [redacted] (now belonging to [redacted]). During his professional life [redacted] collected valuable experiences concerning pharmaceutical product development and regulatory issues, and he established a network of personal contacts in the sector.

Main tasks

The main tasks of [redacted] will be (i) financial issues (ii) contracts (iii) strategic development of the business and (iiii) external relations of Aposcience AG.

Education

1977-1982	[redacted]
1983-1986	

Employments

1986-1994	[redacted]
1994-2000	
2000-2006	

2013-2016	[redacted]
2007-2016	
2016-2018	
Since 2016	

[redacted] is in the function as head of administration of the Prof. Ankersmit's Christian Doppler Laboratory for Cardiac and Thoracic Diagnosis & Regeneration. Since 2016 [redacted] administers the FFG project "APOSEC" and serves as assistant to the Board of Directors of Aposcience AG. [redacted] is responsible for administrative issues concerning finances and human resources and he is concerned with document filing.

Main tasks
The main task of [redacted] is responsible for operative management and the execution of tasks approved by Prof. Ankersmit and [redacted]. His role is to coordinate tasks internally, keep them in evidence, fulfil formal requirements and file documents. [redacted] supports [redacted] by effecting payments, assuming responsibility for human resources issues and for the communication with service providers relevant for the infrastructure of Aposcience AG. [redacted] is also responsible for knowledge management and updating the APOSEC project folder.

Education

1991-1997	[redacted]
1997-2000	
2007-2008	
2009-2011	

Employments

2003-2009	[redacted]
2004-2005	
2011-2015	
Since 2015	
Since 2016	

[redacted] **(male)**
[redacted] joined Aposcience AG as a Postdoc in the context of the FFG project "APOSEC". He is a biologist with extensive experience in laboratory work, especially in the field of stem cells, tissue regeneration and wound healing. and has proven his qualities as scientific co-worker as well as reliability in the execution of managerial tasks. He was involved in the CMC-project (Chemicals Manufacturing and Controls) in which, in collaboration with the [redacted], the GMP production process of APOSEC was analysed, evaluated in terms of risk and appropriate in-process controls were developed. He performed non-GLP (Good Laboratory Practice) stability assays on APOSEC and contributed many research data to the Investigational Medical Product Dossier (IMPD).

Main Tasks
The main task of [redacted] is the management of product development on the regulatory level. Together with our regulatory advisors from [redacted] he will discuss the necessary data for the IMPD (Investigational Medicinal Product Dossier). Together with [redacted] will also assist [redacted] in the coordination of the clinical phase I/II study in DFU Marsyas II on behalf of Aposcience AG as sponsor of the study.

Education

2001-2008	[redacted]
2008-2012	[redacted]

Employments

2012-2014	[redacted]
Since 2015	[redacted]
Since 2016	[redacted]

[redacted] (female)

[redacted] is a highly talented young scientist in the field of biology and laboratory work. For the company, she is working as a scientist and also in a managerial role, having assumed the agenda of quality management. With the assistance of a professional auditor of pharmaceutical companies she has revised the Standard Operational Procedures (SOP) of Aposcience AG making them compliant with the regulatory requirements for pharmaceutical companies performing clinical studies.

Main tasks

The main task of [redacted] will be the leadership of the scientific development of new indications for APOSEC in WP 3. [redacted] has also assumed the responsibility of Quality Management in Aposcience AG.

Education

2002-2010	[redacted]
2010	[redacted]
2010-2013	[redacted]
2013-2015	[redacted]
2015-2018	[redacted]

Employments

2013	[redacted]
2014	[redacted]
2014-2015	[redacted]
2015-2017	[redacted]
Since 2018	[redacted]

[redacted] (feamale)

[redacted] joined Aposcience AG as a PhD student and scientist performing scientific experiments on APOSEC. [redacted] provides experience in clinical research with special focus on burns medicine, burn wound infections and wound healing gained in the Dept. of Plastic Surgery of the Medical University of Vienna.

Main Tasks

The main task of [redacted] will be experimental work within WP 3. She will work on the following projects: (i) to develop experiments evaluating the mechanisms of APOSEC in the wound healing process in the skin (ii) to establish new experimental settings focusing on novel single-cell transcriptome analysis methods (iii) to continue Aposcience's work on characterisation of APOSEC which provides valuable data.

Education

2002-2010	[redacted]
2010-2011	
2011-2017	
Since 2017	

[redacted] (male)

Prof. Mildner works at the Dept. of Dermatology at the Medical University of Vienna. In [redacted] in the field of experimental dermatology. He authored and co-authored ~100 publications, including more than 20 publications on APOSEC. He has been a close scientific collaborator of Prof. Ankersmit since the time of the invention of APOSEC in 2008. [redacted] is, apart from Prof. Ankersmit, the person with the deepest understanding and most comprehensive overview of the scientific background of APOSEC. Together with the employees of Aposcience AG, he has performed and supervised most experiments aimed to characterize the components of APOSEC and their modes of action.

Main tasks

Main tasks of [redacted] will be the support of [redacted] and [redacted] with his scientific knowledge of dermatology and his comprehensive understanding of the APOSEC project in WP3.

Education

1979-1983	[redacted]
1983-1987	
1987-1991	
1992-1994	
1994-1999	
2011-2013	
2016	

Employments

1992-1993	[redacted]
1993-2004	
2004-2013	
2013-2013	
2014-2017	
2016	
Since 2017	

[redacted] (female)

[redacted] is certified in Internal Medicine, Cardiology and Clinical Pharmacology and was awarded Associate Professor in Internal Medicine. She gained experienced in clinical studies at the [redacted]. [redacted] authored the Clinical Study Protocol of the phase I clinical study Marsyas I to evaluate safety and tolerability of APOSEC in healthy human males. She organized the selection processes of the partners of Aposcience AG in the conduct of the clinical study phase I/II, Marsyas II, for the evaluation of APOSEC in the indication diabetic foot ulcers. She will also be responsible for the redaction of the required regulatory documents for the phase I clinical study Ambrosia I to evaluate safety and tolerability of internally administered APOSEC.

Main tasks
Main task of [redacted] is the general management of the clinical phase I/II study in DFU Marsyas II. She has been assigned to the CRO (Clinical Research Organisations) [redacted] (Munich).

Education

1997-1998	[redacted]
1998-1998	[redacted]
1998-2001	[redacted]
2001-2001	[redacted]
2001-2004	[redacted]
2005-2009	[redacted]
2009-2010	[redacted]
2010-2013	[redacted]
2013-2014	[redacted]
2014-2016	[redacted]

Relevant Publications, Patents and Projects

Relevant Publications

Safety and tolerability of topically administered apoptotic PBMC secretome (APOSEC™) 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, Lebherz-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, CA, CN, EP, JP, NZ, RU, ZA, AT, BE, CH, CZ, DE, DK, ES, FR, GB, HU, IT, NL, PL, SE, SK, TR)
- *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, CA, CN, EP, JP, NZ, RU, ZA, 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 APOSEC^{TM} production process.

MARSYAS I: was a phase I (healthy volunteering human males) trial to determine safety and tolerability of the autologous APOSEC^{TM} 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^{TM} can be started by 2018.

Christian Doppler Laboratory for Cardiac & Thoracic Diagnosis and Regeneration (2009-15): Preclinical development of APOSEC^{TM}, 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^{TM}.

Description of any significant infrastructure

- GMP Production process, [redacted] in Austria:
  APOSCIENCE AG has a framework contract with the [redacted] for the production of APOSECTM. 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 APOSECTM for the use in clinical studies. This production plant has the capacity to produce enough APOSECTM 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 [redacted]). From 2019 onwards APOSCIENCE intends to investigate further production sites for APOSEC in the Vienna region (cooperation between APOSCIENCE and the [redacted]).
- [redacted] Framework Agreement
  The relevant infrastructure to perform research is performed at the [redacted], Austria, a long-lasting partner of APOSCIENCE AG. In the non-GLP environment of the Laboratories of the [redacted] basic research on composition and modes of action are investigated, and non-GLP stability tests have been performed. Further intellectual property will be generated based on the involvement of [redacted].
  Office and laboratory rooms including technical equipment are available for APOSCIENCE AG use ruled by the framework program. This includes standard laboratory equipment, ELISA, FACS, molecular biology, proteomics, lipidomics, and cell culture experiments.

4.2 Third parties involved in the project (including subcontracting and use of third party resources)

Please complete, for your company, or for consortia, each participant, the following table (or simply state "No third parties involved", if applicable):

Do you plan to subcontract any tasks? *If yes, describe and justify the tasks to be subcontracted and please **fill in also the table 4**.*	Y
Will any of your linked third parties work in the action tasks? *If yes, describe the third party, the link of the participant to the third party, and describe and justify the foreseen tasks to be performed by the third party.*	N

Will you use contributions in kind provided by third parties? *If yes, describe the third party's contributions.*	N

Does the participant plan to subcontract certain tasks	Y
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.* *A subcontracting budget of* [redacted] *Euro has been planned and calculated related to work-package 1 "clinical trials".* *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.* *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.* *A subcontracting budget of* [redacted] *Euro has been planned and calculated related to work-package 2 "technical innovations".*	
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

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

[redacted]

Table 1

Number	Work Package Number	Task to be subcontracted*	Justification of the 'best value for money'** If you know the subcontractor: explanation why the subcontractor and the price are appropriate. If you don't know the subcontractor: procedure you will follow to ensure best value for money	Name of subcontractor if known	Amount*** (EUR)
1	4	GMP Production of APOSEC and Placebo	[redacted] possesses the only existing GMP production facility for APOSEC certified by the Austrian health agency AGES for the production of APOSEC for clinical studies. [redacted] was audited on behalf of APOSCIENCE AG on 20 April 2018 by [redacted] and [redacted], audit report dated 10 May 2018. The price ensures best value.	[redacted]	[redacted]
2	4	Release testing of APOSEC utilizing APOSEC potency assays	[redacted], in close collaboration with Aposcience AG, has developed potency assays to measure biological activity of APOSEC. These assays will be used for release testing of APOSEC. APOSCIENCE AG possesses the IP of these potency assays. The release tests have to be performed by a certified laboratory. Hence, as APOSCIENCE is not able to perform this task alone, therefore a certified laboratory is needed. To safe a high cost data and technology transfer APOSCIENCE AG decided to assign release testing utilizing potency assays to [redacted]. [redacted] was audited on behalf of [redacted] on 23 July 2018 by [redacted].	[redacted]	[redacted]
3	4	Release testing of APOSEC utilizing test methods according to Pharmacopoe Europea	[redacted] has developed test methods for APOSCIENCE AG to determine residual moisture, pH value, osmolality, uniformity of mass, dissolution time, color, and clarity for APOSEC and placebo. [redacted] was selected in August and September 2013 among three certified laboratories. The other competitors were [redacted]. [redacted] was more than twice as expensive as [redacted]. [redacted] was cost-competitive, however [redacted] excelled in responsiveness and flexibility. As APOSCIENCE AG looked for a partner for various tasks – development of test methods, performance of a GLP stability study, and release testing of APOSEC, these qualities deemed especially important. Release testing utilizing the test methods developed	[redacted]	[redacted]

Number	Work Package Number	Task to be subcontracted*	Justification of the 'best value for money'** If you know the subcontractor: explanation why the subcontractor and the price are appropriate. If you don't know the subcontractor: procedure you will follow to ensure best value for money	Name of subcontractor if known	Amount*** (EUR)
			by [redacted] requires a GLP certified laboratory specialized in these methods. Hence APOSCIENCE is not able to perform release testing alone. APOSCIENCE AG possesses the property rights of the test methods developed by [redacted]; however, the selection of a new partner would require a technology transfer of the test methods. [redacted] was audited on behalf of [redacted] on 1 August 2018 by Mag. [redacted].		
4	2	Preparation of Investigational Medicinal Product Dossier (IMPD), IT-space for the APOSEC project file, development of regulatory strategy for APOSEC, preparation of Scientific Advice with regulatory agency	Collaboration between APOSCIENCE AG and [redacted] startet in 2/2016. [redacted] developed a regulatory strategy for APOSEC. The price ensures best value.	[redacted]	[redacted]
5	3	Conduct of the clinical study Marsyas II, a randomized, placebo-controlled, double-blind study to evaluate safety and dose dependent clinical efficacy of APO-2 at three different doses in patients with diabetic foot ulcer. The clinical study Marsyas II will be performed in 18 study centers in Austria, Germany,	[redacted] was selected by APOSCIENCE AG in an organised process between February and Sept. 2017. At the start, 16 suitable CROs were contacted; mutual confidentiality agreements could be signed with 11 of them, 9 CRO answered APOSCIENCE's Request for Proposal and were invited to a bid defence meeting. The two CRO favoured by APOSCIENCE presented themselves again in a second bid defence meeting and underwent vendor audits on behalf of APOSCIENCE AG. [redacted] was audited by [redacted] on 30 August 2017, study report dated 18 Sept. 2017. Finally, APOSCIENCE decided to partner with [redacted] to perform the clinical study Marsyas II. The study centers were selected by [redacted]. In the process of the CRO selection process a feasibility study was performed by [redacted]. The concern of the feasibility study	[redacted]	[redacted]

Number	Work Package Number	Task to be subcontracted*	Justification of the 'best value for money'** If you know the subcontractor: explanation why the subcontractor and the price are appropriate. If you don't know the subcontractor: procedure you will follow to ensure best value for money	Name of subcontractor if known	Amount*** (EUR)
		Poland and Czech Republic. The Lead-in Phase will be performed in 4 study centres in Austria, the main study in all four countries. The pharmacies of study centres will be responsible for the preparation of APOSEC or placebo for use and will play a role in the randomisation process.	was the availability of patients with diabetic foot ulcers fitting the inclusion criteria of the Marsyas II study in sufficient quantity in order to complete the clinical study. Further concerns were the availability of a pharmacy for IMP preparation in close proximity to the treatment place.		
6	3	Storage and distribution of the Investigational Medicinal Product (IMP) (=APOSEC) and placebo as well as other materials necessary for the clinical study Marsyas II (NuGel, wound dressings, etc.) to the study sites, design and production of labels and packaging for study materials	APOSCIENCE needs a competent partner for storage and distribution of IMP and other study materials to the study sites. [redacted] disposes of appropriate storage rooms and freezers. It was selected out of three companies. Of these three companies one provided labelling for usual pharma distribution, but not for clinical studies. The cost offers of the other two companies were comparable. The decision for [redacted] was based on its location in Vienna and on recommendations. Also [redacted] had already collaborated with [redacted] in a former clinical study. APOSCIENCE has visited [redacted] at its premises. APOSCIENCE received from [redacted] a copy of a GMP audit report on [redacted] of Dec. 2017 from another customer, a copy of the Site Master File and of the operating permit.	[redacted]	[redacted]
7	3	Provision of [redacted] 3D wound measurement system [redacted]. The [redacted]	The selection process of the wound measurement system took place in parallel to the CRO selection process, between February and September 2017. The following wound measurement systems were compared: [redacted],	[redacted]	[redacted]

Number	Work Package Number	Task to be subcontracted*	Justification of the 'best value for money'** If you know the subcontractor: explanation why the subcontractor and the price are appropriate. If you don't know the subcontractor: procedure you will follow to ensure best value for money	Name of subcontractor if known	Amount*** (EUR)
		wound measurement device consists of an iPad with a 3D camera attached. One device will be sent to each study center. The software on the iPad calculates the wound size. The images are sent in anonimized to the eKare cloud space where they are analyzed.	[redacted] is about 5 times as expensive as [redacted], [redacted] is still twice as expensive. [redacted] and [redacted] provide only 2D measurement, hence [redacted] at [redacted] was selected for being equipped with a 3D camera system as there was no comparable measurement system available on the European market.		
8	3	Group of independent experts in the area of wound healing. They will monitor safety data of the clinical study Marsyas I and take the decision after completion of the lead-in phase of the study whether the main study may begin, based on concern for patient safety	The following experts were contacted by APOSCIENCE AG and subcontrated as members of the DSMB: [redacted]	Data Safety Monitoring Board (DSMB)	[redacted]
9	3	[redacted], will help Aposcience in the evaluation of the wound images. Was the wound size measured accurately? Where exactly is the margin of the wound.	[redacted] is an experienced dermatologist at the Dept. of Dermatology of the Medical Department of Vienna. This is a minor financial position.	[redacted] (dermatologist)	[redacted]

* Note that the task to be subcontracted has to be described in section "description of work" of table 3.a "Work Package description"
** Justify per subcontract (i.e subcontracted task or subcontractor). Bear in mind that assurance can only be given on subcontracts that are described in sufficient detail in the proposal.
***Total amount has to match the total amount indicated in Column C (Direct costs of sub-contracting/€), Part A (Proposal submission form), Section 3 (Budget for the proposal)

5. Ethics and security

5.1. Ethics

The Coordinator confirms that there will be **NO**:

- Research activity aimed at human cloning for reproductive purposes.
- Research activity intended to modify the genetic heritage of human beings which could make such changes heritable
- Research activity intended to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer.

Co-ordinator tasks

The co-ordinator shall implement the research project in full respect of the legal and ethical national requirements and code of practice. Wherever authorisations have to be obtained from national bodies, these authorisations shall be considered as documents relevant to the project. Copies of all relevant authorisations shall be submitted to the Commission prior to the commencement of the relevant part of the research project. In addition, the co-ordinator shall take all measures to assure for all contractors that, when dealing with biological material, strict safety procedures are in place in compliance with national and EU regulations on biosafety.

5.2 Regulations and guidelines

The aim of this project is to implement a clinical development program with the lead product APO-2 for healing of diabetic foot ulcer and chronic wounds. Research within APO-2 will be performed in full compliance with European accepted standards regarding Good Clinical Practice (GCP), Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP). Moreover, the proposed research project will adhere to and obey all relevant national and international ethical rules, regulations and conventions as summarized in the following.

Concerning international statutes,

- the Nuremberg Code (1947),
- the Revised Declaration of Helsinki (1975),
- the convention for the protection of human rights and dignity of human with regard to the application of biology and medicine called the "Convention on Human Rights and Biomedicine" (Council of Europe, 1997),
- the "International Ethical Guidelines for Biomedical Research Involving Human Subjects" of the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), 1993 and
- the Recommendation (97) 5 of the Council of Europe on the protection of medical data, are the main international guidelines for medical research. In other aspects, European and national legal and ethical requirements will be fulfilled.

5.1.1 European regulations

Good Clinical Practice

- **Clinical Trials Directive** (Directive 2001/20/EC of 4 April 2001, of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use)
- **Good Clinical Practice Directive** (Directive 2005/28/EC of 8 April 2005 of the European Parliament and of the Council)
- Standards of Good Clinical Practice of the European Union (CPMP/ICH/135/95)

Application Procedure

- EU Eudralex legislation for medicines / Vol 10-Clinical Trials
- Eudract, application to obtain Eudract number

Good Manufacturing Practice

- Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use

Data Protection and Privacy

- The European Data Protection Regulation as of May 25th, 2018 has replaced the directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.
- The European Data Protection Regulation is applicable in all member states to harmonize data privacy laws across Europe.

Research on human biological material incl. blood and blood compounds

- Council Directive 98/79/EC of 27 October 1998 that refers to ethics and requires the respect of the principles of the Convention of the Council of Europe on Human Rights and Biomedicine, with regard to the removal, collection and use of tissues, cells and substances of human origin;
- Directive 2001/83/EC
- Directive 2000/70/EC
- Recommendation 98/463/EC
- Directive 2002/98/EC

Research in animals

- Directive 2010/63/EU of the European Parliament and the Council of 22 September 2010 on the protection of animals used for scientific purposes
- Recommendation 2007/526/EC of 18 June 2007 on guidelines for the accommodation and care of animals used for experimental and other scientific purposes
- EUROPEAN CONVENTION FOR THE PROTECTION OF VERTEBRATE ANIMALS USED FOR EXPERIMENTAL AND OTHER SCIENTIFIC PURPOSES ETS.123 (Strasbourg, 18.III.1986. Text amended according to the provisions of the Protocol (ETS No. 170), as of its entry into force, on 2 December 2005)

5.1.2 National regulations

Following EU member states are involved: Austria, Germany, Poland, Czech Republic
Below the APO-2 research tasks with relevance to national ethical regulations are summarised and grouped by country of conduct:

Country	Ethically relevant research tasks	Study Center	Relevant national regulations	Responsible National Authorities
Austria	Lead in phase Clinical trial Main phase	[redacted], A.ö. [redacted]	Arzneimittelgesetz (AMG) BGBl. I Nr. 146/2009	lead: Ethics Committee of Kepler University (Linz) National Regulatory Board: Austrian Agency for Health and Food Safety AGES/BASG A-1220 Vienna, Spargelfeldgass

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	Research in animals	[redacted]	Tierversuchsgesetz 2012 (TVG 2012)	Bundesministerium für Wissenschaft und Forschung Ref. II/3b (Gentechnik und Tierversuche)
	Collection of patient data and samples	[redacted]	Datenschutzgesetz 2000 (DSG 2000)	
Germany	Clinical trial Main phase	4	BDSG 2018 (Bundesdatenschutz Gesetz); EU – DSGVO; Arzneimittelgesetz (BGBI. I S. 2421)	Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)
Poland	Clinical trial Main Phase	5	EUREC Poland Medical Profession Act of 1996; Pharmaceutical Act of 2004; Act about Medical Devices;	Chief Pharmaceutical Inspectorate
Czech Republic	Clinical trial Main Phase	5	EUREC Czech Republic	State Institute for Drug Control (SUKL)

Table 2: Independent Ethics Committees and regulatory authorities of all study centres

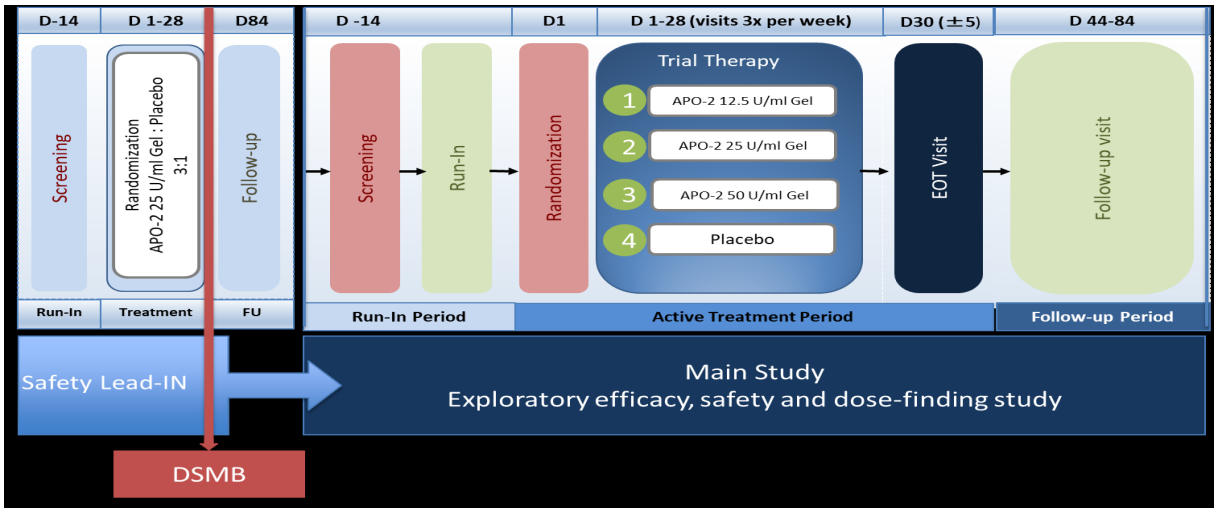
5.2. Research on humans

APOSCIENCE AG intends to perform MARSYAS II, a randomized, placebo-controlled, double-blind study to evaluate safety and dose dependent clinical efficacy of APO-2. In the conduct of this study, the protection of the clinical trial subjects will be the highest priority. This will be ensured by the strict compliance with relevant European and national regulations as identified in Section 5.2 including screening by ethics committees.

5.2.1 Justification of research design

Study design

MARSYAS II, a randomized, placebo-controlled, double-blind study to evaluate safety and dose dependent clinical efficacy of APO-2 at three different doses in patients with diabetic foot ulcer.
Aim of the proposed randomized double-blind multicenter phase II trial will be the evaluation of the efficacy, safety and feasibility of repetitive topical administration of human allogenic APOSEC™ in a total of 120 patients with DFU in a 12weeks (84 day) treatment and follow-up period. This study is preceded by a safety Lead-In period evaluating multiple dose safety of APO-2 in patients with DFU in a cohort of 12 subjects. Subject population and trial design in the safety Lead-In will be identical as the Phase II study. After completion of a 4 weeks treatment period, safety and wound measurement data will be provided to the Data Safety Monitoring Board for evaluation of safety to proceed to phase II study.



Initiation of Clinical sites and implementation of measures
Study conduct will be guided and followed by the CRO [redacted] in close collaboration by the clinical project manager A. Gugerell of APOSCIENCE. The CRO [redacted] is responsible for the preparation of study contracts with the study centers and their pharmacies, for acquiring all necessary permissions from national ethics committees and other authorities, for the preparation of the investigator meeting, for providing the IT-infrastructure for the conduct of the clinical study (eCRF), and for monitoring the study. The CRO will prepare the sites for study start and perform visits at all study centers ensuring availability of all required trial material. This is meant to support sites and applies to all aspects of the study (e.g. clarification of in-/exclusion criteria, sample storage and shipment issues with randomization or eCRF, question to storage/use of study of APO-2. Study visits (foreseen: 17 in person visits) are defined in the study protocol (see annex) and will be done accordingly. Site initiation will also cover relevant trainings of study personnel. Additionally, the CRO will create and maintain the trial master file and deliver it to the APOSCIENCE at the end of the Marsyas II study. [redacted] will also perform statistical analysis and prepare the final study report.

Production and Application of APOSEC™
APOSEC™ is produced at the site of the production partner [redacted], 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 approved for the production of APOSEC for the use in clinical studies 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.

APOSEC™ will be applied in each patient topically 3 times 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 enroll 120 patients in 4 groups of

30 using three dose levels of APO-2 Gel (low dose: 12.5 units (U)/ ml Gel, medium dose: 25 U/ ml Gel, or high dose: 50U/ ml Gel) compared with placebo in subjects with diabetic foot ulcer (DFU).
Complete dissolved lyophilizate (APO-2 and placebo) will be mixed with 3 ml NU-GEL® to achieve a final volume of 4 ml for topical administration. NUGel® is purchased by the sponsor and also provided to the local pharmacy who will blind the IMP after final preparation. The IMP will be packed and labelled according to applicable local regulatory requirements and national laws. The APOSEC™ glass vials will be labelled using stickers provided by [redacted] in English; the pharmacists will label the syringes containing the final IMP after preparation. The local pharmacists and the investigators will be responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of drug records.

Sample size calculation for the primary efficacy endpoint is based on the following assumptions (effect size from the placebo group are driven from published data such as Sheehan 2006, effect size for APO-2 are pure exploratory assumptions):

Significance level = 0.05 (two-sided); Power = 80 %

Group A: 12.5 U/mL APO-2= 45 % wound area reduction at 4 weeks

Group B: 25.0 U/mL APO-2= 50 % wound area reduction at 4 weeks

Group C: 50.0 U/mL APO-2= 55 % wound area reduction at 4 weeks

Group D: Placebo = 40 % wound area reduction at 4 weeks (Sheehan 2006)

Variance of means = 0.003 (calculated based on estimated wound reductions for each group). Standard deviation within groups = 0.156 (estimation based on previous studies and expert opinion). n per group = 23 (Calculated with Nquery Advisor®, Reference: O'Brien, R.G., Muller, K.E. Applied Analysis of Variance in Behavioural Science Marcel Dekker, New York (1993) Chapter 8 pp. 297-344)

Primary endpoints

Wound area reduction after 4 weeks treatment with APO-2 Gel (Visit 14 = end of treatment visit)

- >50 % reduction in wound area after 4 weeks (binary outcome; Visit 14 = end of treatment visit)
- Wound size at baseline, and 1, 2, 3, 4, 6, 8 and 12 weeks after first application of IMP
- Proportion of patients with complete wound closure during 12-week follow-up period (100% re-epithelialization of the wound surface with the absence of drainage)
- Time to complete wound closure
- Recurrence rate of the ulcer during 12-week follow-up period
- Clinical assessment of peripheral neuropathy at baseline, 4, and 12 weeks after first application of IMP
- Number of patients with local adverse events or serious adverse events (SAEs) with causal relationship to study medication
- Evaluation of wound pain by validated visual analogue scale (VAS) at baseline and 1, 2, 3, 4, 6, 8 and 12 weeks after first application of IMP

Evaluation of Quality of Life using Wound QoL questionnaire at baseline, 4, and 12 weeks after first application of IMP.

Data Safety Monitoring Board

A Data Safety Monitoring Board will decide after a safety Lead-In study of 12 subjects performed at the Austrian sites for continuation of the study to the main study (Phase II, proof of concept dose finding study). For the preparation of the main study essential documents including the CSP, the informed consent form translated in local language, the IB, outline of the CRF, insurance certificate, and for the RA the IMPD will be submitted to the Ethics Committees and regulatory authority in Czech Republic, Germany and Poland.

Wound imaging and wound size measurement will be assessed using the eKARE inSight® wound imaging solution at site level and centrally adjudicated by a blinded evaluator. Data for the primary efficacy endpoint will be collected/ will derive from the central adjudication assessment.

Monitoring will be performed by the [redacted], [redacted], Germany, for all sites participating in this study. The CRO will perform data management and statistical analysis for phase II. Descriptive statistics and comparisons between treatment groups with respect to demographic, efficacy, and safety parameters will be applied. All recruited subjects will be included in the primary safety analysis. The CRO will perform statistical analysis finish the study report.

QA measures have different aspects and are applied in two dimensions:

Dimension 1: concerning the conduct of the clinical study Marsyas II
Dimension 2: concerning the APOSCIENCE AG as a company with the goal of building up competence as a pharmaceutical developer which can be corroborated by external audits of the company

IMP storage and distribution
The company [redacted] (Vienna) will support APOSCIENCE AG in the area of storage and distribution of the Investigational Medicinal Drug (IMP), placebo and other materials for the study (such as wound dressing materials).
ABF pharma is specialized in drug storage and distribution; it disposes of adequate storage rooms and refrigerators. Any deviations from the recommended storage conditions will be reported immediately to the sponsor. Use of affected IMP will be suspended until authorization for its continued use has been received from the sponsor.

Quality assurance
Quality assurance for the CRO activities are provided by sponsor and delegates in reviewing all documents that are submitted to external partners. The CRO staff has been informed and trained during several meetings (web-based teleconferences) before study start at CRO level.
QA measures start by training the study personnel in all aspects required for study conduct according to GCP. Regular monitoring visits will ensure 100% source data verification. Audits of sites will complete quality control measures, which, in aggregate, will contribute to study integrity. An eCRF will be designed and validated for the study by the CRO and completed for each patient by trained and authorized personnel at site. Data review process will be performed collaborately between the CRO and APOSCIENCE, Data management will be performed by the CRO. Processes will ensure that data has been entered correctly and accurately from eCRF into database. Checks for logical and structural inconsistencies will be run. Once all data is clean, database will be locked and transferred to study statistician for analysis.
Photos of the diabetic food wounds will be taken by the investigators utilizing 3D-cameras after surgical debridement before every treatment with the Investigational Medicinal Product (IMP). These images will be uploaded to the cloud via internet and checked by APOSCIENCE AG staff for quality.
Inspections by regulatory bodies may be performed at any time of the study with the aim to ensure performance is ensuring subject's safety and study integrity based on adherence to the ICH-GCP, local regulatory and ethical standards.

Data management and statistical management
The CRO [redacted] will perform data management and statistical analysis for phase II. After completion of the data review process and agreement on completely solved queries from SDV and medical data review the data base will be locked. Outputs of the eCRF data will be reviewed and checked for accurateness and consistency by the data management and statistical team before starting the final analysis. During a blinded data review meeting all potential queries will be solved, before unblinding. The database will be merged with data generated externally for wound measurement in a validated data integration process and data will be unblinded by allocation of study participants to treatment group. The statistical analysis will be performed according to the study specific statistical analysis plan. The final analyses will be drafted in a statistical report together with the medical writing team by the CRO who will finish the study report and upon review APOSCIENCE will report results to the trial registry.

Wound measurement

The provider of the wound measurement system is the [redacted]. The system consists of an Apple I-Pad with a 3D-camera attached. The [redacted] wound measurement device is easy to handle for the investigators telling them whether the camera is held too near or too far from the wound; a bar on the screen of the I-Pad signals the prospective quality of the image. The device automatically calculates the surface of the wound and thus can also be used for patient inclusion into the study. The system was selected by APOSCIENCE AG for reasons of price, practicability and data comparability. Hence [redacted]e will be subcontracted for provision of the clinical study Marsyas II with its wound measurement system.

APOSCIENCE AG - sponsor for clinical study Marsyas II
Sponsor responsibility for the phase I/II clinicals study Marsyas II will include, among others, SUSAR management and reporting of clinical study results to authorities.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported by APOSCIENCE to the authorities; clinical study results will be posted according to EMA regulations on the EMA clinical trial portal and database (Clinical Trial Regulation EU No. 536/2014).

Publication of study results of the clinical study Marsyas II
Clinical trial findings will be summarized and described within a manuscript, circulated to all investigators before the publication in an open-access scientific journal.

Internal trainings at APOSCIENCE

APOSCIENCE AG will organize internal trainings for APOSCIENCE staff on the topic of Standard Operational Procedures (SOPs), compliance issues and data privacy.

Informed Consent

In compliance with the Declaration of Helsinki and Art 3(2)(b) of the "Clinical Trials Directive", prior to inclusion of the patient in the study the patient (or his legally acceptable representative) will be given full verbal and written information on the nature, objective, significance, expected benefits, potential risks and consequences of the study by the investigator or authorised designee.

This involves explaining the complex medical diagnoses, prognoses and treatment regimes in simple language, ensuring that patients understand the treatment options, including the advantages and disadvantages of each and answering any questions they may have, to allow the patient to take an informed decision.

The personnel in charge of enrolling patients will conduct interviews with the participants to make sure they understand the issues at stake in the research project. The communication skills of this personnel will be developed and maintained with conscious effort and periodic review to ensure they are able to appropriately explain to the patients all necessary options. A copy of an Informed Consent is uploaded in the Ethical Annex. Translated Versions of the informed Consent will be provided to the study centers in Poland and Czech Republic.

Data protection and Privacy

APO-2 will safeguard the integrity of the study participants. Every precaution will be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject, in accordance with Directive European Data Protection Regulation as of May 25th, 2018 which has been replaced the directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data and with national legislation.

5.3 Research on animals

The number of animals (defined by number of time points, group size) was minimized following national legislation and the principle of 3R (Replace, Reduce and Refine) as a fundamental principle in any work with animals (Directive 2010/63/EU).

Research in animal will be undertaken in Austria and hence will abide to the national legislation, Tierversuchsgesetz 2012, TVG 2012.

5.3.1. Study design

Development of APO-2 in contact dermatitis for providing efficacy of topical application
Acute and chronic contact hypersensitivity will be evaluated in a DNFB-mouse model to determine potential beneficial immunomodulatory actions of APOSEC. Special emphasis will be laid on investigating effects of APOSEC on recruitment and activation status of distinct T cell subpopulations reportedly involved in contact hypersensitivity, such as regulatory T cells, CD4+ and CD8+ T cells, and tissue resident memory T-cells. Moreover, it will be investigated whether APOSEC affects mast cell degranulation and dendritic cell maturation and function in the context of contact hypersensitivity. Mast cell degranulation status will be investigated in DNFB-sensitized mouse ears *in vivo* by histological assessment as well as in IgE-stimulated primary human mast cells in vitro by beta-hexosaminidase assay. Dendritic cells will be generated from human blood-derived monocytes. Dendritic cell maturation will be assessed *in vitro* by evaluating CD1a marker expression after co-incubation with APOSEC. Dendritic cells will furthermore be functionally evaluated by their (in-)ability to stimulate differentiation of CD4+ T cells towards TH1, TH2, TH9, and TH17 lineages.

Analysis of the efficacy of APOSEC™ on scar formation and tissue remodelling after wounding
In an *in vitro* approach, APOSEC™ will be studied regarding parameters of scar formation such as morphology, intracellular accumulated secretion of extracellular matrix and conversion into myofibroblasts. These parameters are also investigated in an *ex vivo* human skin model. Moreover, the effects of APOSEC™ on human skin cells will be determined on transcriptome level. For this aim, the tissue will be digested and the whole cell suspension will be investigated by single cell transcriptomic analysis. The effect of the product on prevention and treatment of scar formation will be evaluated in full-thickness skin wound mouse model.

5.4 Publication of research results

The physicians/researchers conducting the clinical trials are obliged to accurately describe and publish the results of their research. Reports of experimentation not in accordance with the principles laid down in the Declaration of Helsinki should not be accepted for publication.

5.5 Qualified personnel and facilities

APOSCIENCE will ensure that the biomedical research with respect to animal testing or such material is only to be conducted under the supervision of appropriately trained personnel. Similarly, biomedical research with respect to human subjects or material is only to be conducted under the supervision of a clinically competent medical person. The responsibility for the human subject will always rest with a medically qualified person and will never be overruled by the interest in the subject of the research.

All clinical trials will be passed through the necessary ethical committees and relevant permission obtained before the trials are initiated. Clinical trials will be performed at the dedicated facilities selected by FGK Clinical Research and be following GCP regulations. Wherever possible the personnel is named in this proposal, however the nature of these projects might preclude the relevant personnel being named such a long time in advance.

Animal experiments of APOSCIENCE will be performed at the dedicated, state of the art animal facility at the Dept. of Biomedica Research of the Medical University of Vienna. The facility is compliant with all

national regulations applying and is supervised by [redacted]. The responsible person for APOSCIENCE supervising all animal experiments (certified as supervisor for animal experiments) is Univ.-Prof. Dr. Hendrik Ankersmit who will be responsible for guaranteeing proper conduct and control of all experiments according to national regulations. Cell culture experiments will be performed at the Laboratories of the University Clinics of Surgery (FOLAB) of the Medical University of Vienna. The responsible person for APOSCIENCE supervising all cell culture experiments is Univ.-Prof. Dr. Hendrik Ankersmit.

5.6. Security

Please indicate if your project will involve:

☐ activities or results raising security issues: NO

☐ 'EU-classified information' as background or results: NO

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