Project Final Report

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EuroSkinGraft

Logo: 

Project title: A novel generation of skin substitutes to clinically treat a broad spectrum of severe skin defects

Website: http://www.euroskingraft.eu

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VUmc, STICHTING VUMC, Amsterdam, The Netherlands
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1.1 Executive summary

The EuroSkinGraft Consortium was able to successfully perform first-in-man clinical studies applying three, novel skin substitution products on patients. These products are: Novomaix, denovoSkin and denovoDerm. Three patents were filed concerning these products and their production. Novomaix is an easy to apply off the shelf dermal template. DenovoSkin and denovoDerm are bio-engineered personalized skin analogues, hence autologous Advanced Therapy Medicinal Products (ATMPs). As for today, no comparable autologous skin graft is clinically tested in Europe. The significant efforts and progress of the EuroSkinGraft project are expected to have a major impact on both patients and the scientific/medical community.

During the 5 years EuroSkinGraft was running, the following important achievements were made:

- Phase I studies with Novomaix were successfully completed. Phase II studies with Novomaix are close to completion. Novomaix obtained CE marking.
- Phase I studies with denovoSkin were successfully completed (10 patients). Clinical trial phase I for denovoDerm will be continued in collaboration with partner VUMC (Amsterdam and Beverwijk). These studies are planned to begin in Q1 2017.
- Pivotal Phase II studies for denovoSkin have been designed to be compliant with, Swissmedic, European Medicine Agency (EMA) and Federal Drug Administration (FDA) standards.
- Orphan Drug Designation (ODD) for denovoSkin for the treatment of burns were granted by the European Medicine Agency (EMA), by Swissmedic and by the US American Federal Drug Administration (FDA).
- An audit by Swissmedic evaluating the GCP standards and procedures in Zurich was successfully passed.
- A new incubator-like transport box was developed in collaboration with SkyCell AG in Switzerland to allow long term shipping of both skin biopsies and bio-engineered skin grafts.
- A new medical device for the compression of the skin analogues was prototyped, tested and produced.
- Innovative, molecular and biochemical methods were developed to determine the quality of the skin grafts both prior and after transplantation.
- The business plan for the startup CUTISS was prepared and received the Swiss Venture Award for the best business plan in 2015. CUTISS was spun off from the University of Zurich. The CUTISS SA will be incorporated before the end of 2016
- A follow-up project of the EuroSkinGraft was positively evaluated by the newly established Wyss Translational Center Zurich, hence, a sub team of the Tissue Biology Research Unit from University of Zurich received a membership in this prestigious Center. Consequently, pivotal Phase II clinical studies with denovoSkin are now financially supported, and CUTISS can continue the product development of denovoSkin within the Wyss Center.
- In terms of dissemination the work of the Consortium was mentioned at many occassions in TV and newspapers. All scientific and clinical results were published in peer reviewed journals (to see all 26 papers, please consult the project website or the European Commission's Portal (SESAM). Data, findings and statements were also disseminated in the course of public events (such as science days, etc.). A video in which several members of the EuroSkinGraft Consortium were interviewed is available on the major social platforms (Youtube, Linkedin, Facebook and Twitter)

1.2 Summary description of project context and objectives:

Background and Aims

Large full thickness skin defects resulting from burns, congenital giant nevi, disfiguring scars, soft tissue trauma, tumour resection and disease leading to skin necrosis, represent a significant and common clinical problem worldwide (see also Table 1). This problem was so far not solved!

Table 1: Skin defects

Burn injuries		Skin (ST) and soft tissue tumors (STT)	
Worldwide	6 million people injured per year	EU (ST)	100/100'000 inhabitants
EU	4'000 people die per year, 30% are children 5-20/100'000 inhabitants admitted per year 20'000 procedures per year	Germany (STT)	3'000 new diagnoses per year
Germany	1'200 patients with severe injuries per year		

The main challenge encountered is that most autologous skin grafting techniques are based on transplanting split thickness skin (today's gold standard). Split thickness skin contains all of the epidermis, but only remnants of the dermis. This lack of dermal tissue frequently leads to significant scarring, hence to unsatisfying functional and cosmetic results.

Our concept to overcome the obove-mentioned problem is derived from our long standing collaboration between scientists and clinicians. This resulted in the insight that improving the quality of the reconstituted dermis is of paramount importance to significantly ameliorate the clinical outcome. In addition, we are stringently aiming at a one-step surgical procedure (instead of the very common two step procedure that employs acellular templates such as Integra Artificial Skin®). Our pre-clinical studies have revealed that this can be reached with the following products:

1. An acellular template (NovoMaix), which:
    - can be ideally combined with split thickness skin
    - can be applied onto the patient in one single surgical intervention
    - can heal with minimal (or without) scarring and shrinking
2. A tissue engineered, cell-instructive, autologous dermal substitute (denovoDerm), which:
    - can be ideally combined with split thickness skin
    - instantly exerts the cell-instructive properties of a neo-dermis
    - is rapidly and efficiently vascularized
    - is rapidly populated and re-structured by additional mesenchymal cells of the patient
    - develops into a fully functional dermis on the patient
    - can be applied onto the patient in one single surgical intervention
    - heals with minimal (or without) scarring and shrinking
3. A tissue engineered, autologous, dermo-epidermal skin substitute (denovoSkin), which:
    - the dermal component of which is rapidly populated and re-structured by additional mesenchymal cells of the patient
    - is rapidly and efficiently vascularized
    - develops into fully functional full thickness skin on the patient

- can be transplanted without the harvesting of split thickness skin, hence without the generation of temporarily handicapping and painful donor sites.
- can be applied onto the patient in one single surgical intervention
- can heal with minimal (or without) scarring and shrinking

The 3 Products

The three skin substitution products Novomaix, denovoDerm and denovoSkin to be applied in the envisaged clinical trials. (A) Novomaix is an acellular collagen-sponge (scaffold) to be used in combination with autologous split-thickness skin. (B) DenovoDerm is a neodermis-like regeneration graft consisting of a plastically compressed collagen hydrogel into which autologous dermal fibroblasts are seeded. DenovoDerm is to be used in combination with split thickness skin. (C) DenovoSkin is a dermo-epidermal skin substitute based on plastically compressed collagen, seeded with autologous dermal fibroblasts and covered by autologous epidermal keratinocytes.

Table 2: The novel tissue-engineered products for the treatment of large full-thickness skin defects

	NovoMaix	denovoDerm	denovoSkin
Supported by FP6 funding (EuroSTEC)	yes	yes	yes
Material	Porcine collagen type I sponge with unidirectional pores	Compressed bovine collagen type I hydrogel	Compressed bovine collagen type I hydrogel
Human cells	no	Fibroblasts	Fibroblasts and keratinocytes
Used in combination with split-thickness skin	yes	yes	no
Acute or Elective cases	Acute cases	Acute & elective cases	Acute & elective cases
Properties	Turns into a functional dermis and supports split-thickness skin	Turns into a functional dermis and greatly supports split-thickness skin	Turns into a functional dermis and a stratified epidermis
Intellectual Property	Matricel	UZH-TBRU-UCH	UZH-TBRU-UCH
Clinical Indication	Treatment of Full-thickness skin defects	Treatment of Full-thickness skin defects	Treatment of Full-thickness skin defects, chronic ulcers and Vitiligo

Work strategy and general description

The biological basis of the mode of action of these three products is, adequately known (Pontiggia, Biedermann et al. 2009; Biedermann, Pontiggia et al. 2010; Braziulis, Biedermann et al. 2010; Braziulis, Diezi et al. 2010; Schiestl, Biedermann et al. 2010). However, it was highly likely that the clinical use of the products would require adaptations. The research departments in Zurich and Nijmegen as well as Matricel in Aachen were ready to cope with this task.

All three products mentioned above underwent extensive pre-clinical and toxicological testing. Hence, the application of these novel skin-reconstitution products in clinical trials was our central objective. The start of Phase 1 clinical trials was planned 6-9 months after the definitive start of the project. Phase 1 trials were planned to be undertaken

for one year. Thereafter multi-centric Phase 2 trials were planned to be performed in three leading clinical centers in the Netherlands, Germany and Switzerland.

Furthermore, it was the clear intention of the consortium to bring novel products to the European and international markets. This was thought to be initially guided by University-based Technology Transfer Institutions and by two of the involved SMEs. GCP, GMP and IMPD standards were accomplished by the Clinical Trial Centre in Zurich and the Clinical Centres in Amsterdam, Zurich, and Berlin.

Specific scientific and technical objectives

1. One of the most urgent technical objectives was the establishment and optimization of the GMP-production process of the denovoDerm and denovoSkin.

2. Production of NovoMaix and characterization of all cell-free matrix materials used during the clinical trials.

3. Development of the prototype of the collagen compressing device into a clinical/medical device, its production and distribution.

4. Production of denovoDerm and denovoSkin under GMP-conditions for Phase 1 and Phase 2 clinical trials.

5. Histological, biochemical and genetic analyses will be undertaken both, on pre-transplanted skin substitutes and after their transplantation.

Clinical Objectives

A three-armed open prospective controlled and randomised clinical trial shall be performed in three University-based European Burn Centers (in Zurich, Amsterdam, and Berlin) in order to test the dermal template NovoMaix, the tissue engineered dermis denovoDerm as well as the tissue engineered full thickness skin equivalent denovoSkin, in both pediatric and adult patients requiring coverage of full thickness skin defects.

Management structure and procedures

The Project Coordinator ensured the smooth operation of the project and guaranteed that all efforts were focused towards the objectives. With the assistance of ART, he submitted all required progress reports, deliverables, financial statements to the European Commission, and, he was responsible for the proper use of funds and their transfers to participants. The EuroSkinGraft Project Office was established by and based at the coordinator in University Children´s Hospital Zurich and at ART office in Munich. The Project Office at the Coordinator was concerned with the scientific management and the co-ordination of all research activities. The Project Office at ART was responsible for administrative, financial and contractual management and the organisational co-ordination of the project activities.

The General Assembly was in charge of the political and strategic orientation of the project and acted as the arbitration body. It met once a year unless the interest of the project required intermediate meetings. The Steering Committee consisted of all work package leaders and the Coordinator and was in charge of monitoring all activities towards the objective of the project in order to deliver as promised, in due time and in the budget. The Steering Committee met every six months during the funding period. Furthermore, a scientific advisory board was implemented to ensure a high standard of research and monitor the progress of the project by taking part in the annual General Assembly Meetings. The Scientific Advisory Board consisting of 5 internationally recognized experts reviewed the progress of the different work packages. The consortium, in particular the Coordinator put emphasis on ethical standards and regulations. That is why Prof. Wim Dekkers from Radboud University Nijmegen Medical Centre, Netherlands has been asked to be a member of the Ethical Advisory Board. Prof. W. Dekkers agreed to this request. Importantly, a German Patient Organization, CICATRIX e.V. (Gemeinschaft fuer Menschen mit Verbrennungen und Narben) directed by Mrs Regina Heeß, has accepted to regularly participate to consortium annual meetings.

1.3 Description of the main S&T results/foregrounds of EuroSkinGraft

WP01 Accomplishment of GCP, GMP, IMPD and Ethical Standards

The Clinical Trials Center Zurich (01)UZH-CTC, the Clinicians of the University Children's Hospital Zurich and the members of the Tissue Biology Research Unit (Sponsor team) maintained a very close co-operation throughout this five-year project, professionally conducting the clinical trials and accomplishing the international standards for Good Clinical Practice (GCP), Good Manufacturing Practice (GMP) and Investigational Medical Product Dossier (IMPD).

The (01)UZH-CTC was the primary contact for all questions and problems regarding planning, preparation and conduct of the clinical Phase I study with denovoDerm and denovoSkin. It provided templates for the study protocols and quality management documents such as Standard Operating Procedures (SOPs), Working Instructions (WIs) and Related Forms, and supported the writing of the study protocol, the patient information and the informed consent documents according to GCP standards. The (01)UZH-CTC also supported the submission process of the study dossier and several amendments to the local Ethics Committee Zurich and the national authority Swissmedic. Due to the accurate preparation and critical review of study documents by employees of the (01)UZH-CTC, the study documents and all subsequent amendments were approved by these authorities without major claims.

In order to ensure a smooth course of the clinical study, study scenarios were practised with a dummy patient and study processes like transport and handling of study products or the communication with the GMP laboratory were discussed in detail. This required a close collaboration with the clinical team and the Sponsor team. As a result, in-house procedures were well defined and coordinated during the clinical trial, and the clinical staff knew their duties and individual tasks.

During the conduct of the study, the (01)UZH-CTC conducted routine monitoring visits. The general purpose of routine monitoring visits was to verify that the rights and well-being of the participants were protected, that the recorded data were accurate, complete and verifiable from source documents, and that the conduct of the trial was in compliance with the approved protocol and its amendments, with GCP and the applicable regulatory requirements. Monitoring was performed according to the monitoring plan which was established before the beginning of the study. Frequent monitoring visits ensured that internal documentation was up date and queries were resolved, and that safety issues were reported according to timelines, and that protocol non-compliance issues were discussed and resolved. All findings were described in monitoring reports which were sent to the Sponsor to keep him updated.

For the proper data management a working database system (secuTrial®) has been set up and was administered to be ready for programming by Partner (03)UKB and later for data entry by Partner (01c)UZH-UCH, and finally for data export for statistical analysis. Support was successfully given in the form of instructions, troubleshooting and user training to project partners.

In summary, it was evident that the geographical proximity of the laboratory scientists, the clinicians and the Clinical Trials Center Zurich provided optimal circumstances for a fruitful cooperation during this entire project. Open issues, points of discussion and problems could be addressed in uncomplicated face-to-face meetings. The result of the Swissmedic inspection of the Phase I Study with denovoDerm and denovoSkin confirmed that implemented processes worked well, that the conduct of the study complied with applicable national laws and the international Good Clinical Practice guidelines, and that the promising results are reliable.

Perspectives for the future: The collaboration between the Clinical Trials Center Zurich, the Clinical Team of the University Children's Hospital Zurich and the Tissue Biology Research Unit (Sponsor team) will continue beyond the end of the EuroSkinGraft Project. On the one hand, the teams are well-rehearsed and the individuals are used to cooperation. On the other hand, good friendships and team spirit have developed as well as trustful relationships. This is an important prerequisite for the planning, organising and conduct of follow up studies, and eventually to bring the product to the market.

WP02 Production of Novomaix and characterization of matrix materials

The general concept of the EuroSkinGraft project aimed at the development and clinical testing of 3 promising skin substitutes for their safety and effectiveness in acute and elective skin-regenerative therapies. The main objective of work package 02 was the production of all sponge collagen based matrix material (Novomaix) and the characterization of all cell-free matrix materials used during the clinical trials (collagen sponges for Novomaix and collagen hydrogels for denovoDerm & denovoSkin manufacturing).

For dermal scaffolds that are not pre-seeded with cells, rapid population with cell types, such as fibroblasts and endothelial cells is crucial for graft survival and improvement of wound healing. Therefore pore structure (pore size and interconnectivity) and collagen stability are important determinants for the performance of a dermal substitute. Pore generation and its control according to the developed proprietary technology are essential production requirements. In addition, collagen stability is an important parameter to predict its remodelling & degradation behavior in vivo. In order to achieve reproducible product quality and to allow extensive pre-clinical characterization of the different scaffold materials, the following test methods were developed by/available from Partners 04 and 05.

- Nativity characterized by Differential Scanning Calorimetry (DSC) for the collagen sponge and the collagen

hydrogel.

- Purity and Amino Acid Analysis for collagen sponge and hydrogels.
- In-vitro-degradation behavior by collagenase digestion studies of collagen hydrogel and collagen sponge.
- Mechanical properties for the collagen sponge (also to allow comparison to a competitor product with comparable properties).
- Molecular and biochemical analysis of collagen sponge and hydrogel.

Under the responsibility of Partner (05)Matricel, the Novomaix scaffolds were development in compliance with EN ISO 13485/EU Medical Device Directive (MDD) regulations (CE certification in March 2013), production was performed under Good Manufacturing Practice (GMP) conditions and products supplied to the clinical partners, and the prepared regulatory documentation sufficed to obtain approval from the ethical committees for the Phase I and Phase II clinical study with Novomaix.

Based on material-related feedback from the Phase I clinical trial, a scale-up of the Novomaix manufacturing process was initiated to produce larger scaffolds. For the scale-up the directional solidification freezing device needed to be modified to allow freezing of higher volumes of collagen dispersions. All other subsequent steps of freeze-drying and cross-linking had to be adapted as well and the large scaffolds were characterized comprehensively in order to demonstrate equivalence to the smaller size scaffolds.

Combination products of collagen sponge scaffolds and cell-seeded hydrogels hypothetically represent the ideal synergy of the know-how of Partner (01a)UZH-TBRU and Partner (05)Matricel, e.g. combination of fragile hydrogels with stabilizing collagen sponge scaffolds to improve clinical handling properties. For this purpose Partner (05)Matricel developed a freezing process that generates pores in a size that potentially allows the combination with the hydrogel. Analysis of these large pore prototypes by Partner (01a)UZH-TBRU revealed that the constructs showed significant contraction after 7 days in culture. Further in-vitro experiments to investigate the cause of this shrinkage will need to be performed before the combination of Novomaix with collagen hydrogels and keratinocytes can be tested in animal experiments.

Partner (05)Matricel initiated real-time aging studies with the Novomaix scaffolds to investigate the ageing of the scaffolds.

Bottom line:

At the end of the program a documented and validated procedure for the production of Novomaix is available. Novomaix, is a novel generation of collagen sponges, which exhibits unidirectional, perpendicular pores, so that cells and tissue liquids of the wound bed can rapidly enter the sponge, driven by capillary forces. Novomaix is immediately available to be combined with split thickness skin, and transplanted in a one-step surgical procedure onto full thickness skin defects. It will be applied in combination with split thickness skin whenever a full thickness skin defect has to be rapidly treated.

WP03 Development and production of a medical hydrogel compression device

The design program for the Hydrogel compression device began with Design Input activities – Functional Requirements Specification (FRS) and User Requirements Specification (URS) documents were created, using input from partner (01)UZH. Information was also gained from dimensional analysis of an earlier Proof-of-Principle prototype device created by (01)UZH as part of an earlier FP program.

At the project initiation (DoW Annex1 2011-12-05) the list of deliverables required 4 devices to be produced in WP03. The initial intent was for a device that would be entirely re-sterilisable between uses. The compression devices would be located in a GMP facility and be capable of manufacturing 7x7cm sheets of DenovoDerm and DenovoSkin.

Early discussions between (01)UZH and Regulatory Authority SwissMedic, who were required to audit and approve the GMP manufacturing facility, redefined the requirements of certain parts of the design. All components of the device that came in contact with the hydrogel skin graft would be required to be single use sterile disposables. Parts of the device that were not in contact with the skin graft could be re-sterilisable. The design was developed to include single use sterile disposable parts that could be manufactured by injection moulding, using medical grade materials with toxicity clearance to ISO 10993 or USP Class VI. The re-sterilisable parts of the compression device were also specified to be made from materials with ISO 10993 or USP Class VI clearance.

(01)UZH also revised its production plan to accommodate the reprocessing required by the non-disposable parts of the device, and increased its requirements from 4 sets of parts to 5 sets

The critical filtration membrane, which allows fluid to be expelled from the collagen matrix during compression, was sourced from Swiss company Oxyphen, as its performance had already been validated by extensive prototype trials by (01)UZH. Oxyphen were capable of providing the membrane bonded within a sterile single use moulded frame, which would form the core component of the device (the Cell Culture Insert)

The design work on the device resulted in several prototypes that included machined, rapid prototype and 3D printed parts. These prototypes were provided to (01)UZH, along with drawings and 3d illustrations. The feedback from each prototype was used to develop the design of the next prototype

Design control included creating an assembly and part numbering system with revision control. This was essential in dealing with suppliers and obtaining quotations and costs. All parts have a Component Specification listing dimensional and material details, relevant standards and include a manufacturing drawing.

The list below itemises the materials, grades, manufacturer and approval level that applies to all materials used in the EuroSkinGraftGell Compression Machine - Assembly specification MDC-ESG_PRESS-030(current revision)

Description	Part Number	Rev	Material	Manufacturer /supplier	Grade Number	Approval
BASE FRAME	ND-MDC-ESG-017	D	STAINLESS STEEL 316	ALMOND ENG.	AISI 316	ISO 7153-1
TOP TRAY	ND-MDC-ESG-031	F	PEEK (Polyether-ether-ketone)	ENSINGER GmbH	TECAPEEK-MT	ISO 10993
BASE TRAY	ND-MDC-ESG-032	E	PEEK (Polyether-ether-ketone)	ENSINGER GmbH	TECAPEEK-MT	ISO 10993
BLADE HANDLE	ND-MDC-ESG-052	A	PEEK (Polyether-ether-ketone)	ENSINGER GmbH	TECAPEEK-MT	ISO 10993
BLADE FRAME	ND-MDC-ESG-047	B	STAINLESS STEEL 316	ALMOND ENG.	AISI 316	ISO 7153-1
SPACER	ND-MDC-ESG-054	D	STAINLESS STEEL 316	ALMOND ENG.	AISI 316	ISO 7153-1
COMPRESSION WEIGHT	ND-MDC-ESG-023	B	STAINLESS STEEL 316	ALMOND ENG.	AISI 316	ISO 7153-1
PISTON PLATE	D-MDC-ESG-039	B	POLYPROPYLENE + POLYPROPYLENE	BOREALIS	BORMED HD810MO	ISO 10993
POROUS PLATE	D-MDC-ESG-036	C	HDPE	PORVAIR	BIO VYON F	USP Class VI
CELL CULTURE INSERT	D-OXY-ZKE-56cm2	V2	POLYSTYRENE (polystyrol)	OXYPHEN	STYROLUTION PS158N	USP Class VI
INTERFACE FRAME	D-OXY-Interface-56cm2	V2	ABS	OXYPHEN	ABS Cycoloy HC1204HF-8H8D215	USP Class VI / ISO10993
TRANSPORT GRID	D-MDC-ESG-041	A	POLYPROPYLENE	BOREALIS	BORMED HD810MO	ISO 10993
BLADE	D-MDC-ESG-051	C	STAINLESS STEEL 316	GRANTON	ASTM 316	ISO 7153-1

Material selection for the non-disposable parts was driven by a requirement of re-sterilisation at least 500 cycles by autoclaving. Both materials selected for non-disposable parts have capacity for up to 1000 cycles, and were designed to avoid dirt traps that would compromise cleaning. All non-disposable parts are individually identifiable with a unique number code for traceability during use and during sterilisation. All 5 sets of non-disposable parts were initially supplied to (01)UZH in a sterile condition (autoclaved), and have been maintained sterile via a surgical instrument cleaning and sterilising contractor sourced by (01)UZH.

As the design of the system was underway certain additional needs became obvious, requiring design development – especially in the aspects of Transport and Biopsy

Initial plans for locating a compression machine at each clinical centre for local skin graft production were revised due to the logistics and costs of establishing a GMP controlled area in each location. The revised plan is based on centralized GMP skin graft production (in Zurich) with grafts being transported to the relevant clinical centre after completion of their incubation stage.

As a result there was a requirement identified for a method of protecting the grafts during transport. The laboratory incubation T-flask is adequate (though limited), but the graft must be secured during transportation. In response to this need, part D-MDC-ESG-041 Transport Grid was designed and prototyped. Feedback from (01)UZH enabled the design to be developed to the point of quotation for injection moulding as a single use sterile disposable.

The analysis of the compressed hydrogel skin graft is carried out in WP-06, and for this analysis, a biopsy sample needs to be obtained from each skin graft produced. The original graft area was increased from 49cm2 to 56cm2 to provide material for biopsy.

A simple cutting tool was designed from stainless steel and PEEK which could be re-sterilised, and with a single use sterile disposable blade which clipped into the PEEK handle. The biopsy cutter was designed to locate the Oxyphen Cell Culture Insert accurately and cut a 1 cm x 7 cm strip leaving a 7 cm x 7 cm graft ready for implantation.

The design was also developed in parallel with discussions with potential suppliers. The manufacturing process was crucial to both low volume non-disposable parts and higher volume sterile disposable components. All suppliers were selected on the basis of their Quality Management system (QMS), as well as their production capacity. ISO Standards ISO 13485 and ISO 9001 apply to all the suppliers selected.

(06)MDC produced full component specifications for each part, including 2D detail drawings, detailed material specifications, package labelling for the disposable components and inspection criteria for sending to each supplier. (06)MDC also selected and managed all suppliers – Toolmakers, Moulders, Machinists, Packaging & Sterilisation specialists, to ensure that the 5 compression devices were produced on schedule and within budget.

Component specification documents were also supplied to (01)UZH for inclusion in their QMS. The (01)UZH QMS was subject to a successful audit by SwissMedic.

In WP03, deliverables D3.1, D3.2 & D3.3 had all to be completed before WP04 ((01)UZH-TBRU) could begin production of compressed hydrogel skin grafts. Delivery of 5 sets of compression machine parts and the initial small validation batches of disposable components, were used by (01)UZH–TBRU for establishing SOP's and work instructions, and for research.

Volume quantities of parts have been produced, packed, sterilised and supplied to (01)UZH-TBRU, enabling them to produce skin grafts in quantity in support of the Phase I and Phase II clinical trials. TBRU has validated the system by a series of qualification trials and then by manufacturing skin grafts that have been successfully implanted on patients.

Using feedback received from consortium partners, especially (01)UZH, the compression machine and Biopsy cutter have been redesigned as a fully disposable system. This would enable the device to be manufactured in much higher numbers and at lower cost. Using this new design (06)MDChas obtained quotations for mould tooling and unit prices.

Transportation of the skin grafts from laboratory to clinical centre remains a critical area, and, again with input from (01)UZH, (06)MDC has designed and prototyped several transport container systems that would be more space efficient and robust than the current laboratory cell culture T-Flask. These components are being quoted for volume production.

Commercialization of the system – both the equipment and the clinical production facility is highly likely at this time. After completion of FP7 Euroskingraft, (06)MDC intend to work with other members of the consortium on a commercial development of this treatment.

WP04 GMP-production of denovoDerm and denovoSkin and their adaptation to clinical requirements

Data analysis for the Euroskingraft project started on October 1, 2011 and will be concluded with the final report on November 29, 2016.

Objective 1: Establishing and optimizing the GMP-production process ofdenovoDerm and denovoSkin in a brand new GMP-facility.

The GMP production for denovoDerm and denovoSkin was established and the two skin grafts were produced routinely. The GMP facility is located at the Wyss Zurich.

Objective 2: GMP production of the denovoDerm and denovoSkin for the Phase I and Phase II clinical trials.

In 2014, the Phase I safety trials for denovoDerm and denovoSkin began at the University Children's Hospital in Zurich. Until the end of the project, 2/10 denovoDerm were produced and 10/10 denovoSkin were produced. Phase I denovoSkin has been completed and phase II studies will begin soon. DenovoDerm Phase I is still recruiting.

Objective 3: The permanent adaptation of the two types of skin substitutes, denovoDerm and denovoSkin to clinical requirements throughout the duration of the project.

denovoDerm and denovoSkin were permanently adapted to clinical requirements meaning that tools, materials and protocols for their production, culture, validation and shipment were optimized in the last 5 years.

Objective 4: Dissemination of the corresponding data and technology.

In the last 5 years all results of the clinical and scientific data was disseminated via medical, scientific and public conferences. Papers were written and dissemination also occurred via TV, radio and articles in many newspapers.

Future perspectives

Phase I denovoDerm

The production of denovoDerm will continue as further patients will be recruited to complete the phase 1 study. These patients may also be recruited by partner VUMC. Our logistics for the shipment is in place.

Phase II denovoSkin

The Phase II for denovoSkin will be financed by Wyss Zurich. VUmc will still be a partner as a clinical site.

In addition, a start-up, spin off of the University of Zurich, CUTISS AG, is in creation to raise more funds and ensure completion of the initiated programs after the end of EuroSkinGraft, all the way till commercialization.

Conclusion

State of the art GMP production for denovoDerm and denovoSkin was established and optimized. The two grafts were produced for clinical use. Methods, tools, materials and processes were adapted to optimize the production and the logistics around the two products. Dissemination and administration were performed.

WP05 Phase 1 and 2 Clinical Trials

Work Package 5 carried out all the necessary preparations for the Phase I denovoSkin/denovoDerm and Novomaix trials, as well as the Phase II denovoSkin and Novomaix trials, and successfully completed the denovoSkinPhase I clinical trial in Zurich, whilst aiding the execution of the Novomaix Phase I and II clinical trials in the Netherlands. WP5 also carried out a Phase I denovoDerm trial, which could not be completed due to insufficient patient recruitment, despite tremendous efforts from the teams in both Zurich and the Netherlands. Taken together, the achievements of WP5 have demonstrated the following:

Firstly, denovoSkin, a bio-engineered autologoushydrogel-based dermoepidermal skin substitute, manufactured from a small skin biopsy, can be successfully utilized for the coverage of a variety of skin defects in children and adolescents. This study paves the way for future randomized intra-patient controlled phase IIb clinical trials on denovoSkin, covering larger surface areas and objectively comparing the skin analogue to the current standard of care, split thickness skin grafts. The promising results of this clinical trial highlight the potential for this novel bio-engineered skin substitute to become a life-saving therapy in the setting of large skin defects with limited donor sites, such as burns, and we believe will also improve quality of life for patients afflicted with other skin defects.

Secondly, Novomaix, an off-the-shelf acellular dermal regeneration matrix used in conjunction with an overlying autologous split thickness skin graft (STSG), can be successfully utilized for the coverage of full thickness burns in adult patients. From the phase I trial we concluded that the use of Novomaix in combination with STSG for treatment of full thickness wounds was feasible and safe. Moreover, we found indications that scar quality might be better compared to the conventionally treated wounds.

Interim analysis of short term results in the phase II trial did not demonstrate statistically significant improvements over standard treatment yet after analysis of 11/20 patients.

Finally, denovoDerm, a bio-engineered autologous hydrogel-based dermal substitute, manufactured from a small skin biopsy and used in conjunction with an overlying autologous split thickness skin graft, carries significant potential as a dermal substitute, based on the two patients studied. Although we had difficulty recruiting adequate patients for the Phase I trial, we still believe in the merits of denovoDerm as a dermal substitute for the coverage of full thickness skin defects, and we will work to find an alternative funding source to allow for further investigation of this product.

WP06 Biochemical, structural and molecular-biological quality control of skin substitutes

The main objective of work package WP06 was the molecular evaluation of skin substitutes. Performance was assessed using an integrated approach of biochemical analyses, (skin specific) gene expression and morphological characterization. New techniques were developed to allow an objective, unbiased evaluation of skin substitutes. The use of high-density gene expression microarrays may set new standards for the in vivo evaluation of tissue engineered skin substitutes.

More specifically, a novel technology was developed to detect newly formed collagen in skin substitutes both in vitro (using cultured, patient derived cells), and in vivo. This technique allows distinguishing newly formed collagen in skin substitutes prepared from collagen and has been published in Scientific Reports. It has given important insight in the function of cells seeded into the skin substitutes denovoDerm and denovoSkin, and of cells that grow into the collagen scaffold from the surrounding tissue (Novomaix). Newly synthesised human collagen was clearly present in

both denovoDerm and denovoSkin. Using this method it was also shown that in implanted Novomaix (biopsies collected 3 months after implantation) the majority of original Novomaix-collagen was degraded and replaced by newly synthesized collagen.

For the biochemical/molecular-biological evaluation of cultured skin substitutes, it was clearly shown that methods based on RNA and DNA levels are more quantitative and show a higher reproducibility than those based on protein analysis. A paper on this subject will be published in the journal “Burns”.

Using this knowledge, high density gene expression analysis was optimized for small skin biopsies derived from substitutes after implantation using control skin as a reference. A comparison of the gene expression levels of Novomaix treatment and split thickness skin treated wounds to native skin showed that Novomaix resembled native skin somewhat more. No inflammation was observed and the dermis was actively being remodelled. These findings were fully compatible with histology, which also showed absence of inflammation and “young“connective tissue indicating formation of new dermal tissue. Significantly, it showed that comprehensive gene analysis using DNA microarrays is a solid way to analyse the performance of skin substitutes as a whole.

Finally, as a pre-stage for studies on dermal and epidermal compartments, the technology of laser dissection has been optimised to separate dermis from epidermis followed by comprehensive gene expression analysis.

Histology was performed on denovoSkin and denovoDerm after implantation, but due to a lack of available biopsies no gene expression studies have been performed yet.

WP07 Data Analysis

Data analysis for the Euroskingraft project started on October 1, 2011 and will be concluded with the final report on November 29, 2016.

Data were collected in the first part of the project on wound healing complications, short term wound healing outcome and bacteriological status for patients fulfilling the same criteria as the patient groups that were eligible for inclusion in one of the treatment groups of the Euroskingraft trials. These data were collected for each of the three clinics involved, i.e. Kinderspital Zurich, Unfallkrankenhaus Berlin and Red Cross Hospital Beverwijk. These data were considered background data for the safety trials on Novomaix, denovoDerm and denovoSkin.

Data analysis was conducted at VU Medical Center Amsterdam and reported to the consortium partners.

Phase I trials

Next, in collaboration with the clinical groups in Zurich and Berlin, data collection was planned for the Phase I trials on the three products. CRFs were designed and data collections were planned as part of the clinical protocols. Specific attention was paid to training of the clinical groups in the use of the outcome measurement devices Cutometer, Dermaspectrometer and POSAS, as well as reliable methods for assessment of wound healing parameters.

Phase I trial on Novomaix started in Beverwijk and Berlin, data collection was monitored.

Phase I trial on denovoDerm and denovoSkin started according to plans in Zurich.

Data analysis of the Phase I trial Novomaix was conducted by VU Medical Center after completion of the data collection. A report was prepared on the Phase I trial of Novomaix conducted in Beverwijk and Berlin including patients with acute burns and patients undergoing reconstructive surgery for burn scar problems. We concluded that the use of Novomaix in combination with STSG for treatment of full thickness wounds was feasible and safe. Moreover, we found indications that scar quality might be better compared to the conventionally treated wounds.

The Phase I trial on denovoSkin was completed and a safety report was composed. During the inclusion period it was established that inclusion for both denovoDerm and denovoSkin was slower than anticipated. Therefore, the procedure was started to include the centers in Amsterdam and Beverwijk for the Phase I trial on denovoSkin and denovoDerm. Since these products are Advanced Therapy Medicinal Products(ATMPs), not only the relevant Medical Ethical approval was required, but also specific permission from the Dutch Health Inspection Authorities was needed to an Institution with permission (‘fabrikantenvergunning’) for import of these products. The VUmc pharmacy was not licensed for import of ATMPs, therefore another body was required. This was found in the dept. Clinical Pharmacy and Toxicology of Leiden University Medical Center, where two Qualified Persons were found eligible to perform this task.

Before this procedure was finished, total inclusion for denovoSkin Phase I was completed, and the safety report could be finalized, which concluded that no significant safety issues were detected for application of denovoSkin.

Phase II trial preparations were started.

Phase II trials

The clinical trial protocols for Novomaix and denovoSkin were prepared. All regulatory issues for Novomaix Phase II were completed in all clinical Centers. Inclusion was started in Beverwijk and until project end 12 patients were included and 11 patients were treated.

An interim report on treatment data of these 11 patients was prepared by VU Medical Center. In these 11 patients, we were not able to demonstrate significantly improved scar quality by means of the primary outcome parameter, which is skin elasticity measured by Cutometer at 3 months post operation.

Unfortunately, patient inclusion for the Novomaix Phase II trial was hampered in the other clinical centers by engagement in the Phase I studies for denovoDerm and denovoSkin (Zurich) and by late completion of the regulatory procedures (Berlin).

Future perspectives

Follow up

The clinical centers in Zurich and Beverwijk/Amsterdam intend to continue the follow up of the patients presently included in the Phase I/Phase II studies, as indicated in the respective clinical protocols. Data analysis of these data will be further facilitated by VUmc.

Completion of Phase I trial on denovoDerm

Since ATMP import procedures were now complete and established for the Netherlands, we intend to find the means to treat reconstructive patients with denovoDerm in the Netherlands. To pursue this goal, a grant application was filed in the Netherlands. A decision on this application is expected in January 2017.

Completion of Phase II trials

Together with Matricel, we will investigate how the phase II cohort for Novomaix can be completed in the near future.

Furthermore, the (01)UZH-TBRU is presently engaged in composing a new clinical consortium to conduct the phase II trial on denovoSkin. VUmc will be involved to assist in finalizing the clinical protocols, data collection and data analysis.

Conclusion

In this project, safety trials were conducted for a Medical Device dermal replacement product and two skin constructs consisting of cell seeded Advanced Therapy Medicinal Products. Safe application was established for two of the three test products, while the safety evaluation of the third skin construct is still ongoing and could not be finalized within the project period.

For the medical device construct, a Phase II effectivity study was started. Interim analysis after treatment of 11/20 patients was conducted, but no significant improvement of scar quality could be demonstrated yet.

Although no effectivity data on denovoSkin or denovoDerm are available yet, the results on the patients in the safety trial looked promising. Therefore, efforts to collect the effectivity data will continue.

WP08 Data Management

The objectives of WP 08 Data Management could be shortest described as “the usual ones” in Clinical Trials. These would be documenting the trial and ensuring data quality. These goals are generally, and in this project were, achieved through the following strategies and procedures:

- Collecting the necessary information to construct an eCRF from study coordinator, monitor, clinical investigators and sponsor associates.
- Implementing the resulting list of variables with its proper attributes in a clinically feasible and methodologically sound eCRF.

- Designing a database that reflects the flow of data accumulation in the respective trial.
- Testing and validating this database with the members of the clinical team consisting of study coordinator and clinical investigators.
- Defining data base roles and resources for data entry, monitoring and data export according to the specific characteristics of the respective trial.
- Describing and defining all the relevant aspects of data flow, data entry, responsibilities, basic situation and goals of the data management process in the data management plan as an authoritative study document.
- Teaching the general and study-specific functioning of the database to study coordinator and investigators to ensure its proper use.
- Keeping the data base up to date – reacting to amendments of the study protocol relevant to study documentation as well as to corrections that arise not before the database is used to enter real study patient data. Also introducing new investigators to the database and excluding investigators leaving the project.
- For data export, checking carefully the study protocol (and additional documents, if existing) regarding the statements on which data has to be extracted for the statistical analysis.
- Exporting the data for statistical analysis in format the statistician has warranted using the export routines provided by the study software.
- Checking all data used in the statistical analyses for completeness, evaluating the data quality and formulating the appropriate queries to the monitor in case of incompleteness (which did not happen in the project at hand).
- Making the data available to the statistician concerned with the analysis of the study data.

In this project, UKB worked on the majority of the tasks mentioned above. (01)UZH-CTC and (01)UZH-UCH delivered nonetheless invaluable input. (01)UZH-CTC provided IT and SOP infrastructure, whereas (01)UZH-UCH gave the basic input for and helped shaping the eCRF.

All tasks above were fulfilled for the denovoDerm / denovoSkin-phase I-study, with the data export only for study of the clinical phase of denovoSkin patients.

1.4 The potential impact

Socio-economic impact and the wider societal implications of the project

Contribution to Community and social objectives

In contrast to the presently most common, clinically applied, acellular dermal template Integra Artificial Skin, the application of which requires two operations (a second operation three weeks after the first one) all three skin substitution products presented here (NovoMaix, denovoDerm and denovoSkin) are applied in only one surgical intervention. This means a significantly reduced burden to patients, their relatives, and certainly a reduced workload for the teams performing these operations.

Our product, NovoMaix, is a novel generation of collagen sponges, which exhibits unidirectional, perpendicular pores, so that cells and tissue liquids of the wound bed can rapidly enter the sponge, driven by capillary forces. Thus, NovoMaix is rapidly populated by mesenchymal and other cell types. Pre-clinical and clinical data show that scarring and shrinking is minimal, suggesting that NovoMaix has an enormous potential as an off the shelf product to be applied in one-step skin reconstitutions.

DenovoDerm and denovoSkin, can be applied in one surgical intervention. Both substitutes exhibit the structure and function of skin immediately after their transplantation. The medical impact here is the reliable take of these substitutes, and their rapid transition into functional human skin. With both products a neodermis is reconstituted in its full thickness. Using denovoSkin, no split-thickness skin donor sites will be created, which means that significant surgical trauma including all eventually associated morbidity is avoided. Generally and most importantly, the qualities of life of a large group of patients will significantly improve. DenovoSkin is also expected to be an excellent skin substitute to be used to treat chronic wounds (ulcera). In addition, the keratinocytes in denovoSkin may be combined in a distinct ratio with autologous melanocytes to treat certain forms of Vitiligo, in which skin pigment has disappeared due to an autoimmune process.

From the economic point of view, potential users of the three novel products are burn surgeons, plastic reconstructive, and aesthetic surgeons and dermatologists. Clinical application of these novel products is expected to significantly reduce common and central clinical problems. All three skin substitution products (NovoMaix, denovoDerm and denovoSkin) can be applied in only one surgical intervention. Already this means a significant reduction of the economic burden.

Our results show that skin substitutes, such as denovoSkin grow to the same degree as a certain the body site of a child does. Thus, the problems we presently have in particular at the joints of growing children do not seem to occur. Also this will significantly reduce secondary surgical interventions and therefore costs.

Patents on the skin substitutes as well as on the hydrogel compression device are already filed. The hydrogel compression device contains disposable elements. Also these will be patented and separately distributed and sold on the European, perhaps world market.

Commercial marketing of devices, matrix templates and skin substitutes is envisaged.

A costing program has run in parallel with the clinical evaluation of the devices, matrix templates and skin substitutes, to obtain commercial quotations for the manufacture of these products in actual market volumes. The results of this costing program are available and will enable potential investors to quantify the investment needed to commercially exploit these products.

Volume sales will be via a spin off company CUTISS formed to commercially exploit the various products through a conventional manufacturing & sales business model.

Main dissemination activities and exploitation of results

The results of the research in EuroSkinGraft were made available to the larger scientific community via peer-reviewed publications in scientific journals, presentation on the EuroSkinGraft website, presentations and posters at different congresses and symposia, such as at the TERMIS world an EU chapter meetings.

The main results of EuroSkinGraft project were published in high ranked journals. From the 26 publications over the five years we can cite the following representative papers which best describe the major scientific achievements:

Marino D1, Luginbühl J, Scola S, Meuli M, Reichmann E. Bioengineering dermo-epidermal skin grafts with blood and lymphatic capillaries. SciTransl Med. 2014 Jan 29;6(221):221ra14.

Oostendorp C1, Uijtdewilligen PJ1, Versteeg EM1, Hafmans TG1, van den Bogaard EH2, de Jonge PK3, Pirayesh A, Von den Hoff JW4, Reichmann E5, Daamen WF1, van Kuppevelt TH1. Visualisation of newly synthesised collagen in vitro and in vivo.Sci Rep. 2016 Jan 7;6:18780.

Klar AS, Güven S, Biedermann T, Luginbühl J, Böttcher-Haberzeth S, Meuli-Simmen C, Meuli M, Martin I, Scherberich A, Reichmann E. Tissue-engineered dermo-epidermal skin grafts prevascularized with adipose-derived cells. Biomaterials. 2014 Jun;35(19):5065-78.

All the other publications are mentioned on the project website and also in the European Commission Portal (SESAM).

On the 5th September 2016 at the premises of University Children´s Hospital in Zurich, a final EuroSkinGraft event was organized in the form of a public Scientific Symposium.The Symposium was very well visited, more than 70 participants were registered, and led to interesting scientific discussions on the main topics of EuroSkinGraft opening a lot of opportunities for future collaborations and proposals.

The following internationally renowned speakers presented their talks:

Prof.Dr. Sabine Werner, Head, Institute of Molecular Health Sciences, ETH Zurich, Switzerland

"Stromal-epithelial interaction in skin homeostasis and repair"

Dr. Yuval Rinkevich, Head, Cellular Therapeutics in Chronic Lung Disease Research Group, Comprehensive PneumologyCenter, Institute of Lung Biology and Disease, Helmholtz Center Munich, Germany

"Cell lineage perspectives of skin scarring"

Prof.Dr. Lukas Sommer, Head, Division of Cell and Developmental Biology, Institute of Anatomy, University of Zurich, Switzerland

"The role of peripheral nerve cells in wound healing"

Prof.Dr. Colin Jahoda, Professor, School of Biological and Biomedical Sciences, Durham University, UK

"Hair follicle-derived dermal cells in skin and hair follicle models, and skin and appendage regeneration"

Prof.Dr. Enrique Amaya, Professor, Division of Cell Matrix Biology & Regenerative Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, UK

"What can the frog teach us about perfect tissue repair and regeneration?"

Dr.Toin H. van Kuppevelt, Head, Matrix Biochemistry Group, Department of Biochemistry, Radboud University Nijmegen Medical Center, The Netherlands

"New methods for the evaluation of skin substitutes"

Dr. Ingo Heschel, Managing Director, Matricel GmbH, Herzogenrath, Germany

"Development, characterization, production and achievements with the acellular collagen-sponge based dermal substitute Novomaix"

Mr. Jerry Donnan, Director and Design Engineer, The Medical Device Company Ltd., Edinburgh, UK

"Making tools for scientists- the design & manufacture of a tissue compression device"

To all these we would like to mention the very well-structured and comprising presentations about EuroSkinGraft achievements from :

Prof. Ernst Reichmann, Head, Tissue Biology Research Unit, Department of Surgery, University Children's Hospital Zurich

"From EuroSkinGraft via basic research and bio-engineered skin to clinical trials"

Dr. Kim Gardien, Physician Researcher, Plastic, Reconstructive, and Hand Surgery Department, VU University Medical Center, Amsterdam and Dutch Burn Center, Red Cross Hospital, Beverwijk, The Netherlands

"A novel dermal substitute in patients: Safe? Feasible? Improved burn scars?"

PD Dr. Clemens Schiestl, Head, Pediatric Burn Center, Plastic and Reconstructive Surgery, University Children's Hospital Zurich, Switzerland

"Best wishes from the petri dishes- skingineering from bench to bedside"

Prof. Dr. Martin Meuli, Surgeon-in-Chief, Chairman, Department of Surgery, University Children's Hospital Zurich, Switzerland

"Skingineering in human patients- preliminary results and perspectives"

The full programm can be found here: http://www.euroskingraft.eu/fileadmin/websites/euroskingraft/media/Symposium_Agenda_September_2016_EuroSkinGraft_20160830.pdf

The public panel session in the end offered the possibilities to come to open discussions with the patients' representatives and also potential stakeholders and decision makers in the field of skin transplantation.

After the public Scientific Symposium a Press Conference took place. Prof. E. Reichmann, Prof.Dr. Martin Meuli and Dr. Clemens Schiestl talked about the major achievements in the field of skin transplantation and also in the EuroSkinGraft Project. This Press Conference has generated a lot of articles in newspapers and TV news spots, like Swiss TV (SRF) in the "Tagesschau" http://www.srf.ch/news/schweiz/labor-haut-erstmals-kindern-transplantiert, Kinderspital Zürich on 6 September http://www.kispi.uzh.ch/de/medien/medienmitteilungen/2016/Documents/Medienmitteilung_EuroSkinGraft.pdf, TagesAnzeiger Zürich http://www.tagesanzeiger.ch/wissen/medizin-und-psychologie/eine-zweite-haut-aus-dem-labor/story/23262384, Tissue Biology Research Unit Press http://www.skingineering.ch/news-and-media/press-conference-september-6th-2016.html, http://www.tagesanzeiger.ch/wissen/medizin-und-psychologie/Der-Hautmacher/story/23713297

The EuroSkinGraft homepage http://www.euroskingraft.eu/the-group/ is up to date and contains public information about the project meetings, publications, video interviews. So the public-accessible area includes information for specialists (academic and industrial researchers), as well as information for the press and for the lay public.

Medical doctors, scientist and also the lay public may watch the video showing the EuroSkinGraft group leaders talking about their contributions to the EuroSkinGraft project and their estimations for the future of skin regeneration.

The clinical results in particular with denovoSkin are outstandingly encouraging (to judge on denovoDerm more seriously, more patients have to be treated).This is why we are looking forward to clinically apply denovoSkin in the course of the ODDs received by the EMA, the FDA and Swissmedic, to treat burn patients in Europe, the USA and Switzerland. The facilitated market access permitted by these ODDs (to treat a given group of patients), we expect to help us collaborating with selected medical centers and having significant insights on how to optimally produce, ship and use this particular bio-engineered skin graft. We were already asked by burn and plastic surgeons and by dermatologists to extend the application of denovoskin to patients suffering from disfiguring scars, congenital nevi, skin tumors, chronic wounds, epidermolysis bullosa, spina bifida, vitiligo (which is just a problem of the epidermis) and for gender reconstitution operations. It is encouraging to us to see such a broad spectrum of clinical applications waiting for the use of denovoSkin.

Outlook and future research

The EuroSkinGraft Consortium managed to complete Phase I studies with Novomaix, likewise to almost complete Phase II studies with Novomaix, and to complete Phase I studies with denovoSkin.

In the near future: Phase II studies with denovoSkin will be undertaken as a continuation the EuroSkinGraft project. However, these Phase II studies will be more demanding than initially planned, as they will be undertaken as pivotal studies and in at least four different clinical centers (most likely also in one US American center).

DenovoDerm Phase I studies will be continued in Amsterdam. After the completion of these studies it will be decided whether denovoDerm Phase II studies will be performed.

As both Phase I and II clinical studies will continue as initially planned (after the end of the EuroSkinGraft project) we do not see any impact of deviations of Milestones and Deliverables (on the long run). The partners in the Netherlands and in Zurich will continue their collaboration with the goal to make denovoSkin, denovoDerm and Novomaix available to a large group of patients, both in Europe and the USA. The envolved partners anticipate that the startup CUTISS (which came into being as a consequence of EuroSkinGraft) will play a significant role in reaching this goal. They are presently working under conditions and in an environment that greatly support their efforts. Based on these pre-conditions they are highly motivated to make this dream come true.

Section 2 – Use and dissemination of foreground

Please see SESAM.

Section 3 – Report on societal implications

Please see SESAM.