19 November 2015
EMA/833320/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Episalvan

International non-proprietary name: birch bark extract

Procedure No. EMEA/H/C/003938/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

µg	Micrograms
AE	Adverse event
AK	Actinic keratosis
API	Active Pharmaceutical Ingredient
CFU	Colony forming unit
CI	Confidence interval
CNS	Central Nervous System
COX-2	Cyclooxygenase-2
CRO	Contract research organisation
DER	Drug extract ratio
EB	Epidermolysis Bullosa
EC_{50}	Effective Concentration, 50 %
eCRF	Electronic case report form
EoT	End of treatment
F	Female
FID	Flame Ionization Detection
GC	Gas Chromatography
GLP	Good Laboratory Practice
h	Hours
hPK	Human Primary Keratinocytes
HPLC	High Performance Liquid Chromatography
HuR	ELAV-like Protein 1, Human Antigen R
i.p.	Intraperitoneal
IC_{50}	Half Maximal Inhibitory Concentration
IL	Interleukin
INV	Involucrin
ITT	Intention to treat set
IWRS	Interactive Web Response System
kg	Kilograms
KRT10	Keratin 10
LD_{50}	Median Lethal Dose
LLOQ	Lower Limit of Quantification
M	Male
MAPK	Mitogen-activated protein kinases
mbar	milli bar
MedDRA	Medical Dictionary for Regulatory Activities
min	Minute
ml	Mililiter

MS	Mass Spectrometry
MTWDC	Mean time to wound dressing change
n.d.	not determined
n/a	not applicable
NF-κB	Nuclear Factor κB
ng	Nanograms
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NRU	Neutral Red Uptake
PBS	Phosphate buffered saline
PEG	Polyethylene Glycol
Ph. Eur.	Pharmacopoeia Europaea (European Pharmacopoeia)
PIF	Photo-Irritation-Factor
PIP	Paediatric Investigational Plan
PK	Pharmacokinetics
PP	Per protocol set
s.c.	Subcutaneous
SAE	Serious adverse event
SAWP	Scientific advice working party
SD	Standard Deviation
SEM	Standard Error of the Mean
SmPC	Summary of Product Characteristics
SOC	System organ class
STAT3	Signal Transducer and Activator of Transcription 3
STSG	Split-thickness skin graft
$t_{1/2}$	Half-Life
TBSA	Total body surface area
TE	Triterpene dry extract from birch bark, i. e., i.e., API of Episalvan
TGM	Transglutaminase
TK	Toxicokinetics
t_{max}	Time at which maximum plasma concentration is observed
TPP	Treatment per protocol set
TRPC	Transient Receptor Potential Superfamily of Cation Channels
USP	United States Pharmacopeia
UV	Ultraviolet
W/W	Weight per weight
WHM	Wound Healing Model

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Birken AG submitted on 10 October 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Episalvan, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 February 2014.

The applicant applied for the following indication: Treatment in adults for accelerated healing of partial thickness wounds.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that Birch bark extract from *Betula pendula* Roth, *Betula pubescens* Ehrh. as well as hybrids of both species with n-heptane as extraction solvent was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0156/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0156/2013 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

New active Substance status

The applicant requested the active substance birch bark extract from *Betula pendula* Roth, *Betula pubescens* Ehrh. as well as hybrids of both species with n-heptane as extraction solvent contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 17 November 2011. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: Natalja Karpova

- The application was received by the EMA on 10 October 2014.
- The procedure started on 29 October 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 January 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 22 January 2015.
- During the meeting on 26 February 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 February 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 July 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 August 2015.
- During the CHMP meeting on 24 September 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 October 2015.
- During the meeting on 19 November 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Episalvan.
- The CHMP adopted a report on similarity of Episalvan with NexoBrid on 23 April 2015.

2. Scientific discussion

2.1. Introduction

Human skin consists of three layers, epidermis, dermis and subcutis. Epidermis and dermis are separated by a thin sheet of fibres called the basement membrane. Above the basement membrane basal keratinocytes of the stratum basale are located which continuously regenerate the epidermis. Based on their prominent abundance in the epidermis keratinocytes are of paramount importance for the re-epithelialisation of partial thickness wounds.

A skin wound is a type of injury in which skin is torn, cut or punctured, or where blunt force trauma causes a contusion. Generally, wounds can be classified according to their depth based on the skin layers involved:

- Partial thickness wounds:
    - Superficial partial thickness wounds involve loss of epidermis and extend into the dermis. The basement membrane is lost, but skin adnexae remain.
    - Deep partial thickness wounds (also termed: deep-dermal wounds) involve a near-complete loss of dermis and are associated with a reduced number of skin adnexae.
- Full thickness wounds involve the entire dermis, extend into the subcutis and are not able to heal spontaneously within 3 weeks. Full thickness wounds typically receive surgical intervention (skin grafting) to avoid excessive scarring and to promote a timely wound closure (Wolfe, Roi et al. 1983; Black and Black 2012).

Partial thickness wounds are able to regenerate the epidermis and (depending on wound depth) to heal within 1 to 3 weeks with minimal or no scarring. Partial thickness wounds can have an iatrogenic cause (e.g., split-thickness skin grafting) or can be caused by accident (e.g., burns, abrasions, contusions).

Split-thickness skin graft (STSG) donor site wounds

Split-thickness skin grafting is the transplantation of a patient's own cutaneous tissue harvested from an area of normal healthy skin, used to replace an area of skin loss or injury and is one of the most commonly performed operations in plastic and reconstructive surgery. The partial thickness wound of the STSG graft donor site heals by re-epithelialisation. Often the graft donor site is slow to heal, and it is the source of most postoperative pain.

The STSG donor site, as an iatrogenic partial thickness wound created in a surgical setting, represents a highly standardised, homogeneous and clean wound. It is therefore considered a model wound for partial thickness wounds of all types. Consequently, STSG donor sites can be used in clinical studies to generate insights into wound healing which are of relevance to all partial thickness wounds.

Burn wounds

Burn injury can lead to severe morbidity and significant mortality and also has a considerable health-economic impact. Burns are classified according to the depth of injury into 1st degree (epidermal with redness and erythema), Grade 2a (superficial partial thickness extending to dermis), Grade 2b (deep partial thickness extending to dermis, and unable to regenerate epidermis within 3 weeks), 3rd degree (full thickness, extending through entire dermis) and 4th degree (charred). Epithelialisation and wound closure for Grade 2a burns generally occurs within 7 to 17 days. The current standard of care for Grade 2a burn wounds

is that the wound is either covered with an alloplastic epidermal substitute without need for dressing changes (which may disrupt the healing process) or with antiseptics (e.g., octenidine, polyhexanide) and fatty gauze or other dressings which enables evaluation of the wound at regular changes of the wound dressing.

Despite major advances in recent decades in the understanding of the mechanism of wound healing on a molecular level, treatment options remain limited. Standard of care for treatment of partial thickness wounds is dominated by medical devices, mostly different types of wound dressing. These aim to protect the wound, to provide an optimal environment for endogenous wound healing, and to reduce the risk of complications (e.g. infections).

Partial thickness wounds are very painful, much more so than deep wounds, because sensory nerve endings are abundant in the remaining dermal tissue in the wound bed. Besides being very painful, there is an increased risk of infection due to the compromised skin barrier. Thus, any acceleration in wound healing would meet an important medical need. An accelerated rate of wound healing would also be expected to be associated with a lower risk of scarring and hypopigmentation, which are common features of delayed wound healing.

About the product

Episalvan gel contains dry extract from *Betulae* cortex (birch bark).

The patient population studied with Episalvan gel included patients with treatment of partial thickness wounds, including both superficial partial thickness and deep partial thickness wounds: split-thickness skin graft (STSG) donor site wounds and Grade 2a burn wounds.

Indication and dosage

The initially proposed indication was “Treatment in adults for accelerated healing of partial thickness wounds”.

The recommend indication is treatment of partial thickness wounds in adults (see SmPC sections 4.1, 4.4 and 5.1). The gel should be applied to the wound surface at a thickness of approximately 1 mm and covered by sterile wound dressing. The gel should be re-applied at each wound dressing change, until the wound is healed, for up to 4 weeks (see SmPC section 4.2).

2.2. Quality aspects

2.2.1. Introduction

Episalvan, a sterile gel, is a herbal medicinal product consisting of the herbal preparation dry extract from *Betulae* cortex as active substance and sunflower oil as excipient. The extract with the oil forms a colourless to slightly yellowish, opalescent gel without any further ingredients.

2.2.2. Active Substance

Herbal substance (crude birch bark)

General information of the herbal substance

The definition of the herbal substance is the fine cut and sieved particles (crude birch bark) forming the starting point for the herbal preparation dry extract of birch bark from *Betula pendula* Roth (silver birch), *Betula pubescens* Ehrh. (white birch) and hybrids of both species. The birch is growing in the wild in Northern Europe and cut and transported to factories where birch bark is processed to fine particles.

The part of the birch used is the white part of the bark, *Betula* cork (phellem), which is the outer part of the bark, produced by the cork cambium (phellogen) in woody plants. It is confirmed that the herbal substance complies with the guideline on Good Agricultural and Collection Practice (GACP) for starting material of herbal origin. The main constituents in the bark of birch are pentacyclic triterpenes that comprises of three major triterpene groups, (1) lupane, (2) oleanane and (3) ursane (Figure 1 and Table 1). The most interesting and major compound in birch bark is betulin and its derivative betulinic acid. Other quantified triterpene compounds that are of interest are oleanolic acid, erythrodiol and lupeol. In order to definitely assure correct birch species, the collected birch trees are compared to a certified herbarium specimen.

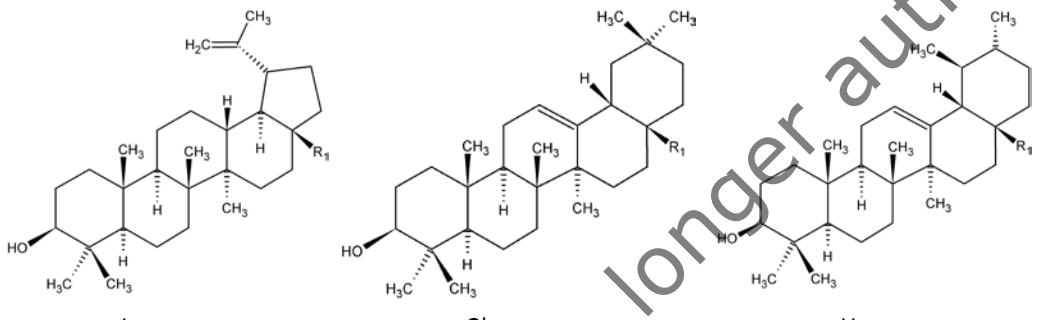


Figure 1: Structure of Triterpene Families

Table 1: Triterpenes

Triterpene Family	Triterpene	R_1 (C_{28})	M [g/mol]	Abbreviation
Lupane	lupeol	CH_3	426.70	LU
	betulin	CH_2OH	442.72	BE
	betulinic acid	COOH	456.71	BA
Oleanane	ß-amyrin	CH_3	426.70	bAM
	erythrodiol	CH_2OH	442.72	ER
	oleanolic acid	COOH	456.71	OA
Ursane	ursolic acid	COOH	456.71	UA

Manufacture, characterisation and process controls of the herbal substance

Prior to manufacturing, the birch is stored outside as wet stocks and watered before stripping of the cork from the logs is performed. The cork is then dried and reduced in size and sieved until specified fine particles size is reached. A QP declaration confirming GMP compliance of the herbal substance manufacturer where fine particles < 1.25 mm are obtained has been provided.

Complete information about the botanical classification is given. Macroscopic and microscopic characterization as well as phytochemical characterization of the herbal substance is provided.

Specification of Herbal substance

The specification includes critical tests that ensure the identity and the quality of the herbal substance. For example, macro- and microscopic identification test for *Betula pendula* Roth and *Betula pubescens* Ehrh, test of fine particle size (<1.25 mm), assay of triterpenes, pesticides, microbiological quality, aflatoxins, heavy metals, loss of drying, total ash, foreign matter and fingerprint chromatogram.

Drug substance herbal preparation (dry extract from birch bark)

General information of the herbal preparation (drug substance)

The herbal preparation, i.e. the drug substance, is the dry extract of birch bark. It is declared as a refined "quantified extract" as defined in the EMA 'Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products' (EMA/HMPC/CHMP/CVMP/287539/2005/rev 1). The quantification is determined with respect to the betulin content, which is determined to 72-88 % (w/w) and with a DER value of 5-10:1. Besides betulin, other four major triterpenes: betulin acid, oleanolic acid, erythrodiol and lupeol are present in the herbal preparation.

n-Heptane is used as extraction solvent.

Manufacture, characterisation and process controls of the herbal preparation (drug substance)

Manufacture of dry extract is performed in accordance with GMP.

The extraction process is considered as a standard process hence validation of the process is not required. Nonetheless, detailed description and validation of extraction, crystallisation and drying process were provided with justification for the designated process parameters. The developed manufacturing process is able to refine the dry extract in term of characterised constituents with target quality. The physicochemical and rheological properties of the dry extract are controlled using suitable tests, e.g. particle surface area. Information regarding phytochemical composition of the herbal preparation obtained with the manufacturing process is provided. Possible presence of impurities was sufficiently discussed and supportive data was presented.

Specification of herbal preparation (drug substance)

Release- and shelf-life specification includes critical tests that control the quality and the identity of the herbal preparation. The specification includes such parameters as visual description, identification by GC-FID fingerprints and HPLC-fingerprints, GC-FID assay of 5 major triperpenes and total triterpenoids, amount of Cr and Ni (ICP-OES), residual solvent n-heptane, consistency test, oil segregation test, specific surface area and microbiological contamination limits.

Reference standards of purified triterpenes have been established in accordance with Ph.Eur. 5.12.

Batch analysis demonstrated that the quality of the drug substance is satisfactory and comply with set acceptance limits.

Stability of the herbal preparation (drug substance)

Three production scale batches have been tested at long-term (25°C/60% RH) for 36 months and at accelerated condition (40°C/75% RH) for 6 months. However, data from these batches could not be accounted for assigning a re-test period for the drug substances due to critical tests (e.g. bioburden and specific surface area) were not tested during the stability studies. The proposed re-test period for the drug substance is 36 months when stored below 30 °C.

New stability data of 9 months was appended for three production scale batches that include tests in accordance to amended specification.

Photostability studies and stability studies were conducted according to ICH guidelines. It is demonstrated that the finished product is not light sensitive.

Based on the overall data, the re-test period for the drug substance (e.g. herbal preparation) is assigned to 15 months when stored below 30 °C.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The dosage form of the finished product is a semi-solid preparation, which is an oleogel; a lipophilic gel for cutaneous application. The finished product is a colorless to slightly yellowish, opalescent, gel. The finished product is packed and stored in white 25 ml collapsible aluminum tubes, with a sealing compound in the fold, closed by an aluminum membrane (i.e. tamper evident) and a white PP screw cap.

The development of the formulation provides the justification to the selection of the final composition. During the early stage of the development formulations with oil and water were investigated. Water-free formulation was chosen for further development work where different concentrations were investigated with regard to such quality attributes as segregation of oil and consistency of the gel. Content of 10 % of dry extract was chosen for the final composition.

Compatibility studies between the product formulation and several wound dressing materials were investigated. All of the dressing evaluated reported no incompatibility with regard to efficacy and safety of the product. Moreover, there were no detrimental effects observed on the dressing material in contact with the finished product.

The choice of primary packaging is justified. The container closure system for the finished product is an aluminum tube with protective internal and external lacquer. Sufficient documentations were provided and the container closure system for the finished product is judged to be acceptable and complies with Ph. Eur. and with foodstuff legislation of EU. No risk for BSE and TSE were found. The finished product is packed in a single dose container, which is tamper-evident.

The development of the manufacturing process has been sufficiently described. The effects of the sterilisation process on the chemical, physicochemical and rheological properties were studied and elaborated discussions of the matter were provided together with experimental data. Thus, it is concluded that sterilisation is sufficient to guarantee sterility of the product at production scale. The potential for syneresis occurring after irradiation and on storage was investigated and results showed no syneresis potential. Furthermore, the product is proven to be non-hygroscopic. Due to this characteristic a low bioburden of the finished product was demonstrated.

Manufacture of the finished product and process controls

The manufacturing process of the finished product is relatively simple where the API, i.e. the dry extract from birch bark, is mixed with sunflower oil. The bulk gel is filled into the aluminium tubes, labelled and packed into folding boxes and shipping cartons. Bioburden is controlled prior to sterilisation.

The manufacturing process has been thoroughly assessed: a developed process and control strategy ensures appropriate quality level of the finished product. Adequate IPCs are presented for the manufacturing process.

The validation of the manufacturing process was performed on three consecutive production scale batches. Process validation protocol and reports were submitted and the validation performed was found acceptable.

Product specification

The release- and shelf-life specification for the finished product was revised with relevant tests; assay of betulin and amount of dry extract, sterility, acid value, peroxide value, fineness of grind, viscosity, thixotropy, segregation of oil and consistency. The product is tested for sterility (e.g. Ph. Eur. 2.61.) at release and at start and end of stability study.

Stability of the finished product

Stability data (e.g. long-term-, intermediate- and accelerated condition) that covered a period of 12 months and 6 months was appended and tests were performed in accordance to amended specification. The analytical methods were shown to be stability indicating. The presented results were all within acceptance limits.

Photostability studies showed that the finished product is not light sensitive.

Thus, according to ICH Q1E *Evaluation of stability data* a shelf-life of 24 months when stored below 30°C as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

2.2.4. Discussion on the chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the procedure, new and updated information has been provided.

GMP compliance of the manufacturer of the birch bark has been discussed throughout the procedure. It was concluded that the manufacturing process of grinding bark into fine particles (<1.25 mm) must indisputably be conducted under GMP conditions.

In the overall, the quality of the drug substance and finished product is assured and proven consistent over time.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The cellular and molecular process involved in initiation, maintenance, and completion of epithelialisation are essential for wound closure. Wound healing is a complex process that can be roughly divided into the following overlapping phases:

- Inflammatory phase
- New tissue forming phase
- Remodelling phase

The major cellular components of the epidermis are the keratinocytes. The different stages of wound healing include induction of pro-inflammatory mediators, proliferation, cell-migration and differentiation of keratinocytes. During epithelialisation, keratinocytes become activated, and the activation process is achieved by expression of several cytokines and growth factors. The activated phenotype is marked by changes in the cytoskeleton network and cell surface receptors, allowing keratinocytes to migrate into the wound to fill the defect (Pastar *et al*., 2014).

To study the wound healing properties of Episalvan gel (also referred throughout this report as Oleogel-S10) and triterpene dry extract from birch bark (TE), the Applicant performed a variety of *in vitro* and *ex vivo* studies. For example, the porcine *ex vivo* wound healing model (WHM) was used, considered to mimic the clinical situation in treatment of partial thickness wounds of patients. In the porcine *ex vivo* wound healing model, punch biopsies were taken from the plicae of pig ears, with the epidermis being removed from a central area. Directly after wounding, test compounds were applied into the wound. Furthermore, the *in vitro* wound scratch test using human primary keratinocytes was used as a model to study re-epithelialisation.

Safety pharmacology studies were performed in dogs via intraduodenal administration and in mice and rats via intraperitoneal (i.p.) administration. Isolated ileum from guinea pig was also used in an *in vitro* safety pharmacology study. The safety pharmacology studies were completed in accordance with the relevant International Conference on Harmonization / Committee for Proprietary Medicinal Products (ICH/CPMP) Note for Guidance.

No specific *in vitro* and *in vivo* pharmacokinetic studies were conducted with triterpene dry extract from birch bark (TE) due to low absorption following dermal administration. However, plasma levels of betulin and betulinic acid were analysed as part of toxicity studies in rats, dogs and minipigs.

Toxicity studies of TE were performed in mice and rats via intraperitoneal and subcutaneous route of administration. In pivotal repeat-dose toxicity studies rats, Beagle dogs and minipigs were administered TE via intraperitoneal, subcutaneous and topical route of administration, respectively.

As for genotoxicity studies, triterpene dry extract was studied in Ames test, chromosomal aberration test and *in vivo* micronucleus test.

No carcinogenicity, reproductive and developmental toxicity studies have been performed due to low dermal absorption and low systemic exposure.

Evaluation of toxicokinetic data has been included in 2 pivotal studies in Beagle dogs (s.c.) and minipigs (dermal administration).

Local tolerance has been assessed in guinea-pigs in a test model according to Magnusson and Kligman consisting of intracutaneous and topical rote of administration.

All pivotal toxicity studies were conducted in line with GLP requirements as claimed by the Applicant.

2.3.2. Pharmacology

The main constituent of triterpene dry extract from birch bark (TE) is betulin (72-88 % W/W of the dry extract). Other constituents are betulinic acid, lupeol, oleanolic acid, and erythrodiol.

Primary pharmacodynamic studies

Non-clinical pharmacodynamics studies conducted with TE and/or betulin and the main findings of these are summarised in **Table 2**.

Table 2. Summary of primary pharmacodynamics studies conducted with triterpene dry extract from birch bark and betulin

Test system / Study number (Reference)	**Test item / concentration**	**Major findings**
Ex vivo / porcine wound healing model (WHM) Ebeling et al. 2014 / Report Number 2010-01 (ZIM)	10 % TE in 90 % sunflower oil; TE (10 µg/ml) in PBS; Betulin (8.69 µg/ml) in PBS	Oleogel-S10 and TE (10 µg/ml) exhibited acceleration of dermis re-epithelialisation compared to controls (vaseline or PBS, respectively) in the porcine *ex vivo* wound healing model (WHM) .
	TE (10 µg/ml) in PBS; Betulin (8.69 µg/ml) in PBS	Treatment with TE and betulin dissolved in PBS 72 hours after wounding for 24 hours resulted in an improved skin barrier function e*x vivo*
	TE (10 µg/ml) in PBS	TE increased mRNA levels of IL-6 and COX-2 in the WHM 6h after wounding, but not 48 h after wounding.
	TE (10 µg/ml) Betulin (8.69 µg/ml) Betulinic acid (0.35 µg/ml) Lupeol (0.4 µg/ml)	TE, betulin, lupeol and betulinic acid did not induce proliferation in the WHM.
Scratch assay *in vitro* / human primary keratinocytes (hPK) Ebeling et al. 2014 / Report Number 2010-01 (ZIM)	TE (1 µg/ml)	TE enhanced migration of hPK in the scratch assay. The migratory activity was measured by calculating the percentage of closed areas.

Test system / Study number (Reference)	**Test item / concentration**	**Major findings**
In vitro / human primary keratinocytes (hPK); Ebeling et al. 2014 / Report Number 2010-01 (ZIM)	TE (1 and 5 µg/ml) Betulin (4.34 µg/ml) Lupeol (0.20 µg/ml) Betulinic acid (0.18 µg/ml)	Treatment of hPK for 8 h with 5 µg/ml of TE increased mRNA of COX-2, IL-6 and IL-8. At 1 µg/ml of TE the levels of mRNA increased after 24h. Betulin (4.34 µg/ml) also increased the mRNA levels after 8 h. Lupeol and betulinic acid exhibited no effect on the mRNA of these mediators.
	TE (1 and 5 µg/ml) Betulin (0.87 and 4.34 µg/ml)	High and low concentrations of TE and betulin increased protein levels of COX-2 after 24 h treatment. Protein levels of IL-6 and IL-8 were increased after 24 h and 48 h of treatment with 1 and 5 µg/ml of TE and 0.87 µg/ml of betulin. For IL-6 and IL-8 release, the highest levels were observed at 5 µg/ml of TE after 48 h.
	TE (1 µg/ml) Betulin (0.87 µg/ml) Betulinic acid (0.04 µg/ml) Lupeol (0.04 µg/ml)	TE and betulin had no influence on transcription factor nuclear factor κB (NF-κB) DNA binding. Betulinic acid and lupeol were also inactive under these conditions. In the literature, NF-κB has been reported to be involved in the transcriptional regulation of inflammatory cytokines. Treatment with TE and betulin for 24 h prolonged the half-life of COX-2 and IL-6 mRNA (mRNA stabilization).
	TE (1 µg/ml)	Combined treatment of p38 MAPK inhibitor and TE decreased half-life of COX-2 mRNA, but not to the level of the control. The half-life of IL-6 mRNA was lower than the control. In the literature, p38 mitogen-activated protein kinase (MAPK) has been reported to be involved in COX-2 and IL-6 mRNA stability. Another mRNA stabilizing factor, HuR, was also studied. TE enhanced cytosolic levels of HuR. No change in nuclear HuR-level was observed. It is speculated if TE is involved in the stabilizing effect of COX-2 and IL-6 mRNA.
	TE (1 µg/ml)	TE activates the transcription factor STAT3 (increased STAT3 phosphorylation) after 12, 16 and 24 h incubation (12 h showed highest activation). In the literature, STAT3 has been reported to be involved in the proliferation and migration of keratinocytes.
	TE (0.51, 5.1 and 51 ng/ml; 0.5 and 1 µg/ml) Betulin (0.44, 4.42 and 44.24 ng/ml) Lupeol (0.43, 4.43 and 43.50 ng/ml)	Treatment with TE, betulin, lupeol and erythrodiol for 2 hours affected the actin cytoskeleton.
	TE (5.1 ng/ml) Betulin (4.42 ng/ml) Lupeol (4.43 ng/ml)	TE, betulin and lupeol activated Rho GTPases involved in regulation of the actin cytoskeleton
	TE (1 and 5 µg/ml) Betulin (0.87 and 4.34 µg/ml) Betulinic acid (0.04 and 0.2 µg/ml) Lupeol (0.04 and 0.2 µg/ml)	TE, betulin, lupeol and betulinic acid did not induce proliferation of hPK when incubated for 48 hours.

Test system / Study number (Reference)	Test item / concentration	Major findings
In vitro / human primary keratinocytes Woelfle *et al*. 2010	TE (10 µg/ml)	Different types of keratinocytes (proliferating, early and late confluent as well as senescent hPK) were incubated with TE for 24 h and apoptosis was measured. TE-induced apoptosis in all types of hPK in a dose-dependent manner. Senescent hPK were most susceptible to apoptosis induced by TE. In all further experiments, hPK between the proliferating and early confluent stage (subconfluent or 70 % confluent cells) were used. The differentiation-promoting effect of TE was investigated by incubating subconfluent hPK with 10 mg/ml TE for 24 h. 2mM calcium, referred to as high $[Ca^{2+}]$ex was used as positive control. Gene expression was investigated in hPK for the early differentiation markers involucrin (INV) and keratin 10 (KRT10) as well as the late differentiation marker transglutaminase (TGM). KRT10, INV, and TGM mRNA levels were increased in cells cultured in the presence of either high $[Ca^{2+}]$ex or TE TE caused induction of the transient receptor potential superfamily of cation channel 6 (TRPC6) expression on mRNA and protein level in hPK 24 hours post treatment, thus leading to increased calcium influx.
Ex vivo / human biopsy Woelfle *et al*. 2010	TE (10 µg/ml)	TE induced TRPC6 expression in human skin explants. TE induces DNA fragmentation of distal stratum granulosum cells *ex vivo*

Secondary pharmacodynamic studies

No studies addressing pharmacological effects on targets other than the skin were submitted.

Safety pharmacology programme

The safety pharmacology studies are summarised in **Table 3**. All safety pharmacology studies were conducted in compliance with Good Laboratory Practice (GLP) as claimed by the Applicant.

Table 3. Summary of safety pharmacology studies performed with Triterpene Dry Extract from Birch Bark

Organ systems evaluated	Species / Strain	Method of administration	Doses (mg / kg)	Findings
Isolated ileum (*in vitro*) Study no 13540/00	*In vitro* (Guinea pig / Dunkin-Hartley)	-	Agonistic and antagonistic properties: 3.16 x 10^{-6} to 5 x 10^{-4} g/mL bath fluid TE in bath fluid	Betulin possessed no agonistic or antagonistic properties up to the highest concentration tested (5 x 10^{-4} g/ml bath fluid) on isolated guinea pig ileum.
Cardiovascular/ Respiratory Study no 13536/00	Dog / Beagle (anaesthetized) 5 M	Consecutive intra-duodenal injection administered with ascending TE dose levels	0, 30, 100 and 300 mg/kg consecutively TE suspended in sesame oil	No test item-related influence on the cardiovascular parameters (peripheral, pulmonal and capillary blood pressure, heart rate, QT interval, cardiac output, stroke volume, systolic left ventricular pressure, dp/dt max, central venous pressure and blood gas analysis) or the respiration.

Organ systems evaluated	Species/ Strain	Method of administration	Doses (mg/kg)	Findings
Renal Study no 13537/00	Rat / Sprague-Dawley 10 F	i.p. single dose	0, 125, 250 and 500 mg/kg TE suspended in sesame oil	No test item-related influence on the diuresis or saluresis.
CNS Study no 13538/00	Mouse / CD-1 8 F	i.p.	0, 30, 100 and 300 mg/kg TE suspended in sesame oil	No influence was observed on the hexobarbital sleeping time in mice.
CNS Study no 13539/00	Mouse / CD-1 8 F	i.p.	0, 30, 100 and 300 mg/kg TE suspended in sesame oil	Increases noted for active moving and slight static movements for all dose groups due in particular to some individual animals. The observations are considered to be caused by the irritating properties of the test substance following i.p. administration.
GI Study no 13541/00	Mouse / CD-1 8 F	i.p.	0, 30, 100 and 300 mg/kg TE suspended in sesame oil	TE reduced intestinal motility starting at a dose of 30 mg/kg b.w. i.p. in one animal. At 300 mg/kg b.w. i.p. all animals were affected. The effect is considered to be due to non-specific irritating properties of the test substance.

Safety pharmacology studies with triterpene dry extract from birch bark (TE) in sesame oil were performed in dogs via intra-duodenal administration and in mice and rats via intraperitoneal administration. Isolated ileum from guinea pig was also used in an *in vitro* safety pharmacology study.

Cardiovascular and respiratory parameters were studied at doses of up to 300 mg of TE/kg in beagle dogs, central nervous parameters at doses of up to 300 mg TE/kg in mice, gastrointestinal parameters at doses of up to 300 mg of TE/kg in mice and renal parameters at doses of up to 500 mg TE/kg in rats. No test item related effects have been observed.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were performed. This was considered acceptable given the low systemic exposure from topical application of Episalvan to patients.

2.3.3. Pharmacokinetics

No specific in vitro and in vivo pharmacokinetic studies were conducted with triterpene dry extract from birch bark (TE) due to low absorption following dermal administration. However, plasma levels of betulin, the main component of TE, were evaluated as part of the 4-week repeated dose toxicity studies in rats and dogs. Plasma levels of betulin and betulinic acid were analysed as part of the 4-week repeated dose local tolerance and toxicity study in mini-pigs.

2.3.4. Toxicology

Single dose toxicity

Four single toxicity studies, two in mice and two in rats were performed. These are summarised in **Table 4**.

One single toxicity study with intraperitoneal route of administration was performed in each species: mouse (13597/00) and rat (13598/00). Doses of 250, 500, 1000, 2000 mg/kg of triterpene dry extract (TE) were administered. In both studies all animals showed white, coarse deposits in the abdominal cavity at dose 250 mg/kg or higher and organs adhered at dose 500 mg/kg or higher. As for adverse clinical signs, all animals showed reduced motility, ataxia, dyspnoea and reduced muscle tone at dose 500 mg/kg or higher. No lethality occurred in any of these studies.

A single toxicity study with TE administered subcutaneously has been performed in each mice and rats, at dose 2000 mg/kg. In 6 out of 10 mice and 4 out of 10 rats necrotic application sites occurred. No toxic symptoms and no lethalities were observed in any species.

Table 4. Summary of single dose toxicity studies with triterpene dry extract

Study ID	Species / Sex / Number / Group	Dose / Route	Approx. lethal dose / observed max non-lethal dose
13597/00	Mouse, CD-1 5 M + 5 F	250, 500, 1000, 2000 mg/kg Intraperitoneal (administration volume: 20 ml/kg)	Lethal dose: >2000 mg/kg males and females Non-Lethal: 2000 mg/kg males and females
	Major findings: No lethality occurred in the study. **Adverse clinical signs:** ≥500 mg/kg: all animals showed reduced motility, ataxia, dyspnoea and reduced muscle tone **Macroscopic pathology**: ≥250 mg/kg: all animals showed white, coarse deposits in the abdominal cavity ≥500 mg/kg: all animals showed organs adhered		
13487	Mouse, CD-1 5 M + 5 F	2000 mg/kg Subcutaneous (administration volume: 50 ml/kg)	Lethal dose: >2000 mg/kg males and females Non-Lethal: 2000 mg/kg males and females
	Major findings: No lethality occurred in the study. **Adverse clinical signs:** No toxic symptoms **Macroscopic pathology**: 2000 mg/kg: necrotic application sites for 3 M and 3 F		
13598/00	Rat, Sprague-Dawley 5 M + 5 F	250, 500, 1000, 2000 mg/kg Intraperitoneal (administration volume: 20 ml/kg)	Lethal dose: >2000 mg/kg males and females Non-Lethal: 2000 mg/kg males and females

Major findings:
No lethality occurred in the study.
Adverse clinical signs: ≥500 mg/kg: all animals showed reduced motility, ataxia, dyspnoea and reduced muscle tone
Macroscopic pathology: ≥250 mg/kg: all animals showed white, coarse deposits in the abdominal cavity
≥500 mg/kg: all animals showed organs adhered

13488/00	Rat, Sprague-Dawley 5 M + 5 F	2000 mg/kg Subcutaneous (administration volume: 50 ml/kg)	Lethal dose: >2000 mg/kg males and females Non-Lethal: 2000 mg/kg males and females

Major findings:
No lethality occurred in the study.
Adverse clinical signs: No toxic symptoms
Macroscopic pathology: 2000 mg/kg: necrotic application sites for 1 M and 3 F

Repeat dose toxicity

Repeat-dose toxicity was studied in rats, Beagle dogs and minipigs. The pivotal study in rats monitored toxicity after intraperitoneal administration of the triterpene dry extract (TE) and the subcutaneous route of administration was applied in the pivotal study in dogs. These studies are summarised in **Table 5.**

Table 5. Pivotal repeat-dose studies in rats and dogs

Study ID	***Species/Sex/ Number/Group***	***Dose/Route***	***Duration***	***NOEL/ NOAEL (mg/kg/day)***
13839/00	*Rat, Sprague-Dawley 10 M + 10 F*	*0, 60, 180, 540 mg/kg Intraperitoneal (administration volume 10 ml/kg)*	*4 weeks, once daily*	*Not established*
	Vehicle/control: *sesame oil*			
13904/01	*Dog, Beagle 3 M + 3 F*	*0, 30, 100, 300 mg/kg Subcutanous (administration volume 5 ml/kg)*	*4 weeks, once daily*	*Not established*
	Vehicle: *PEG 400 (15 %) in 0.9 % NaCl solution*			

In the rat study, there were no major clinical observations but macroscopic pathology examination revealed whitish-yellow oily aqueous liquid in the abdominal cavity in the animals of the control group and of all dose groups. In addition, disperse areas with whitish deposits were noted in all test substance-treated groups. Furthermore, in all test substance groups discolorations and adhesions in various abdominal organs were observed.

Inflammation in the abdominal cavity of all rats of the high dose group correlated with the results of macroscopic post mortem examinations. Similar changes, though less pronounced, were noted in the control group.

Subcutaneous administration in dogs resulted in a pronounced inflammatory, granulomatous reaction at the injection site, which was considered to be related to the insolubility of the triterpenes. Other findings in this study, including increased cellularity in the spleen and bone marrow, were also considered to be likely indirect effects from the inflammatory reaction. There were no findings indicating systemic toxicity in the 4-week dog study

Pivotal repeat-dose study in mini-pigs

Mini-pig was the only species to receive TE via the same route of administration as is intended for human use. To characterise the local and systemic toxicity of Oleogel-S10 (10 % TE in sunflower oil) following repeated dermal administration on the intact and abraded skin over 4 weeks. In addition, the reversibility of any effect after a recovery period of 14 days was evaluated. Mini-pigs were randomised in three treatment groups to be applied either 150 mg/kg TE (2.25 g/250 cm²) on intact skin, 150 mg/kg TE (2.25 g/250 cm²) on abraded skin-graft excised skin, or foam-bandage Mepilex (control, 0 g/kg) on abraded skin (skin graft-excised) (**Table 6**).

Table 6. Pivotal repeat dose study in minipigs

Study ID	Species/Sex/ Number/Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg/day)
26742	Mini-pig, Göttingen mini-pig 6 (4+2) M + 6 (4+2) F	Group 1: 150 mg/kg TE* (2.25 g/250 cm²) on intact skin Group 2: Foam-bandage Mepilex (control, 0 g/kg) on abraded skin (skin graft-excised) Group 3: 150 mg/kg TE* (2.25 g/250 cm²) on abraded skin (skin graft-excised) Dermal, occlusive	4 week, three times weekly at 48-hour and 72-hour intervals for four weeks (on test days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26 with a final administration on test day 29); in total 13 administrations.	Not established

*The dose of Oleogel-S10 applied was 1.5 g/kg (22.5 g/250 cm²) equals to 150 mg/kg triterpene dry extract (TE) (2.25 g/250 cm²).

Treatment area:

To approximately 12.5 x 20 cm = 250 cm² per animal (corresponding to approximately 5 % of the total body surface area), 1 mm thick layer of Oleogel-S10 was applied. To allow for treated and untreated skin localizations the right shoulder of the scheduled animals (groups 2 and 3) was shaven. Additionally, a separate split-thickness skin graft was excised (untreated abraded skin, not covered).

Additional treatment:

Before the split-thickness skin graft, the mini-pigs were anaesthetized using 0.2 ml/kg Ursotamin® and 0.05 ml/kg Stresnil®, intramuscularly.

To prevent or mitigate pain the analgesic Metamizol was given directly after dermatome treatment at a dosage of 1 ml/10 kg intramuscularly. If necessary, the analgesia regimen was prolonged. Animals of groups 2 and 3 were treated for 4 consecutive days with Metamizol after the skin abrasion. If necessary, the analgesia regimen was prolonged.

If appropriate, the mini-pigs were treated with the antibiotic Duphamox at a dose of 1 ml/10 kg, intramuscularly.

Methodology:

Clinical signs, body weight, food and drinking water consumption, laboratory examinations, haematology, coagulation, clinical biochemistry, urinalysis, organ weight and ophthalmological and auditory examinations were included as parameters in this study.

Macroscopic skin reactions, i.e. signs of erythema, eschar formation and oedema, were scored as described in **Table 7** (based on DRAIZE, Appraisal of the Safety of Chemicals in Food, Drugs and Cosmetics, Association of Food and Drug Officials of the United States, Austin, Texas, 1959) on the administration days and on test day 30, daily during recovery period and on test day 44 and 45.

Table 7. Scoring system for skin reactions in study 26742

Erythema and eschar formation	Value	Oedema formation	Value
No erythema and eschar formation	0	No oedema	0
Very slight erythema (barely perceptible)	1	Very slight oedema (barely perceptible)	1
Well-defined erythema	2	Slight oedema (edges of area well defined by definite raising)	2
Moderate to severe erythema	3	Moderate oedema (raised approx. 1 millimetre)	3
Severe erythema (beef redness) or eschar formation (injuries in depth) preventing erythema reading	4	Severe oedema (raised more than 1 millimetre and extending beyond area of exposure)	4

Oleogel-S10 treated intact and abraded skin areas were examined histologically after preparation of paraffin sections and haematoxylin-eosin staining and compared with foam-bandage covered abraded skin areas and untreated abraded and intact skin areas.

Furthermore, immune histochemical examinations for cell proliferation in the skin using the Ki67 marker were performed in 3 male animal and 3 female animals of group 3. Five serial sections from each of the skin areas (treated abraded, untreated abraded, untreated intact skin) per animal and positive control sections from duodenum, jejunum and ileum were examined. The examination of cell proliferation showed no test item

related influence on cell proliferation in the epidermis and corium. The positive reaction of some nuclei in the epidermis of the skin was considered to reflect a normal cell proliferation. There was no difference between the treated and untreated skin localizations. The CHMP however considered that the cell proliferation assay using Ki67 as a marker was not performed according to commonly accepted standards.

The Applicant also submitted a computerised re-evaluation of the Ki67 cell proliferation data at the request of the CHMP which did not however show any differences compared to the primary analysis.

Systemic exposure:

In all plasma samples from group 3 betulin and betulinic acid concentrations were below LLOQ (5 ng/ml). When Oleogel-S10 was applied to intact skin of mini-pigs, betulinic acid was detected in 3 out of 12 animals (4 / 216 samples on day 1 and day 29; 5.68, 6.42, 8.15 and 6.8 ng/ml). Measurable betulin concentrations were detected in single animals (7 out of 12 animals) at single time points: 33 out of 216 samples were above 5 ng/ml. All values were below 40 ng/ml; with 15/216 samples showing a concentration of >10 ng/ml. The results suggested a tendency of increasing plasma levels with treatment duration.

Major findings:

Local tolerance (macroscopy): 150 mg/kg of TE did not cause any local intolerance reactions to the intact skin. At the end of the recovery period, erythema and eschar formation due to the healing process of the skin wound was still observed for both male animals treated previously with foam-bandage control (abraded skin) and one of two female animals treated previously with 150 mg/kg of TE (abraded skin). No erythema and eschar formation was noted at the end of the recovery period in both male animals treated previously with 150 mg/kg of TE (abraded skin) and one of two females treated previously with foam-bandage control (abraded skin).

As requested by the CHMP, the applicant submitted additional evaluations of the safety study in mini-pigs, i.e. histopathological examination of all preserved organs and tissues in accordance with the EU repeat-dose toxicity guideline (CPMP/SWP/1042/99), peer-review of the histopathology report, including skin sections and samples of all organs according to (CPMP/SWP/1042/99) and a re-evaluation of Ki67 using a computerized image analysis.

The histopathological evaluation of internal organs and tissues (skin samples excluded) did not reveal any findings related to Oleogel-S10 treatment. The observed organ weight changes are not considered to be associated with Oleogel-S10 treatment.

In the histopathological evaluation of skin samples, there were some histopathological differences between untreated intact skin and Oleogel-S10-treated intact skin in females, e.g. presence of epithelial hyperplasia in Oleogel-S10 treated intact skin both during the treatment period and after recovery (group 1). The applicant concludes that these findings are not associated with Oleogel-S10 treatment. It is agreed with the applicant that the histopathological findings in Oleogel-S10-treated intact skin in female mini-pigs are comparable to the background findings observed in female mini-pigs presented by Jeppesen and Skydsgaard, 2015. In addition, there are no findings in the pharmacological studies (e.g. the evaluation of the proliferation marker Ki67) that raise safety concerns related to the presence of epithelial hyperplasia in Oleogel-S10-treated intact skin.

In the histopathological evaluation of skin samples, there was also an increased incidence and severity of lympho-histiocytic inflammatory cell infiltration in association with the presence of multinucleate giant cells in

Oleogel-S10 treated abraded skin (group 3). It is agreed with the applicant that the inflammatory reactions in Oleogel-S10 treated abraded skin in mini-pigs could be caused by the presence of low soluble test item material. It is also agreed with the applicant that these reactions could persist for a few weeks but then resolve. The increased incidence and severity of lympho-histiocytic inflammatory cell infiltration in Oleogel-S10 treated abraded sites in mini-pigs is not considered a safety issue to patients.

Genotoxicity

The Genotoxicity studies performed with TE are summarised in **Table 8**.

Table 8. Genotoxicity studies of triterpene dry extract from birch bark (TE)

Type of test / study ID / GLP	**Test system**	**Concentrations / Concentration range / Metabolising system**	**Results Positive / negative / equivocal**
Gene mutations in bacteria 13542/00	Salmonella strains TA98, TA100, TA102, TA1535, TA1537	Plate incorporation test 31.6-3160 µg/plate +/- S9 Preincubation test 31.6-1500 µg/plate +/- S9 Positive controls: +S9 mix: 2-amino-anthracene, cyclophosphamide -S9 mix: sodium azide, 2-nitro-fluorene, amino-acridine, methylmethane sulfonate	Adequate positive and negative controls produced expected effects. Precipitation: plate incorporation test +S9 1000 µg/plate and -S9 3160 µg/plate preincubation test +S9 1000 µg/plate and –S9 1500 µg/plate **Negative**
Chromosomal aberrations *in vitro* 13543/00	Primary human peripheral lymphocytes	250-1000 µg/ml medium + S9, 4h - S9, 4h and 24 h Positive controls: mitomycin C, cyclophosphamide	Adequate positive and negative controls produced expected effects. -S9: mean incidence of chromosomal aberrations 1.5-3.9 % (background data of the negative control 0-5.0 %) at 1000 µg/ml the mean incidence of chromosomal aberrations was noted to 8.7 % at 24 h exposure, concentration-related cytotoxicity was observed +S9: mean incidence of chromosomal aberrations 1.0-2.5 %, no cytotoxicity was observed **Negative**
Chromosomal aberrations *in vivo* 13544/00	Mouse CD-1, micronuclei in bone marrow 5 M + 5 F	125, 250, 500 mg/kg single dose i.p. sampling 24 and 48 h Positive controls:	Adequate positive and negative controls produced expected effects.

	i.p. administration	cyclophosphamide	**Negative**

In the Ames test, no mutagenic effects were observed in the plate incorporation test or in the pre-incubation test without and with metabolic activation up to the highest concentration of 3160 and 1500 µg/plate, respectively. Test item precipitation was observed in the plate incorporation test at the test concentrations 1000 and 3160 µg/plate with and without metabolic activation and in the pre-incubation test at the test concentrations 1000 and 1500 µg/plate with and without metabolic activation. No cytotoxicity was observed in the plate incorporation test up to the highest concentration of 5000 µg/plate.

In the chromosomal aberration test *in vitro*, the test result was negative up to the test concentration of 500 µg/ml TE. In the test without metabolic activation the mean incidence of chromosomal aberrations ranged from 1.5-3.9 %. The background data on incidence of chromosomal aberrations of the negative controls ranged from 0-5.0 % for the last 30 experiments. At the highest concentration of 1000 µg/ml only an increase in the incidence of chromosomal aberrations was noted to 8.7 % at 24 h exposure. Concentration-related cytotoxicity was observed in the experiments without metabolic activation. In the presence of metabolic activation no cytotoxicity was observed ant the mean incidence of chromosomal aberrations ranged from 1.0-2.5 %.

In the *in vivo* micronucleus test, the maximum tolerated dose of 500 mg/kg i.p resulted in no increase in the incidence of micronucleated polychromatic erythrocytes (PCE). In this study, betulin plasma levels have not been determined in mice following intraperitoneal administration of TE. Thus, the validity of the *in vivo* genotoxicity study could be debated. However, it was recognized that the product is intended for local use with negligible or no systemic absorption. From this perspective, i.e. with focus on local effects in the skin, the negative results of the two *in vitro* genotoxicity studies were reassuring and considered sufficient to cover the use of TE in the applied indication.

No genotoxic / mutagenic effects are published in the public domain for betulin, betulin acid, lupeol, oleanolic acid and erythrodiol.

Carcinogenicity

No carcinogenicity studies were submitted.

Reproduction Toxicity

No reproductive and developmental toxicity studies were submitted.

Toxicokinetic data

Toxicokinetics were included in the pivotal repeat dose toxicity studies in dogs via subcutaneous administration (13904/01) and minipigs via dermal route of administration (26742) providing evaluation of systemic exposure to betulin after subcutaneous and dermal administration of triterpene dry extract from birch bark (TE). The results of these studies are summarised in **Table 9**.

The maximal dose level in clinical use is calculated to 155 mg/kg triterpene dry extract from birch bark (TE) per day (assuming a maximal treatment area of 1 000 cm^2 at a maximal single dose of 93 g Oleogel-S10 and a mean body weight of 60 kg).

Table 9. Toxicokinetic results from studies 13904/01and 26742

Study ID	Daily Dose (mg/kg)	Animal plasma concentration betulin (ng/ml)		Animal:Human Exposure Multiple
13904/01 Dog, beagle	30 mg/kg subcutaneous administration once daily for 4 weeks	♂ Day 1: <50 Day 28: 115--153	♀ Day 1: <50-78 Day 28: 189-234	n.a.
	100 mg/kg subcutaneous administration once daily for 4 weeks	♂ Day 1: <50-108 Day 28: 183-194	♀ Day 1: <50-56 Day 28: 261-331	n.a.
	300 mg/kg subcutaneous administration once daily for 4 weeks	♂ Day 1: <50-77 Day 28: 286-336	♀ Day 1: <50-55 Day 28: 297-364	n.a.
26742 Minipig	150 mg/kg dermal administration three times weekly for 4 weeks	♂ Intact skin: <5-17 Abraded skin: <5	♀ Intact skin: <5-37 Abraded skin: <5	n.a.

Local Tolerance

The potential of triterpene dry extract from birch bark (TE) to provoke skin sensitisation reactions in 20 male guinea-pigs was studied in a test model according to Magnusson and Kligman (Maximisation test). A 0.01 % concentration of TE in sesame oil chosen for the 1st (intracutaneous) induction stage produced a discrete or patchy to moderate and confluent erythema in all animals. Two ml of a 15 % concentration of TE in sesame oil chosen for stage 2 (topical) induction was not irritating to the skin. Hence, the skin was coated with sodium laurylsulfate on the day before stage 2 induction (day 7 after the first induction) in order to induce a local irritation. A 15 % concentration of TE in sesame oil was the highest technical possible suspension.

The challenge on day 21 with a 15 % suspension in sesame oil revealed no sensitizing properties for the depilated skin. The vehicle employed and the 15 % birch bark extract concentration employed during the challenge stage 3 revealed no skin reactions per se. As a positive control animals of this strain were treated

with benzocaine and exhibited a sensitising reaction.

Other toxicity studies

Phototoxicity *in vitro* (Balb/c 3T3 cells)

Triterpene dry extract from birch bark (TE) was assayed in a 3T3 NRU *in vitro* phototoxicity test. The cytotoxicity was studied in the presence and absence of exposure to a non-cytotoxic dose of UVA/VIS light. The test concentrations ranged from 0.0078-1.0 µg/ml (with and without UV irradiation). The selected test concentrations were based on the preliminary test resulting in pronounced cytotoxicity at concentrations from 3 µg/ml. No signs of cytotoxicity were observed up to the top concentration of 1.0 µg.

Criteria for the choice of an appropriate light source included the essential requirement that the light source emits wavelengths absorbed by the test item and that the dose of light (achievable in a reasonable time) was sufficient for the detection of known photo-sensitisers.

At UVA (= 5 J/cm2; UVB =0.79 mW/cm2), exposure time 9.18 minutes, the EC_{50} (-UV) and EC_{50} (+UV) could not be calculated and TE was considered to be not phototoxic. Chlorpromazine was used as the positive reference. In the presence of UVA/vis light an EC_{50} value of 0.75 µg/ml was calculated. In the absence of UVA/vis light an EC_{50} value of 7.2 µg/ml was calculated. Hence, a photo-irritationfactor of PIF = 9.6 was calculated.

Photosensitisation female guinea-pig

In the photosensitisation assay in guinea-pigs with and without UV irradiation, Oleogel-S10 (10 % dry extract from birch bark in sunflower oil) was studied. The dose level was 48 mg triterpene dry extract from birch bark (TE).

TE did not show phototoxic properties in the 3T3 NRU in vitro phototoxicity assay. Photosensitisation was studied in guinea-pigs and the skin reactions erythema, eschar and oedema formation were evaluated. In this study, TE revealed no photosensitising properties. However it is not known whether these results can be used to predict photo-allergy in humans.

2.3.5. Ecotoxicity / environmental risk assessment

In accordance with the “Guideline on the environmental risk assessment of medicinal products for human use“ (EMEA/CHMP/SWP/4447/00 corr 2) the Applicant provided a justification for not submitting environmental risk assessment studies due to the nature of the constituents of this product.

2.3.6. Discussion on non-clinical aspects

The applicant performed a variety of *in vitro* and *ex vivo* studies to evaluate the wound healing properties of the triterpene dry extract from birch bark (TE). There were no safety concerns raised from the assessment of the pharmacological data.

Pharmacokinetic studies were not performed and this was considered acceptable due to the negligible systemic exposure following topical application of the product.

The pivotal 4-week local tolerance and subchronic toxicity study in mini-pigs via dermal administration is considered central for the non-clinical safety assessment of Episalvan gel. The histopathological evaluation of internal organs and tissues (skin samples excluded) did not reveal any findings related to Episalvan gel

treatment. However, in the histopathological evaluation of skin samples, there were some histopathological differences between untreated intact skin and Episalvan gel-treated intact skin in females, e.g. presence of epithelial hyperplasia in Episalvan gel treated intact skin both during the treatment period and after recovery. The CHMP considered that the histopathological findings in Episalvan gel-treated intact skin in female mini-pigs were comparable to the background incidence rates observed in female mini-pigs as reported in the scientific literature (Jeppesen and Skydsgaard, 2015) and were not associated with Episalvan gel treatment.

In the histopathological evaluation of skin samples, there was also an increased incidence and severity of lympho-histiocytic inflammatory cell infiltration in association with the presence of multinucleate giant cells in Episalvan gel treated abraded skin. The CHMP considered that that the inflammatory reactions observed were most likely associated with foreign body reactions and considered to be caused by the presence of low soluble test item material or wound dressing. The CHMP therefore concluded that the increased incidence and severity of lympho-histiocytic inflammatory cell infiltration in Episalvan gel-treated abraded skin in mini-pigs does not translate to a safety issue for patients.

The histopathological evaluation of internal organs did not reveal any findings related to the test item Oleogel-S10 or the procedure itself in any internal organs examined microscopically. Small differences in organ weight changes were observed in animals which had received treatment on abraded skin and this finding was considered be caused by the technical procedure to produce skin graft-excised areas on the skin using a dermatome.

The genotoxicity potential of TE was studied in *in vitro* mutagenicity assays (Ames test and chromosome aberrations test in human lymphocytes). Episalvan gel was non-genotoxic. An *in vivo* micronucleus test in mice was negative as well; however, betulin plasma levels were not determined in this study. Since the product is intended for local use with negligible or no systemic absorption, the negative results of the two *in vitro* genotoxicity studies are considered sufficient to cover the use of TE in the present indication. *In vivo* tests are not expected to yield useful information considering the low systemic exposure (EMA/CHMP/ICH/126642/2008).

Carcinogenicity studies and reproductive and developmental toxicity studies were not submitted. This was acceptable considering to the low systemic exposure of betulin following topical application of Episalvan gel.

The potential of TE to provoke skin sensitisation reactions was studied in a test model in guinea-pigs and in the 3T3 NRU *in vitro* phototoxicity assay. In these experiments TE did not reveal any photosensitising or skin sensitisation properties.

No studies addressing pharmacological effects on targets other than the skin were submitted. This was considered acceptable given the negligible systemic exposure following dermal application of Episalvan to patients.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical program conducted for TE was not exhaustive and this was considered acceptable, due to the limited systemic exposure, following Episalvan gel application. The CHMP considered that the provided information was sufficient to support the use of the product in the treatment of partial thickness wounds in adults and that there are no specific non-clinical issues that require further action post-marketing. Nevertheless, Section 5.3 of the SmPC states that repeated dose toxicity and local tolerance have been studied for up to 4 weeks to reflect the limited duration of the studies in the non-clinical program.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- Tabular overview of clinical studies

Study No. (Location)	**Design**	**Treatment Regimen**	**N**
Treatment of split-thickness skin graft donor site wounds			
BSH-12 (Austria, Bulgaria, Czech Republic, Finland, Germany, Poland)	Phase III open, blindly evaluated, prospective, intra-individually controlled, randomised, multicentre trial	• Oleogel-S10 + wound dressing (same dressing as used as control) • Non-adhesive wound dressing (standard of care) Application was at each wound dressing change, which was at least every third or fourth day until full wound closure was achieved (max. 28 days). The graft donor site wound area of each patient was divided into two treatment areas of approximately the same size. The treatment allocation to the two halves of the wound (distal vs. proximal) was determined by randomisation.	107
BSG-12 (France, Greece, Latvia, and Spain)	Phase III open, blindly evaluated, prospective, intra-individually controlled, randomised, multicentre trial	• Oleogel-S10 + wound dressing (same dressing as used as control) • Non-adhesive wound dressing (standard of care) Application was at each wound dressing change, which was at least every third or fourth day until full wound closure was achieved (max. 28 days). The graft donor site wound area of each patient was divided into two treatment areas of approximately the same size. The treatment allocation to the two halves of the wound (distal vs. proximal) was determined by randomisation.	112
BSH-10 (Germany)	Phase II open, blindly evaluated, prospective, intra-individually controlled, randomised, multicentre trial	• Oleogel-S10 + Mepilex® moist wound dressing • Mepilex® moist wound dressing Application was at each wound dressing change. The treatment period was for 14 days from the day of skin graft surgery. The graft donor site wound area at the upper leg was divided into two equal halves, one proximal and one distal. The treatment allocation to the two halves of the wound was determined by randomisation.	24
Treatment of Grade 2a burn wounds			
BBW-11 (Germany, Sweden, Switzerland, UK)	Phase III open, blindly evaluated, prospective, intra-individually controlled, randomised, multicentre trial	• Oleogel-S10 + fatty gauze wound dressing • Octenilin® wound gel + fatty gauze wound dressing Application was at each wound dressing change, which was at least every second day until full wound closure was achieved (max. 21 days). The target burn wound area of each patient was divided into two treatment areas of approximately the same size, or two comparable wounds were selected.	61

Study No. (Location)	Design	Treatment Regimen	N
		The treatment allocation to the two halves of the wound (distal vs. proximal or right vs. left or lower vs. upper) was determined by randomisation.	
Treatment of epidermolysis bullosa hereditaria skin lesions			
BEB-10 (Germany)	Phase II open, blindly evaluated, prospective, intra-individually controlled, case series documentation	• Oleogel-S10 + non-adhesive wound dressing • Non-adhesive wound dressing Application was at each wound dressing change. Treatment was for 14 days for recent wounds and 28 days for wounds with delayed healing. The target wound area was divided into two treatment areas of approximately the same size, or two comparable wounds were selected.	10

Patient base: all patients who received at least one dose of study treatment

2.4.2. Pharmacokinetics

As plasma sampling for bioanalysis of the major component of the extract, betulin, revealed low and sporadic levels were found, it was concluded that the systemic absorption was minimal. Therefore no further studies on the distribution, elimination, dose-proportionality, time dependencies, potential drug-drug interactions of betulin or in special populations were performed.

Bioavailability

In three clinical studies, plasma sampling was performed before treatment and at certain time-points during treatment, to measure the systemic concentration of betulin (**Table 10**). In studies BSH-12 and BSG-12, sampling was performed on days 0, 7, 14, 21, 28 and at end of treatment, in study BBW-11, on days 0, 7, 14 and at end of treatment. In total, 929 plasma samples were taken.

Of the 929 plasma samples, 37 (4%) had quantifiable betulin concentrations, 14 of these were pre-dose samples and 23 during the treatment period.

Table 10. Summary of betulin concentration measurements in plasma samples from study BSH-12, BSG-12 and BBW-11

			<LLOQ	≥LLOQ				
					Predose		Treatment period	
Study	No. Patients	No. plasma samples tested	n (%)[a]	n (%)[a]	n[a]	Range, ng/mL	n[a]	Range, ng/mL
BSH-12	107	388	383 (98.7)	5 (1.3)	2	1.3-3.0	3	1.2-4.6
BSG-12	112	402	381 (94.8)	15 (3.7)	2	4.1-43.9	13	1.1-68.6
BBW-11	61	139	122 (87.8)	17 (13.9)	10	1.1-7.6	7	1.4-6.6
TOTAL	280	929	886 (95.4)	37 (4.0)	14	1.1-43.9	23	1.1-68.6

[a]- number (%) of plasma samples

LLOQ: lower limit of quantification (1 ng/mL)

The applicant noted that some common nutrients such as lingonberries, olives and apples contain betulin, and considered that they could be a source of measurable betulin plasma levels and also explain the positive pre-dose samples.

2.4.3. Pharmacodynamics

Primary pharmacology

No clinical studies investigating the pharmacodynamic effects of Episalvan gel were submitted.

Secondary pharmacology

No information on secondary pharmacology is available. Considering the insolubility of the active ingredient TE in water and the topical route of administration, this was considered acceptable.

2.4.4. Discussion on clinical pharmacology

Application of Episalvan gel to STSG donor site wounds and Grade 2a burn wounds did not lead to plasma levels of betulin higher than natural background levels originating e.g. from nutritional sources such as olive oil, based on 929 plasma samples from 280 patients in studies BSH-12, BSG-12 and BBW-11. As betulin is the major component of Episalvan gel, and the systemic uptake of this component seems to be very limited, measurement of betulin only in plasma was considered acceptable.

Occasional samples with measurable concentrations of betulin were found both pre- and post-dose, and all reported positive samples had betulin levels in the range of 1-70 ng/ml. Plasma levels resulting from topical treatment of Episalvan were not higher than natural background levels originating from nutritional sources, such as lingonberries, olives and apples which are known to contain betulin.

The CHMP noted that in the studies where pharmacokinetic data were collected, the treated wound area was limited in size. However, as the the two patients with the largest wound areas in the clinical studies had plasma betulin levels below the LLOQ, and preclinical data suggested that larger wound areas (5% of body surface) in mini-pigs did not result in detectable betulin levels, the CHMP considered that it was unlikely that application of Episalvan gel on larger wound areas would result in significant increases to systemic exposure.

Nevertheless, the limited wound sizes that have been studied in the clinical program are reflected in Section 4.4 of the SmPC, which specifically states that the median wound size treated with Episalvan in clinical studies in split thickness donor site wounds was 67.5 cm^2 (range 8-300 cm^2) and 85 cm^2 (range 23-395 cm^2) in the Grade 2a burn wound study.

No further studies on the on the distribution, elimination, dose-proportionality, time dependencies, potential drug-drug interactions of betulin or in special populations were submitted, and this was considered acceptable by the CHMP.

No clinical studies investigating the pharmacodynamic effects of Episalvan gel were submitted and this was considered acceptable by the CHMP. The Applicant referred to published literature on the primary pharmacology of betulin which comprised approximately 72-88% of the dry extract from *Betula* cortex, which have suggested a number of plausible mechanisms of action for betulin.

Several *in vitro* and *ex vivo* experimental approaches have been employed in these studies to demonstrate that TE and its main compound, betulin, has an effect on skin wound healing. These effects could be mediated by different mechanisms, including the modulation of several pro-inflammatory mediators such as COX-2, IL-6 and IL-8 during the inflammatory phase, enhanced migration of keratinocytes and promotion of keratinocyte differentiation and neo-formation of the epithelium.

The CHMP considered that evidence from the published literature they provide plausible explanations in support of an effect of betulin in the wound healing process.

2.4.5. Conclusions on clinical pharmacology

Systemic absorption of betulin following Episalvan gel application on wounds is not different to background plasma levels following nutritional exposure to products which contain betulin. Therefore, the CHMP considered that there was no need to characterise the pharmacokinetic profile of Episalvan gel, further to the information provided by the Applicant.

The pharmacology of Episalvan gel was considered sufficiently characterised.

2.5. Clinical efficacy

2.5.1. Dose response studies

No conventional dose-response studies were performed.

Episalvan gel contains 10% dry extract from *Betula* cortex (birch bark) and 90% sunflower oil. The product is an oleogel, meaning that blending of the dry *Betula* cortex extract with an oil results in the formation of a gel. The API concentration of 10% W/W provides for good physical properties of the formulation, being a thick gel that allows for good coverage of the wound.

In the clinical development program the 10% concentration was selected for the partial thickness wound clinical development programme, which was initiated with two Phase II studies: the STSG donor site wound study BSH-10 and the Epidermolysis Bullosa (EB) study BEB-10.

The performed Phase II studies in 24 patients with STSG donor site wounds and in 10 patients with EB lesions are assessed as small but give some support for the clinical development of the product.

The CHMP considered that the provided information was sufficient for the selection of the chosen concentration, as the systemic exposure of Episalvan is very low and does not allow for conventional dose response studies.

2.5.2. Main studies

Study BSH-12

An open, blindly evaluated, prospective, controlled, randomised, multicentre, phase III clinical trial to compare intra-individually the efficacy and tolerance of Oleogel-S10 versus standard of care in accelerating the wound healing of split-thickness skin graft donor sites

Methods

This was a randomised, open, blindly evaluated, prospective, controlled, multicentre, phase III clinical trial to compare intra-individually the efficacy and tolerance of Oleogel-S10 versus standard of care in accelerating the wound healing of split-thickness skin graft donor sites.

Study Participants

Inclusion criteria

1. Patients at least 18 years old who provided written informed consent;

2. Presenting an STSG donor site wound with a minimum size of 15 cm^2 and with a minimum width of 3 cm;

3. Patient was able to understand the informed consent form (ICF) provided and prepared to comply with all study requirements, including the following: Visiting the trial site for wound dressing change and photo documentation every third or fourth day until both wound halves were closed (but no longer than 28 days after surgery);

4. Willing to perform all necessary wound dressing changes at the trial site. Also the patient needed to agree to return to site for 3 and 12 months follow-up visits;

5. Women of childbearing potential were to apply highly effective method of birth control (failure rate less than 1% per year when used consistently and correctly [e.g. implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices, sexual abstinence, or a vasectomised partner]).

Exclusion criteria

1. Diseases or conditions that could, in the opinion of the investigator, interfere with the assessment of safety or efficacy;

2. A skin disorder that is chronic or currently active and which the investigator considers will adversely affect the healing of the acute wounds or involves the areas to be examined in this trial;

3. A history of clinically significant hypersensitivity to any of the drugs, surgical dressings or excipients to be used in this trial;

4. Known multiple allergic disorders;

5. Taking, or have taken, any investigational drugs within three months prior to the screening visit;

6. Pregnant or breast feeding women are not allowed to participate in the study;

7. Inappropriate to participate in the study, for any reason, in the opinion of the investigator;

8. Mental incapacity or language barriers precluding adequate understanding of the ICF or co-operation or willingness to follow study procedures;

9. Previous participation in this study;

10. Employee at the investigational site, relative or spouse of the investigator.

Treatments

The test treatment was Oleogel-S10, which was applied at every change of wound dressing. The duration of treatment period was until full wound closure of both wound halves, but no longer than 28 days after the start of study treatment.

About 1 cm of Oleogel-S10 string (approximately 100 mg) per cm^2 (i.e. approximately 1 mm thick) was applied to one half of STSG donor site by applying it onto the wound-facing side of the wound dressing.

The reference treatment was non-adhesive wound dressing alone applied at every change of wound dressing.

The study treatment period was 28 days based on previous studies showing that STSG donor sites take approximately two to three weeks to heal. If full wound closure was not achieved within 28 days, study participation ended, and the investigator decided how to continue treatment. Two follow-up visits were scheduled 3 and 12 months after the skin graft for evaluation of the cosmetic outcome. The schedule of planned assessments is provided in **Table 11**.

Concomitant therapy

Any medication considered necessary for the patient's welfare, and not expected to interfere with the evaluation of the study medication, was given at the discretion of the investigator.

All treatments given in addition to study medication were to be recorded in the eCRF together with the indication, quantity or dose administered, dates, and time of administration.

Table 11. Schedule of assessment for patients in Study BSH 12

	Screening	Surgery	Treatment period	EoT	Follow-up[a]
	Day -28 to 0	Day 0	Dressing change[b]	Day 28[c]	Months 3 and 12 (± 14 days)
Informed consent[d]	X	X[i]			
Inclusion + exclusion criteria		X			
Demographics + medical history	X	X[i]			
Concomitant medication	X	X	X	X	
Pregnancy test	X				
STSG harvest		X			
Marking of treatment site		X	X		
Overview photo		X			
Randomisation		X			
Macro photo		X	X	X	X
Application of Oleogel-S10 + non-adhesive wound dressing		X	X		
Plasma blood sample		X	X[e]	X	
Assessment of efficacy[f]			X[e]	X	X
Assessment of tolerability[f]			X[e]	X	X
Epithelialisation[g]			X	X	
Adverse events			X	X	
Cosmetic outcome[h]					X

[a] After start of the treatment (±14 days).
[b] To be performed at least every three or four days.[5]
[c] First observation of wound closure of both wound sites, or maximum Day 28.
[d] Written informed consent obtained from the patient before any screening procedures were performed.
[e] At Days 7 (±1 day), 14 (±1 day), 21 (±1 day), and 28 (±1 day), in case one or both wound halves were open.
[f] Evaluated by investigators and patients using a questionnaire.
[g] Epithelialisation percentage = (area of epithelialisation/size of wound at Day 0) x 100%, evaluated by a study team member.
[h] Performed in the follow-up period. The assessment will be reported in the follow-up report, and not in this report which only covers the treatment period.
[i] Only in case the surgery was performed on the day of screening.
EoT = end of treatment, STSG = split-thickness skin graft.

Objectives

The objectives of the study was to compare intra-individually the efficacy and tolerability of Oleogel-S10 versus wound dressing alone in accelerating the wound healing of STSG donor sites.

Outcomes / endpoints

Primary efficacy endpoint

- Intra-individual difference in time to wound closure (at least 95% epithelialisation) between wound halves either treated with Oleogel-S10 and non-adhesive wound dressing or treated with non-adhesive wound dressing alone, based on photo evaluation by three independent, blinded experts.

Secondary efficacy endpoints

- Intra-individual difference in time to wound closure (at least 95% epithelialisation) between wound halves either treated with Oleogel-S10 and non-adhesive wound dressing or treated with non-adhesive wound dressing alone, separately for each of the three independent, blinded experts;
- Time from surgery until wound closure is achieved, separately for wound halves treated with Oleogel-S10 and non-adhesive wound dressing versus non-adhesive wound dressing alone;
- Percentage of patients with earlier healing of wound area treated with Oleogel-S10 compared to non-adhesive wound dressing alone;
- Percentage of patients with wound closure at different time points;
- Percentage of wound epithelialisation at different time points as assessed by a study team member during wound dressing change;
- Assessment of efficacy (evaluated by investigators and patients).

Further efficacy parameters

- Percentage of patients with earlier healing of wound half treated with Oleogel-S10 compared to non-adhesive wound dressing alone, as evaluated by the unanimous decision of the three independent, blinded experts;
- Relative intra-individual difference in time to wound closure between wound halves;
- Additional analyses specified after unblinding in an Addendum to the statistical analysis plan included absolute and relative intra-individual difference in time to wound closure based on the investigator assessment, and time from surgery until wound closure based on the investigator assessment.

Sample size

It was assumed that enrolling 105 patients would result in a width of the confidence interval (CI) of 1.722 days: it was further assumed that with a sample size of 105 patients, a two-sided 95% CI for the difference in paired means extends 0.861 from the observed mean, assuming a standard deviation of 4.500 and a CI based on the large sample z statistic. A sample size of N =105 patients was also deemed sufficient to allow for substantial identification and reporting of AEs with the probability of observing at least one event of 0.95 when the probability of an event was 0.028.

Randomisation

Method of assigning wound halves to treatment

With the treatment open to investigators and patients, special emphasis was placed on a tamper-proof randomisation method. Before the STSG surgery the designated donor site was divided into two areas of

equal size and marked as proximal and distal half or left and right half, depending on the location of the wound in regard to the centre of the body. After STSG harvest and complete marking of the two wound halves an overview photo was taken, which showed the complete STSG donor site wound area with markings of the wound halves and the location on the patient's body as illustrated in **Figure 2**. The overview photo was uploaded to the eCRF for randomisation by IWRS. An automatic check validated that the photo had been taken the same day the photo was uploaded for randomisation. The investigator then received the randomised allocated treatment for the two wound halves from the IWRS. This procedure precluded any investigator bias in the assignment of treatment to wound halves. For all randomisation pictures it was subsequently verified that they showed the wound which received treatment with the study medication, that the STSG had been harvested, and that the division into two wound halves had been marked on the skin.

Figure 2. Skin grafting, wound half assessment, randomisation, photo documentation and treatment in Study BSH-12

Blinding (masking)

Although the treatment was open to patients and investigators, the evaluation of the clinical efficacy was performed in a blinded manner. Photographs of the treated wound halves taken by the site staff were evaluated by three independent wound healing experts having no information about the treatment regimen of any of the photographed wounds for an unbiased, blinded judgement.

Observer-blinded assessment of wound healing based on photographs

Assessment of efficacy was primarily based on blinded photo evaluation. Special care was taken with a quality control check of photographs to ensure blinding of evaluators. Blinded reader assessment results were used as source data for calculation of the primary endpoint and several secondary endpoints. In addition, other secondary endpoints were based on direct investigator assessment or questionnaire-based patient responses. Those were performed open-label.

The baseline photo was taken on Day 0 before treatment. At each wound dressing change, the wound was cleaned, photographed and the photo uploaded to the eCRF for the blinded read.

The treatment period (and thus photo documentation) lasted until wound closure was determined by the investigator for both wound halves but no longer than 28 days after start of study treatment.

Preparation of photographs for blinded read

Two parties were involved in preparing the photographs for the blinded read. The eCRF provider (first party) removed markings as well as a 1 cm wide middle section and provided one separate image per wound half. These images were then controlled by an unblinded expert at FGK Clinical Research GmbH (second party) for any signs that could interfere with blinding, e.g. visible residual markings or gel residues.

If it was not possible to remove signs that could interfere with blinding, both images (of the Oleogel-S10 treated and of the corresponding standard of care treated wound half) were excluded from the blinded read - even if one of the two images was “clean”. An example for an “interfering sign” is the characteristic residue of Oleogel-S10 gel on the wound.

If only a Day 0 photo was available or remained after the quality control process described above, this patient was entirely excluded from the subsequent blinded read - thus no photos from this patient were presented to the blinded experts (‘patient excluded from blinded read’).

All photographs of a wound half which had passed the quality control process were assembled to photo series and a unique ID number per expert were assigned for the blinded read.

Photo evaluation by blinded experts

Photographs eligible for the blinded read were independently evaluated by each of the three wound healing experts.

All available photos from one wound half (Oleogel-S10 treated or standard of care treated) comprising a ‘photo series’ were presented to the blinded expert with no information on the treatment and in randomised order of the photo series. Photos were presented in chronological order but with no information on the specific treatment day at which the respective photo was taken. With a zoom view, the blinded experts were able to magnify areas of interest to the full resolution of the original macro photograph.

The blinded experts provided the following assessments:

- Rate the photograph quality and decide whether the photograph series of the respective wound half is evaluable. If due to the quality of the presented photographs a decision is not possible whether a photograph in the series had reached wound closure (defined as at least 95% epithelialisation) or not, rate the photo series as ‘not evaluable’.
- If ‘evaluable’, determine which photograph is the first to show wound closure (epithelialisation of at least 95% of the wound area) or whether wound closure is not detectable in any of the photos.

Separate photo series of both wound halves for each patient were assessed independently by the three blinded readers as described, with the exception of those patients for whom the series had been excluded from the blinded read.

Statistical methods

The primary endpoint, difference in time to wound closure between wound sites (Oleogel-S10 treated *minus* standard of care treated half), was tested using a two-sided paired t-test. For censored observations (wound closure not observed), it was assumed that wounds were closed +1 day after the last observation. Such an approach would be appropriately conservative and likely to not introduce a bias in favour of Oleogel if the

number of wounds not closed at the end of observation was lower in the Oleogel treated group The ITT analysis set i.e. all patients who had been treated at least once with Oleogel-S10 was the primary analysis set.

Secondary time-to-event analyses were performed as described for the primary analysis. For time from surgery until wound closure Kaplan-Meier analyses were additionally performed. For the percentage of patients with earlier healing a non-parametric Sign-test was used. The differences in percentage of wound epithelialisation was analysed by a t-test and Sign-test. For all tests, a two-sided significance level of 5% was applied. All secondary endpoints and safety analyses were generally done descriptively. The percentage of patients with application site reactions was compared between the two treatment regimens using McNemar's test.

Results

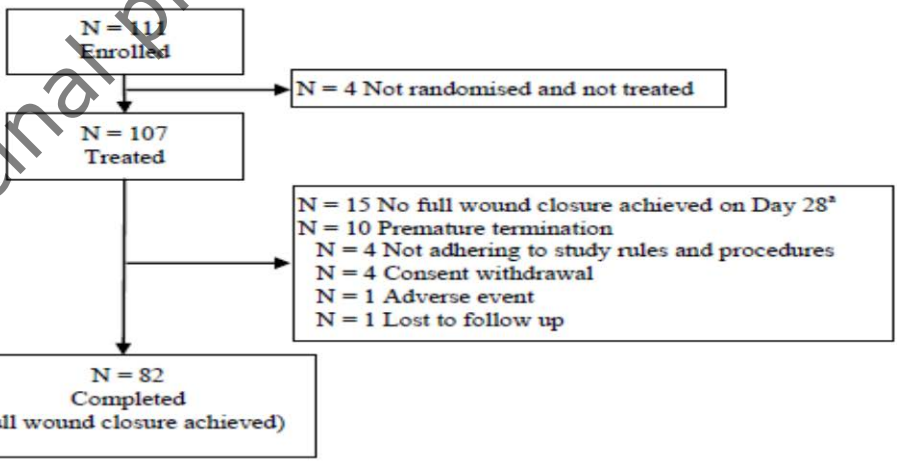
Participant flow

A total of 111 patients were enrolled at 18 centres in six countries: Germany (8 centres), Czech Republic (2 centres), Poland (1 centre), Finland (1 centre), Austria (2 centres), and Bulgaria (4 centres).

Of the 111 enrolled patients, 107 patients received treatment with Oleogel-S10 plus wound dressing and wound dressing alone (standard of care).

A total of 82 (77%) patients completed the treatment period as scheduled and achieved full wound closure. Of the 25 patients who did not achieve wound closure in the treatment period, 15 patients completed treatment and did not achieve full wound closure until Day 28 and 10 patients were prematurely discontinued. Of the 15 patients not achieving full wound closure, for 10 patients both halves were not fully closed, for 4 patients only the Oleogel-S10 treated wound half was fully closed, and for 1 patient only the wound half treated with standard of care was fully closed.

Figure 3. Patient disposition in Study BSH-12



[a] One of these patients was discontinued due to an AE on Day 28.
N = number of patients.

Recruitment

First subject enrolled: 3rd August 2012; last subject completing treatment period: 23rd August 2013.

Conduct of the study

There were no substantial protocol amendments introduced in study BSH-12.

Major protocol deviations are summarised in **Table 12**.

Table 12. Major Protocol Deviations in Study BSH 12

Deviation	n (%)[a]		Exclusion from
Total patients with major protocol deviation	**76**	**(71.0)**	
Early discontinuation	10	(9.3)	Completer, TPP, PP analysis
Different wound dressing	2	(1.9)	TPP, PP analysis
Treatment not according to protocol	1	(0.9)	TPP, PP analysis
Wound surface refreshed by scalpel	1	(0.9)	TPP, PP analysis
Major protocol deviations with regard to photo documentation (as of BDRM)	62[b]	(57.9)	PP analysis
Both photo series not valid and no wound closure for both photo series observed	20	(18.7)	PP analysis
Both photo series not valid and wound closure for both photo series observed	5	(4.7)	PP analysis
Both photo series not valid and wound closure for one photo series observed	2	(1.9)	PP analysis
One photo series not valid and no wound closure for this photo series observed	31	(29.0)	PP analysis
One or both photo series rated not evaluable by ≥2 of 3 blinded readers	3	(2.8)	PP analysis
Patient not part of blinded reads (only Day 0 photo available)	1	(0.9)	PP analysis

Note that one patient could present with several protocol deviations.
[a] Percentages are based on the total number of patients in the SAF.
[b] Only includes patients who were not excluded from the completer and TPP analysis sets due to other major protocol deviations.
BDRM = blind data review meeting, N = number of patients in the analysis set, n = number of patients with respective protocol deviation, PP = per-protocol, SAF = safety analysis set, TPP = treatment per-protocol.

Availability of wound photos for blinded evaluation

The numbers of patients whose photos were excluded from the blinded read, and (for these patients) the proportion of photos that were missing from each series are summarised in **Table 13**.

Table 13. Exclusion of photos from blinded review in Study BSH 12 (ITT, N = 107)

		N = 107
Exclusion of patient from blinded read	n (%) patients	3 (2.8)
No photo excluded	n (%) patients	34 (31.8)
One or more photos excluded	n (%) patients	70 (65.4)
		N' = 70
Proportion of photos excluded from the blinded evaluation for patients for whom photos were excluded	Median (P25, P75)	25.0 (20.0, 33.3)
	Mean ± SD	28.6 ± 14.3

P25: 25th percentile; P75: 75th percentile.
ITT = intention to treat, N = number of patients in the analysis set, N' = number of patients for whom photos were excluded, n = number of patients with respective characteristic, SD = standard deviation.

In study BSH-12, for 70 patients (65%) some photos were found in quality control to be not amenable to blinding (e.g. due to gel residues) and were excluded from the blinded read. For these patients, the mean proportion of excluded photos was 29%. Due to the large number of excluded photos the CHMP requested a

re-evaluation of the photo series with all photos included even if the blinding would be difficult to maintain. In addition, the applicant was requested to provide a table showing the number of excluded photos in which: a) wound on the active side was closed, b) wound on the control side was closed, c) both were closed and d) both were open. In addition, the applicant was asked to provide a statistical analysis on the difference between the two treatment groups in the proportion of patients with wound closure at the pre-specified time points. This request extended to all the clinical studies which were considered during the evaluation of this application and are therefore presented in the "Analysis performed across trials (pooled analyses and meta-analysis)" section of this report.

Baseline data

The demographic characteristics of patients in study BSH-12 are summarised in **Table 14**.

Table 14. Demographics, baseline and skin characteristics BSH-12 (SAF, N=107)

Age (years)	**Median (Range)**	**56**	**(18 - 86)**
Sex			
Male	n (%)	68	(63.6)
Female	n (%)	39	(36.4)
Race			
White (Caucasian)	n (%)	107	(100.0)
Skin type Fitzpatrick			
I	n (%)	3	(2.8)
II	n (%)	82	(76.6)
III	n (%)	19	(17.8)
IV	n (%)	3	(2.8)
Height (cm)			
Male	Mean (SD)	178.0	(7.4)
Female	Mean (SD)	163.6	(7.4)
Weight (kg)			
Male	Mean (SD)	83.6	(14.7)
Female	Mean (SD)	70.7	(14.0)
BMI (kg/m²)			
Male	Mean (SD)	26.4	(4.4)
Female	Mean (SD)	26.5	(5.4)

Percentages are based on the total number of patients in the safety analysis set.
BMI = body mass index, n = number of patients with respective characteristic, N = number of patients in the analysis set, SAF = safety analysis set, SD = standard deviation.

Baseline characteristics of STSG donor sites

Characteristics of the STSG donor sites are summarised in **Table 15**. The majority of STSG donor sites were located on the legs, with 52% on the right leg, and 36% on the left leg. The median wound size was 58 cm² ranging from 20 cm² to 600 cm².

Table 15. Baseline characteristics of STSG donor sites in Study BSH 12 (SAF, N = 107)

Wound location	**n**	**(%)**
Left arm	2	(1.9)
Right leg	56	(52.3)
Left leg	39	(36.4)
Right foot	1	(0.9)
Other	9	(8.4)
Wound dimensions	**Median**	**(Range)**
Width [cm]	6.0	(3 - 24)
Length [cm]	9.0	(4 - 25)
Size [cm²]	57.5	(20 - 600)

N = number of patients in the analysis set, n = number of patients with respective wound location, SAF = safety analysis set, SD = standard deviation, STSG = split-thickness skin graft.

The wound location of STSG donor sites in the completer and PP analysis sets were similar to those described above.

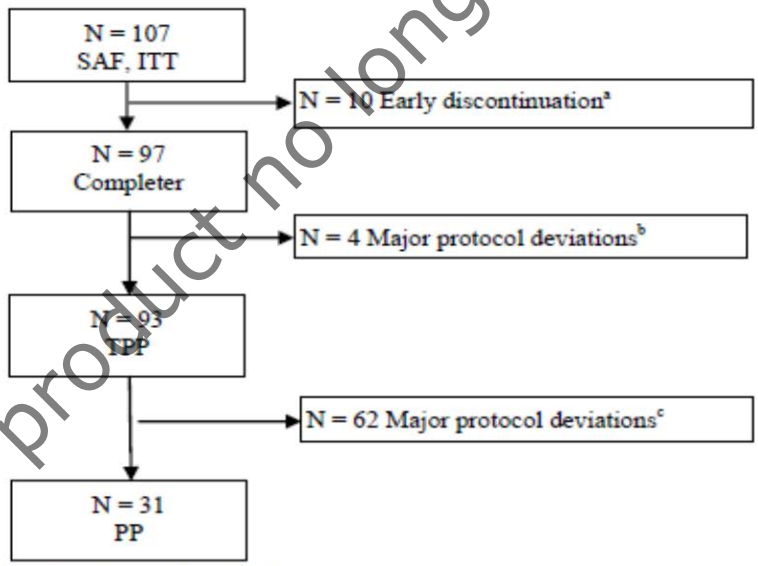
Numbers analysed

Analysis sets

Patients with major protocol deviations were excluded from the "Per protocol" (PP) analysis set. Major protocol deviations included issues related to the photos. After database lock, but before communication of study results to the sponsor, a "treatment-PP"(TPP) analysis set was defined because the initially defined criteria for the PP set excluded about 70% of patients from the analysis mainly due to issues related to photos.

This TPP analysis set included all patients who were treated according to protocol without consideration of issues concerning photo documentation for the blinded read. Thus the TPP dataset reflects protocol adherence by investigators and patients, while the PP dataset reflects full completeness of the photo documentation for the blinded read. These analysis sets are described in **Figure 4**.

Figure 4. Analysis sets in Study BSH-12



[a] One patient that is listed as early discontinuation was lost to follow up.
[b] Unrelated to photo documentation.
[c] Related to photo documentation.
BDRM = blind data review meeting, ITT = intention to treat, N = number of patients, PP = per-protocol, SAF = safety analysis set

Outcomes and estimation

Study BSH-12 Primary analysis

The mean, based on photo evaluation by three independent and blinded experts, intra-individual difference in time to wound closure between the wound halves (Oleogel-S10 and wound dressing *minus* standard of care) was -1.4 days, i.e. smaller than zero, indicating that wound halves healed faster with Oleogel-S10 treatment

regimen than with standard of care (**Table 16**). The between-treatment difference was statistically significant (p <0.0001, two-sided paired t-test, see table below).

Table 16. Difference in time to wound closure in Study BSH 12- mean blinded expert evaluation (ITT, N = 107)

n	Difference in time to wound closure (days) (Oleogel-S10 and wound dressing – standard of care)[a]					
	Mean	SD	Median	Min, Max	95% CI	p-value[b]
107	-1.4	2.3	-0.3	-10.0, 2.3	-1.8, -0.9	<0.0001

[a] Difference in time to wound closure was set to 0 for photo series rated 'not evaluable'. If wound closure was not observed, it was calculated to have occurred one day after the last photograph in the series.

[b] Based on a two-sided paired t-test evaluating the mean difference as different from 0.

CI = confidence interval, ITT = intention-to-treat, Max = maximum, Min = minimum, n = number of patients included in the analysis, N = number of patients in the analysis set, SD = standard deviation.

The time from surgery to wound closure and the difference in time to wound closure can be seen in **Table 17**.

Table 17. Time from surgery to wound closure in Study BSH 12 (mean blinded expert evaluation, conservative estimation, ITT, N = 107)

Treatment	n[a]	Number of days from surgery to wound closure				
		Mean	SD	Median	Min, Max	95% CI
Oleogel-S10	102	15.5	6.4	14.3	4.0, 29.0	14.2, 16.8
Standard of care	102	17.1	6.8	15.2	4.0, 29.0	15.8, 18.5

Conservative estimation means that the first observation of wound closure was taken as time of wound closure. If wound closure was not observed, it was calculated to have occurred one day after the last photograph in the series.

[a] For five patients data were missing.

CI = confidence interval, ITT = intention-to-treat, Max = maximum, Min = minimum, n = number of evaluable wound halves, N = number of patients in the analysis set, SD = standard deviation

Derivation of primary endpoint

Wound closure could not be determined for all photo series by the blinded experts. If wound closure was not observed in one or both photo series for a patient, no definite time to calculate a difference in wound healing time was available ('censored values') and certain assumptions had to be made to calculate the intra-individual difference in time to wound closure. If wound closure had not been observed for one of the two wound halves, the time to wound closure for the unknown half was set to the day of the last photo +1 day. By using this 'day of last photo +1' approach, the time difference to wound closure of the other wound half, and thus the treatment effect size, was very likely underestimated. The number of patients for whom derivations of censored values were to be made to calculate the intra-individual time difference in wound closure are summarised in **Table 18** based on the data available after the blinded read.

Table 18. Number of patients with different derivation categories of primary endpoint by expert in Study BSH 12 (ITT, N = 107)

Basis for derivation	Derivation of intra-individual difference in time to wound closure *(calculation)*	Number (%)[a] of patients					
		Expert 1		Expert 2		Expert 3	
Wound closure observed for both wound halves	Time difference based on wound closure observation for both wound halves[b]	19	(17.8)	41	(38.3)	22	(20.6)
Wound closure observed for wound half treated with Oleogel-S10 only	Time advantage of Oleogel-S10 very likely underestimated *(time to wound closure with Oleogel-S10 - [day of last photo +1 day])*	38	(35.5)	21	(19.6)	42	(39.3)
Wound closure observed for wound half treated with standard of care only	Time advantage of standard of care very likely underestimated *([day of last photo +1 day] - time to wound closure with standard of care)*	1	(0.9)	8	(7.5)	2	(1.9)
No wound closure observed for either wound half	Difference set to 0	42	(39.3)	21	(19.6)	31	(29.0)
Patient not evaluable[c]	Difference set to 0	4	(3.7)	13	(12.1)	7	(6.5)
Patient not part of blinded read[d]	Difference set to 0	3	(2.8)	3	(2.8)	3	(2.8)

[a] Percentages are based on the total number of patients in the ITT.
[b] Difference in time to wound closure = time to wound closure of the wound half treated with Oleogel-S10 *minus* time to wound closure of the wound half treated with standard of care.
[c] As rated by the respective blinded expert (e.g. due to insufficient photo quality).
[d] Patients H-04-01, H-604-01, and H-605-01 were not presented to the blinded readers since only the Day 0 photo would have been available for photo evaluation.
ITT = intention-to-treat, N = number of patients in the analysis set

Results of the primary endpoint for the completer, TPP, and PP analysis sets (**Table 19**) confirmed the results of ITT analysis showing quicker healing of wound halves treated with Oleogel-S10 and wound dressing than the wound halves treated with standard of care.

Table 19. Difference in time to wound closure in Study BSH 12– mean blinded expert evaluation (Completer, TPP and PP analysis)

Analysis set	n	Difference in time to wound closure (days) (Oleogel-S10 and wound dressing – standard of care)[a]					
		Mean	SD	Median	Min, Max	95% CI	p-value[b]
Completer analysis (N = 97)	97	-1.4	2.4	-0.3	-10.0, 2.3	-1.9, -0.9	<0.0001
TPP analysis (N = 93)	93	-1.4	2.4	-0.3	-10.0, 2.3	-1.9, -0.9	<0.0001
PP analysis (N = 31)	31	-1.7	2.4	-0.7	-10.0, 1.7	-2.6, -0.8	0.0006

[a] Difference in time to wound closure was set to 0 for photo series rated 'not evaluable'. If wound closure was not observed, it was calculated to have occurred one day after the last photograph in the series.
[b] Based on a two-sided paired t-test evaluating the mean difference as different from 0.
CI = confidence interval, Max = maximum, Min = minimum, n = number of patients included in the analysis, N = number of patients in the analysis set, PP = per-protocol, SD = standard deviation, TPP = treatment-per-protocol.

Sensitivity analysis

Because of the high proportion of censored values in the calculation of the primary endpoint, sensitivity analyses were done to assess whether the size of treatment effect was truly reflected in the primary endpoint. In the primary analysis, one day was added to the day of the last photograph available for the assessment of time to wound closure in cases in which wound healing was not observed. However, as wound dressings were changed every three to four days, three to four days would be the minimal duration for which healing would have been observed in the study, a much longer interval than one day used in the primary analysis. Thus in the sensitivity analysis, different intervals (+2 days, +3 days, +4 days, +7 days, and +MTWDC) were added to the last day for which a photo was available (**Table 20**).

Table 20. Difference in time to wound closure in Study BSH 12– mean blinded expert evaluation, sensitivity analysis (ITT, N = 107)

Estimator for time period between last observation and day of wound closure if no wound closure was observed	Difference in time to wound closure (days) (Oleogel-S10 and wound dressing – standard of care)[a]					
	Mean	SD	Median	Min, Max	95% CI	p-value[b]
+2	-1.7	2.5	-0.7	-10.3, 2.3	-2.2, -1.2	<0.0001
+3	-1.9	2.8	-1.0	-11.3, 3.0	-2.5, -1.4	<0.0001
+4	-2.2	3.1	-1.3	-12.3, 3.7	-2.8, -1.6	<0.0001
+7	-3.1	4.0	-2.3	-15.3, 5.7	-3.8, -2.3	<0.0001
+MTWDC[c]	-2.0	2.8	-1.0	-11.4, 3.1	-2.5, -1.4	<0.0001

[a] Difference in time to wound closure was set to 0 for photo series rated 'not evaluable'. If wound closure was not observed, it was calculated to have occurred 2, 3, 4, or 7 days, or MTWDC after the last photograph in the series, as indicated.

[b] Based on a two-sided paired t-test evaluating the mean difference as different from 0.

CI = confidence interval, ITT = intention-to-treat, Max = maximum, Min = minimum, MTWDC = mean time to wound dressing change, n = number of patients included in the analysis, N = number of patients in the analysis set, SD = standard deviation.

Secondary efficacy endpoints

Intra-individual difference in time to wound closure (at least 95% epithelialisation) between wound halves, separately for each of the three independent, blinded experts

Similar to the results for the primary endpoint, each of three blinded experts reported faster healing of wound halves treated with Oleogel-S10 and wound dressing than the wound halves treated with standard of care (-1.1, -1.5, and -1.5 days, respectively, two-sided paired t-test p<0.0001, ITT).

Time from surgery until wound closure was achieved, separately for wound halves with Oleogel-S10 and non-adhesive wound dressing versus non-adhesive wound dressing alone

The mean time from skin grafting surgery (Day 0) to wound closure for Oleogel-S10 treated wound halves was shorter than that for wound halves treated with wound dressing alone (15.5 days versus 17.1 days). The corresponding expert opinions, investigator assessments, and the centre-, country-stratified analyses showed similar results.

Percentage of patients with earlier healing of wound area treated with Oleogel-S10 compared to non-adhesive wound dressing alone

The percentage of patients showing faster healing of the Oleogel-S10 treated wound half was higher than the percentage of patients showing faster healing of the wound half treated with standard of care (61.7% versus 7.5%). For 31% of patients no difference in wound healing was observed, photographs were not evaluable, or none of the wound areas achieved complete wound closure.

Percentage of patients with wound closure at different time points

According to the mean expert evaluation, the percentage of wound halves achieving full wound closure was higher for the Oleogel-S10 treated wound halves than the standard of care wound halves on Day 10 (25.5% and 15.7% of patients, respectively), Day 14 (49.0% and 37.3%, respectively), Day 18 (70.6% and 61.8%, respectively), Day 21 (77.5% and 71.6%, respectively) and Day 28 (94.1% and 90.2%, respectively). Similar results were observed in the analyses based on individual expert assessment.

Further efficacy endpoints

Percentage of patients with earlier healing of wound half with Oleogel-S10 compared to non-adhesive wound dressing alone, as evaluated by the unanimous decision of the blinded experts

According to the unanimous decision of the blinded experts, 100% of patients for whom a between-treatment difference in wound healing was observed (n = 16) showed earlier healing of their wound halves treated with the Oleogel-S10 regimen while none of the wound halves treated with the standard of care showed an earlier healing. For 91 out of 107 patients no difference in wound healing was observed, photographs were not evaluable, or no unanimous decision could be reached.

Study BSG-12

An open, blindly evaluated, prospective, controlled, randomised, multicentre, phase III clinical trial to compare intra-individually the efficacy and tolerance of Oleogel-S10 versus standard of care in accelerating the wound healing of split-thickness skin graft donor sites.

Methods

The design of this study was identical to Study BSH-12.

Results

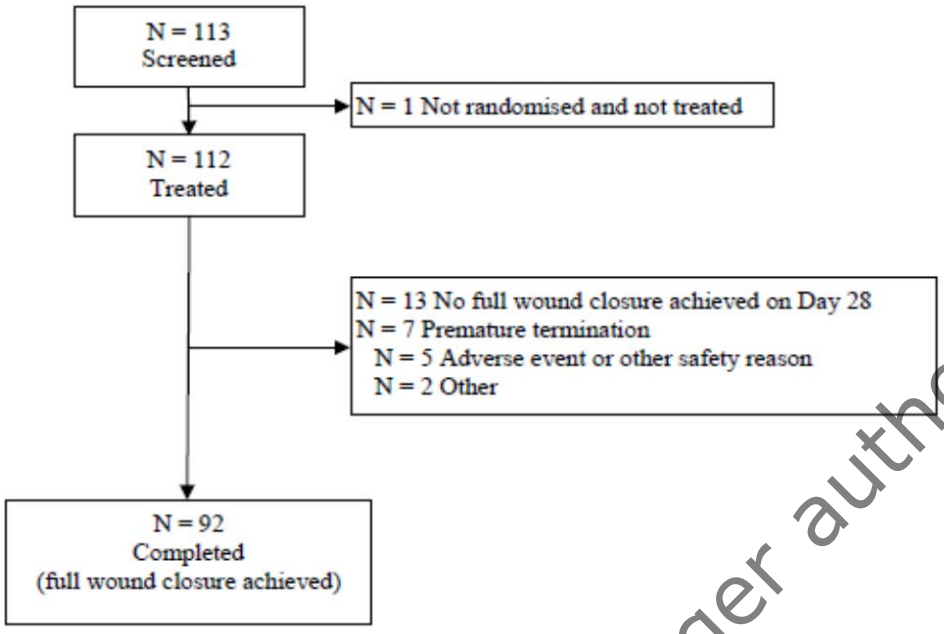
Participant flow

A total of 113 patients were screened and enrolled at 14 centres in 4 countries: Spain (6 centres), Greece (3 centres), Latvia (2 centres) and France (3 centres).

Of the 113 screened patients, 112 received treatment with Oleogel-S10 and wound dressing or standard of care. One patient was not treated with study medication, as the STSG surgery was cancelled.

A total of 92 patients completed the treatment period and achieved full wound closure by Day 28 or before as scheduled. Of the remaining 20 patients, 13 patients did not achieve full wound closure until Day 28 and 7 patients were prematurely discontinued. Of the 13 patients who did not achieve full wound closure by Day 28, both halves were not fully closed for 4 patients, only the Oleogel-S10 treated wound half was fully closed for 5 patients, and only the wound half treated with standard of care was fully closed for 4 patients. Patient disposition in this study is illustrated in **Figure 5**.

Figure 5. Patient disposition in Study BSG-12



N = number of patients.

Recruitment

First subject enrolled: 4th April 2013; last subject completing treatment period: 25th September 2013.

Conduct of the study

There were no substantial protocol amendments introduced in Study BSG-12.

Major protocol deviations are summarised in **Table 21**.

Availability of wound photos for blinded evaluation

The numbers of patients whose photos were excluded from the blinded read, and (for these patients) the proportion of photos that were missing from each series are summarised in **Table 22**. As mentioned previously the CHMP requested a re-evaluation of the photo series with all photos included even if the blinding would be difficult to maintain. In addition, the applicant was requested to provide a table showing the number of excluded photos in which: a) wound on the active side was closed, b) wound on the control side was closed, c) both were closed and d) both were open. In addition, the applicant was asked to provide a statistical analysis on the difference between the two treatment groups in the proportion of patients with wound closure at the pre-specified time points. This data is presented in the "Analysis performed across trials (pooled analyses and meta-analysis)" section of this report.

Table 21. Major Protocol Deviations BSG-12

Deviation	n (%)[a]		Exclusion from
Total patients with major protocol deviation	**73**	**(65.2)**	
ICF not signed by LAR	2	(1.8)	ITT, Completer, TPP, PP analysis
Early discontinuation	6	(5.4)	Completer, TPP, PP analysis
Treatment not according to protocol	6	(5.4)	TPP, PP analysis
Not treated as randomised	1[b]	(0.9)	TPP, PP analysis
Major protocol deviations with regard to photo documentation (as of BDRM)[c]	61[d]	(54.5)	PP analysis
Both photo series not valid and no wound closure for both photo series observed	15	(13.4)	PP analysis
Both photo series not valid and wound closure for both photo series observed	14	(12.5)	PP analysis
Both photo series not valid and wound closure for one photo series observed	7	(6.3)	PP analysis
One photo series not valid and no wound closure for this photo series observed	16	(14.3)	PP analysis
One photo series not valid and wound closure for this photo series observed	8	(7.1)	PP analysis
Patient not part of blinded read (only Day 0 photo available)	1	(0.9)	PP analysis

Note that one patient could present with more than one protocol deviation.

[a] Percentages are based on the total number of patients in the SAF.

[b] This patient (G-1120-20) showed faster healing with Oléogel-S10 than standard of care (when treatment as received is considered, Listing 3.2.1, Appendix 16.3.3). In the efficacy analyses which were done 'as randomised' this patient was included as having faster healing with standard of care.

[c] One additional patient (G-0802-11) had a Day 14 photo erroneously uploaded to the eCRF on Day 10 (see 'Note to file' in Appendix 16.1.9).

[d] Only includes patients who were not excluded from the completer and TPP analysis sets due to other major protocol deviations.

BDRM = blind data review meeting, ICF = informed consent form, ITT = intention-to-treat analysis set, LAR = legally accepted representative, N = number of patients in the analysis set, n = number of patients with respective protocol deviation, PP = per-protocol, SAF = safety analysis set, TPP = treatment-PP.

Table 22. Exclusion of photos from blinded review (ITT, N = 110) BSG-12

		N = 110	
Exclusion of patient from blinded read	n (%) patients	2	(1.8)
No photo excluded	n (%) patients	34	(30.9)
One or more photos excluded	n (%) patients	74	(67.3)
		N' = 74	
Proportion of photos excluded from the blinded evaluation for patients for whom photos were excluded	Median (P25, P75)	33.3 (20.0, 50.0)	
	Mean ± SD	35.1 ± 16.7	

P25: 25th percentile; P75: 75th percentile.

ITT = intention to treat, N = number of patients in the analysis set, N' = number of patients for whom photos were excluded, n = number of patients with respective characteristic, SD = standard deviation.

In study BSG-12, in 74 patients (67%) one or more photos were excluded from the blinded read; for these patients, the mean proportion of photos excluded from the blinded read was 35%. In most cases photos were excluded from the blinded read due to gel residues.

Baseline data

The demographic characteristics of patients in BSG-12 can be seen in **Table 23**.

Table 23. Demographics, baseline and skin characteristics BSG-12 (SAF, N=112)

Age (years)	Median (Range)	49	(19 - 90)
Sex			
Male	n (%)	73	(65.5)
Female	n (%)	39	(34.8)
Race			
Not applicable	n (%)	11	(10.0)
White (Caucasian)	n (%)	98	(87.5)
Black or African American	n (%)	1	(0.9)
Other	n (%)	2	(1.8)
Skin type Fitzpatrick			
I	n (%)	1	(0.9)
II	n (%)	32	(28.6)
III	n (%)	40	(35.7)
IV	n (%)	19	(17.0)
V	n (%)	20	(17.9)
Height (cm)			
Male	Mean (SD)	176.2	(7.4)
Female	Mean (SD)	162.9	(5.7)
Weight (kg)			
Male	Mean (SD)	82.3	(17.0)
Female	Mean (SD)	70.7	(14.4)
BMI (kg/m^2)			
Male	Mean (SD)	26.5	(5.1)
Female	Mean (SD)	26.6	(4.8)

Percentages are based on the total number of patients in the safety analysis set.
BMI = body mass index, n = number of patients with respective characteristic, N = number of patients in the analysis set, SAF = safety analysis set, SD = standard deviation

Baseline characteristics of STSG donor sites

In study BSG-12, the majority of STSG donor sites were located on the legs, with 40% on the right leg, and 46% on the left leg. The median wound size was 76 cm² ranging from 15 cm² to 375 cm².

Table 24. Baseline characteristics of STSG donor sites, BSG-12 (SAF, N = 107)

Wound location	n	(%)[a]
Chest front	5	(4.5)
Right arm	4	(3.6)
Left arm	1	(0.9)
Right leg	44	(39.3)
Left leg	51	(45.5)
Left foot	1	(0.9)
Other	6	(5.4)
Wound dimensions	**Median**	**(Range)**
Width [cm]	7.0	(3 - 15)
Length [cm]	11.8	(4 - 25)
Size [cm²]	75.9	(15 - 375)

[a] Percentage based on the total number of patients.
N = number of patients in the analysis set, n = number of patients with respective wound location, SAF = safety analysis set, SD = standard deviation, STSG = split-thickness skin graft

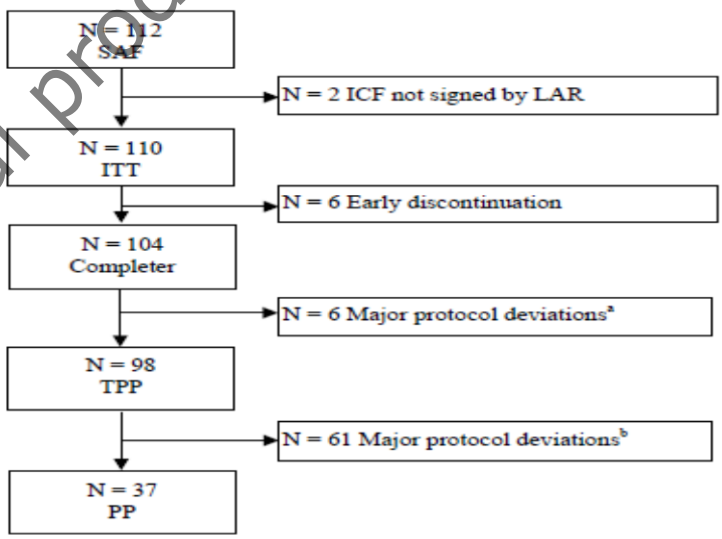
The wound location of STSG donor sites in the completer and PP analysis sets were similar to those described above.

Numbers analysed

Analysis sets

Patient populations studied were defined in the same fashion as in Study BSH-12, including the TPP population and are described in **Figure 6**.

Figure 6. Analysis sets BSG-12



[a] Unrelated to photo documentation.
[b] Related to photo documentation.
ICF = informed consent form, ITT = intention to treat, LAR = legally accepted representative, N = number of patients, PP = per-protocol, SAF = safety analysis set.

Outcomes and estimation

Primary analysis

The mean intra-individual difference in time to wound closure between the wound halves (Oleogel-S10 and wound dressing *minus* standard of care) was -0.8 days, i.e. smaller than zero, indicating that wound halves heal faster with Oleogel-S10 treatment regimen than with the standard of care. The between-treatment difference was statistically significant (p = 0.0232, two-sided paired t-test, **Table 25**).

Table 25. Difference in time to wound closure – mean blinded expert evaluation in Study BSG-12 (ITT, N = 110)

n	Difference in time to wound closure [days] (Oleogel-S10 and wound dressing – standard of care)[a]					
	Mean	SD	Median	Min, Max	95% CI	p-value[b]
110	-0.8	3.6	0.0	-18.3, 12.3	-1.5,-0.1	0.0232

[a] Difference in time to wound closure was set to zero for non evaluable photo series. If wound closure was not observed, it was calculated to have occurred one day after the last photograph in the series.

[b] Based on a two-sided paired t-test evaluating the mean difference as different from zero.

CI = confidence interval, ITT = intention-to-treat, Max = maximum, Min = minimum, n = number of patients included in the analysis, N = number of patients in the analysis set, SD = standard deviation.

The time from surgery to wound closure and the difference in time to wound closure is reported in **Table 26**.

Table 26. Time from surgery to wound closure in Study BSG-12 (mean blinded expert evaluation, conservative estimation, ITT, N = 110)

Treatment	n[a]	Number of days from surgery to wound closure				
		Mean	SD	Median	Min, Max	95% CI
Oleogel-S10	108	15.1	5.3	14.3	4.0, 29.0	14.1, 16.1
Standard of care	108	16.0	6.0	14.5	4.0, 29.0	14.8, 17.1

[a] For two patients data were missing.

Conservative estimation means that the first observation of wound closure was taken as time of wound closure.

CI = confidence interval, ITT = intention-to-treat, Max = maximum, Min = minimum, n = number of evaluable wound halves, N = number of patients in the analysis set, SD = standard deviation.

Derivation of primary endpoint

As with Study BSH-12, wound closure could not be determined for all photo series by the blinded experts. If wound closure was not observed in one or both photo series for a patient, no definite time to calculate a difference in wound healing time was available ('censored values') and certain assumptions had to be made to calculate the intra-individual difference in time to wound closure. If wound closure had not been observed for one of the two wound halves, the time to wound closure for the unknown half was set to the day of the last photo +1 day (**Table 27**).

By using this 'day of last photo +1' approach, the time difference to wound closure of the other wound half, and thus the treatment effect size, was very likely underestimated. The number of patients for whom

derivations of censored values were to be made to calculate the intra-individual time difference in wound closure are summarised in the table below by expert based on the data available after the blinded read.

Table 27. Number of patients with different derivation categories of primary endpoint by expert (ITT, N = 110)

Basis for derivation	Derivation of intra-individual difference in time to wound closure *(calculation)*	Number (%)[a] of patients		
		Expert 1	Expert 2	Expert 3
Wound closure observed for both wound halves	Time difference based on wound closure observation for both wound halves[b]	70 (63.6)	51 (46.4)	22 (20.0)
Wound closure observed for wound half treated with Oleogel-S10 only	Time advantage of Oleogel-S10 very likely underestimated *(time to wound closure with Oleogel-S10 - [day of last photo +1 day])*	16 (14.5)	17 (15.5)	36 (32.7)
Wound closure observed for wound half treated with standard of care only	Time advantage of standard of care very likely underestimated *([day of last photo +1day] -time to wound closure with standard of care)*	7 (6.4)	10 (9.1)	11 (10.0)
No wound closure observed for either wound half	Difference set to 0	12 (10.9)	22 (20.0)	37 (33.6)
Patient not evaluable[c]	Difference set to 0	3 (2.7)	8 (7.3)	2 (1.8)
Patient not part of blinded read[d]	Difference set to 0	2 (1.8)	2 (1.8)	2 (1.8)

[a] Percentages are based on the total number of patients in the ITT.
[b] Difference in time to wound closure = time to wound closure of the wound half treated with Oleogel-S10 *minus* time to wound closure of the wound half treated with STC.
[c] As rated by the respective blinded expert (e.g. due to insufficient photo quality).
[d] Patients G-0806-02, and G-0806-04 were not presented to the blinded readers since only the Day 0 photo would have been available for photo evaluation.
ITT = intention-to-treat, N = number of patients in the analysis set.

Results of the primary endpoint for the completer, TPP, and PP analysis (**Table 28**) confirmed the results of the ITT analysis showing quicker healing of wound halves treated with Oleogel-S10 and wound dressing than the wound halves treated with the standard of care.

Table 28. Difference in time to wound closure – mean blinded expert evaluation (Completer, TPP, and PP analysis)

Analysis set	n	Difference in time to wound closure [days] (Oleogel-S10 and wound dressing – standard of care)[a]					
		Mean	SD	Median	Min, Max	95% CI	p-value[b]
Completer analysis (N = 104)	104	-0.8	3.7	0.0	-18.3, 12.3	-1.5, -0.0	0.0368
TPP analysis (N = 98)	98	-0.7	3.6	0.0	-18.3, 12.3	-1.4, 0.0	0.0604
PP analysis (N = 37)	37	-1.3	4.7	0.0	-18.3, 4.3	-2.9, 0.3	0.1036

Right censored observations (wound closure was not achieved during observation period) were handled using the day of last wound dressing +1 approach.
[a] Difference in time to wound closure was set to zero for non evaluable photo series.
[b] Based on a two-sided paired t-test evaluating the mean difference as different from zero.
CI = confidence interval, ITT = intention-to-treat, Max = maximum, Min = minimum, n = number of patients included in the analysis, N = number of patients in the analysis set, PP = per-protocol, SD = standard deviation, TPP = treatment-PP.

Sensitivity analysis

Similar to Study BSH-12, due to the high proportion of censored values in the calculation of the primary endpoint, sensitivity analyses were done to assess whether the size of treatment effect is truly reflected in the primary endpoint. In the primary analysis, one day was added to the day of the last photograph available for the assessment of time to wound closure in cases in which wound healing was not observed. However, as wound dressings were changed every three to four days, three to four days would be the minimal duration for which healing would have been observed in the study, a much longer interval than one day used in the primary analysis. Thus in the sensitivity analysis, different intervals (+2 days, +3 days, +4 days, +7 days, and +MTWDC) were added to the last day for which a photo was available.

Table 29. Difference in time to wound closure – mean blinded expert evaluation, sensitivity analysis in Study BSG-12 (ITT, N = 110, additional analysis)

Estimator for time period between last observation and day of wound closure if no wound closure was observed	Difference in time to wound closure (days) (Oleogel-S10 and wound dressing – standard of care)[a]					
	Mean	SD	Median	Min, Max	95% CI	p-value[b]
+2	-0.9	3.8	0.0	-18.7, 13.0	-1.6, -0.2	0.0129
+3	-1.0	4.0	0.0	-19.0, 13.7	-1.8, -0.3	0.0078
+4	-1.2	4.3	0.0	-19.3, 14.3	-2.0, -0.4	0.0051
+7	-1.5	5.1	0.0	-20.3, 16.3	-2.5, -0.6	0.0021
+MTWDC[c]	-1.1	4.2	0.0	-19.2, 14.0	-1.9, -0.3	0.0063

[a] Difference in time to wound closure was set to 0 for photo series rated 'not evaluable'. If wound closure was not observed, it was calculated to have occurred 2, 3, 4, or 7 days, or MTWDC after the last photograph in the series, as indicated.

[b] Based on a two-sided paired t-test evaluating the mean difference as different from 0.
CI = confidence interval, ITT = intention-to-treat, Max = maximum, Min = minimum, MTWDC = mean time to wound dressing change, n = number of patients included in the analysis, N = number of patients in the analysis set, SD = standard deviation.

Study BSG-12 Secondary efficacy endpoints

Intra-individual difference in time to wound closure (at least 95% epithelialisation) between wound halves, separately for each of the three independent, blinded experts

Similar to the results for the primary endpoint, each of three blinded experts reported faster healing of wound halves treated with Oleogel-S10 and wound dressing than the wound halves treated with standard of care (-0.7, -0.7, and -1.0 days, respectively, two-sided paired t-test p=0.080, p=0.083, p=0.015 respectively, ITT).

Time from surgery until wound closure was achieved, separately for wound halves with Oleogel-S10 and non-adhesive wound dressing versus non-adhesive wound dressing alone

The mean time from skin grafting surgery (Day 0) to wound closure for Oleogel-S10 treated wound halves was shorter than that for wound halves treated with wound dressing alone (15.1 days versus 16.0 days). The corresponding expert opinions, investigator assessments, and the centre-, country-stratified analyses showed similar results.

Percentage of patients with earlier healing of wound area treated with Oleogel-S10 compared to non-adhesive wound dressing alone

The percentage of patients showing faster healing of the Oleogel-S10 treated wound half was higher than the percentage of patients showing faster healing of the wound half treated with standard of care (45.5% versus 30.0%). For about a quarter of patients (24.5%) no difference in wound healing was observed, photographs were not evaluable, patients were excluded from the blinded read, or none of the wound areas achieved complete wound closure in all 3 expert assessments.

Percentage of patients with wound closure at different time points

According to the mean expert evaluation, the percentage of patients achieving full wound closure was higher for the Oleogel-S10 treated wound halves than for the standard of care wound halves on Day 10 (14.8% and 8.3% of patients, respectively), Day 18 (79.6% and 71.3%, respectively), Day 21 (86.1% and 80.6%, respectively) and Day 28 (96.3% and 91.7%, respectively).

Further efficacy endpoints

Percentage of patients with earlier healing of wound half with Oleogel-S10 compared to non-adhesive wound dressing alone, as evaluated by the unanimous decision of the blinded experts

According to the unanimous decision of the blinded experts, around 78% of patients for whom a between-treatment difference in wound healing was observed (n =14) showed earlier healing of their wound halves treated with the Oleogel-S10 regimen while 22% of the wound halves treated with the standard of care showed an earlier healing. For 92 out of 110 patients, no difference in wound healing was observed, photographs were not evaluable, or no unanimous decision could be reached.

BBW-11

Open, blindly evaluated, prospective, controlled, randomised, multicentre, phase III clinical trial to compare intra-individually the efficacy and tolerance of Oleogel-S10 versus standard of care in accelerating the healing of Grade 2a partial thickness burn wounds

Methods

This was an open, blindly evaluated, prospective, controlled, randomised, multicentre, phase III study enrolling patients with Grade 2a partial thickness burn wounds. One half of the target wound was treated with Oleogel-S10 and covered with fatty gauze; the other half was treated with Octenilin® Wound Gel and also covered with fatty gauze.

Study Participants

Inclusion criteria

1. Patients at least 18 years old who provided written informed consent;

2. Presenting with acute Grade 2a burn wounds (as graded by an expert surgeon assisted by laser Doppler imaging [LDI] or a multispectral imaging system) within 48 hours after injury;

3. Burn wound caused by fire burn, heat burn or scalding;

4. Burn patients with Grade 2a burn wounds between 80 cm^2 and less than 25% of their total body surface area (TBSA) (alternatively, two comparable wounds with size more than 40 cm^2 each and less than 12.5% of the TBSA each were allowed);

5. Patient was able to understand the informed consent form (ICF) and prepared to comply with all study requirements, including the following: Visiting the trial site for wound dressing changes at least every second day (if patient was not hospitalised) and photo-documentation until full wound closure or until the investigator decided to change medication and/or treatment after Day 21 after start of treatment;

6. Willing to perform all necessary wound dressing changes at the trial site. Also the patients needed to agree to return to site for 3 and 12 months follow-up visits;

7. Women of childbearing potential were to apply highly effective method of birth control (failure rate less than 1% per year when used consistently and correctly [e.g. implants, injectables, combined oral contraceptives, some intrauterine contraceptive devices, sexual abstinence, or a vasectomised partner]). In Sweden and UK the following point was added: Birth control method was to be applied for at least 1 monthly cycle prior to first administration of study drug, be maintained during the study treatment phase and continued for at least 30 days after the last administration of study drug. In Switzerland 'sexual abstinence' was removed.

Exclusion criteria

1. Suffering from chemical burns, or electrical burns or sunburns;

2. Having already received treatment for their burn with silver sulfadiazine (obscures photographic wound evaluation);

3. Positive blood culture after the burn;

4. Diseases or conditions that could have, in the opinion of the investigator, interfered with the assessment of safety, tolerability or efficacy;

5. A skin disorder that was chronic or currently active and which the investigator considered would adversely affect the healing of the acute wounds or involved the areas to be examined in this trial;

6. A history of clinically significant hypersensitivity to any of the drugs or surgical dressings to be used in this trial;

7. Known multiple allergic disorders;

8. Taking, or have taken, any investigational drugs within three months prior to the screening visit;

9. Pregnant or breast feeding women were not allowed to participate in the study;

10. Inappropriate to participate in the study, for any reason, in the opinion of the investigator;

11. Mental incapacity or language barriers precluding adequate understanding or cooperation or willingness to follow study procedures;

12. Previous participation in this study;

13. Employee at the investigational site, relative or spouse of the investigator.

Treatments

The Grade 2a burn wound (size at least 80 cm^2) was cleansed by disinfectant, e.g. octenidine solution or polyhexanide solution (silver sulfadiazine was not allowed as it obscures photobased evaluation of wounds). After cleaning, about 1 cm of gel string Oleogel-S10 (approximately 100 mg) per cm^2 (i.e. approximately 1 mm thick) was applied to one half of the burn wound according to the randomisation and covered with fatty

gauze as wound dressing. The other half of the wound was covered with Octenilin® Wound Gel (a branded octenidine hydrogel) and fatty gauze as wound dressing.

To avoid confusion about which half has to be treated with Oleogel-S10, the healthy skin next to the wound was marked with ink with 'V' for verum and '-' for the wound half treated with Octenilin® Wound Gel and fatty gauze as wound dressing.

Octenilin® Wound Gel is a commercial medical device product of Schülke & Mayr GmbH, Norderstedt, Germany, containing the antiseptic agent octenidine.

The schedule of planned assessments is provided in **Table 30**.

Table 30. Schedule of assessments

	Screening	Treatment period		EoT	Follow-up[c]
		Day 0	Dressing change[a]	Day 21[b]	Months 3 and 12
Informed consent[d]	X				
Inclusion + exclusion criteria	X				
Demographics + medical history	X				
Concomitant medication	X	X	X	X	
Pregnancy test	X				
Date of the burn injury, location and size		X			
Assessment of burn wound depth		X			
Marking of treatment site		X	X[e]		
Overview photo		X			
Randomisation		X			
Macro photo		X	X	X	X
Oleogel-S10 + Octenilin® Wound Gel application		X	X		
Plasma blood sample		X	X[f]	X	
Microbial colonisation			X[f]	X[g]	
Assessment of efficacy[h]			X[f]	X	
Assessment of tolerability[h]			X[f]	X	X
Epithelialisation[i]			X	X	
Adverse events		X	X	X	
Skin appearance and POSAS[j]					X

[a] To be performed at least every second day.
[b] Earlier than Day 21, when full wound closure was achieved, or later, if the investigator decided to change medication and/or treatment due to unsatisfying wound closure after Day 21.
[c] After start of the treatment (±14 days).
[d] Written informed consent obtained from the patient before any screening procedures were performed.
[e] If renewal required.
[f] At Days 7 (±1 day) and 14 (±1 day), in case one or both wound halves were open.
[g] Microbial colonisation was only tested at the end of treatment when the wound was still open.
[h] Evaluated by both investigators and patients using a questionnaire.
[i] Epithelialisation percentage = (Epithelialisation size/size of wound at Day 0) x 100%.
[j] Performed in the follow-up period. The assessment will be reported in the follow-up report, and not in this report which only covers the treatment period.
EoT = End of treatment. POSAS = Patient and Observer Scar Assessment Scale.

Selection and timing of dose for each patient

Oleogel-S10 and Octenilin® Wound Gel were applied at each change of wound dressing (at least every second day) until full wound closure was achieved. If one half or both halves of the wound were still open after Day 21, treatment was either terminated or still continued until the investigator decided to change medication and/or treatment. In case one wound half was closed earlier than the other, it was necessary to treat both wound halves with the assigned treatment regimen until both wound halves were closed or until the investigator decided to change medication and/or treatment (after Day 21).

Concomitant therapy

Any medication considered necessary for the patient's welfare, and not expected to interfere with the evaluation of the study medication, was given at the discretion of the investigator. All treatments given in addition to study medication were to be recorded in the eCRF together with the indication, quantity or dose administered, dates, and time of administration.

Objectives

To compare intra-individually the efficacy and tolerability of Oleogel-S10 with fatty gauze as wound dressing versus standard of care (defined as Octenilin® Wound Gel) with fatty gauze as wound dressing in accelerating the healing of Grade 2a burns.

Outcomes/endpoints

Primary efficacy endpoint

Percentage of patients with earlier healing (at least 95% epithelialisation) of the wound half treated with Oleogel-S10 compared to standard of care (Octenilin® Wound Gel), as evaluated by the majority decision of three independent, blinded experts.

Secondary efficacy endpoints

- Percentage of patients with earlier healing of wound half treated with Oleogel-S10 compared to Octenilin® Wound Gel, evaluated separately for each of the three independent, blinded experts;
- Percentage of patients with earlier healing of wound half treated with Oleogel-S10 compared to all other patients (earlier healing of wound half treated with Octenilin® Wound Gel or no difference between treatment regimens);
- Intra-individual difference in time to wound closure between wound halves, either treated with Oleogel-S10 and fatty gauze as wound dressing or treated with Octenilin® Wound Gel and fatty gauze as wound dressing;
- Time from study start after burn accident until wound closure achieved separately for wound halves treated with Oleogel-S10 and fatty gauze as wound dressing versus Octenilin® Wound Gel and fatty gauze as wound dressing;
- Percentage of patients with wound closure at different time points;
- Percentage of wound epithelialisation at different time points as assessed by the investigator;
- Assessment of efficacy (evaluated by both the investigators and patients).

Further efficacy parameters

- Percentage of patients with earlier healing of wound half treated with Oleogel-S10 compared to Octenilin® Wound Gel, as evaluated by the unanimous decision of the three independent, blinded experts;
- Relative intra-individual difference in time to wound closure between wound halves either treated with Oleogel-S10 and fatty gauze as wound dressing or treated with Octenilin® Wound Gel and fatty gauze as wound dressing.

Sample size

Assuming a proportion of patients who showed an earlier healing with Oleogel-S10 for burn wounds ('winner') of 0.712 compared to patients who show an earlier healing with Octenilin® Wound Gel, and a power of 80% to reject the null-hypothesis, the sample size was calculated to be 45 patients. Assuming that for 25% of patients, no difference in wound healing can be evaluated by the majority of the blinded experts, a total of 66 patients were enrolled.

Randomisation

Method of assigning wound halves to treatment

With the choice of study medication open to investigators and patients, special emphasis was placed on a tamper-proof randomisation method. Of the potentially multiple wounds of varying wound depth, a suitable study wound was selected and divided into two halves of equal size. In case of two separate wounds the investigator made sure that both halves were similar in size, depth, location (e.g. with regard to skin thickness or hairy versus hairless skin) and originated from the same accident. Due to the intra-individual comparison of two wound halves to be covered with either Oleogel-S10 and fatty gauze or with Octenilin® Wound Gel and fatty gauze, one of these halves was closer to the centre of the body (proximal [p] wound half) than the other (distal [d] wound half). A skin compatible ink marker was used to clearly divide the wound into two halves. If the wound location and orientation was not appropriate to divide the wound area into proximal and distal treatment halves, the wound area was divided and marked into right [r] or left [l] halves. If, in very specific cases, this was also not appropriate, the wound area was then divided and marked into upper [u] or lower [l] halves.

After complete marking of the two wound halves an overview photo was taken, which showed the complete wound area with markings of the wound halves and the location on the patient's body. The overview photo was uploaded to the eCRF for randomisation by IWRS. An automatic check validated that the photo had been taken the same day the photo was uploaded for randomisation. The eCRF acting as IWRS provided information on randomisation number for the individual patient, and the wound half that was to be treated with Oleogel-S10. For all randomisation pictures it was subsequently verified that they showed the wound which received treatment with the study medication and that the division into two wound halves (or two comparable wounds) had been marked on the skin. In accordance to the randomisation, the investigator treated the patient's assigned wound halves.

Blinding (masking)

Although the treatment was open to patients and investigators, the evaluation of the clinical efficacy was performed in a blinded manner as outlined in the primary endpoint description.

Photographs of the treated wound halves taken by the site staff were evaluated by three independent wound healing experts having no information about the treatment regimen of any of the photographed wounds for an unbiased judgment.

Statistical methods

The primary endpoint was tested using a one-sided, exact binomial test using a significance level of alpha = 0.025.

Secondary efficacy endpoints were generally evaluated two-sided using the exact binomial test for percentage of patients with earlier healing, a paired t-test for between treatment difference in time to wound closure, time from study start until wound closure, and percentage of wound epithelialisation. Time from study start until wound closure was also analysed using Kaplan-Meier estimates and percentage of wound epithelialisation additionally with a Sign test.

Safety analyses were generally done descriptively. The percentage of patients with application site reactions was compared between the two treatment regimens – both overall and within each system organ class - using McNemar's test.

Results

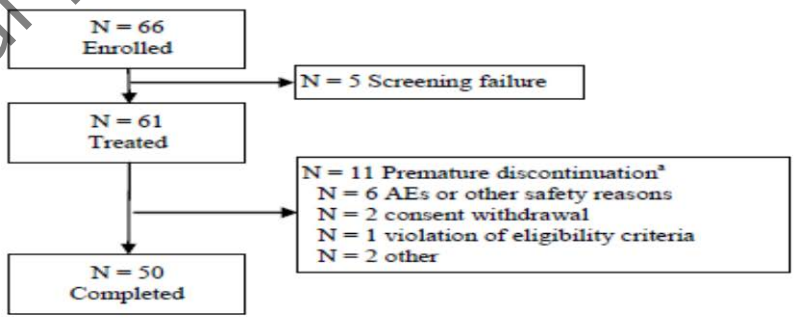
Participant flow

Sixty-six (66) patients were enrolled at 10 centres in total, Germany (4 centres), Sweden (2 centres), Switzerland (1 centre) and the UK (3 centres).

Of the enrolled 66 patients, 61 patients received treatment with both Oleogel-S10 and Octenilin® Wound Gel and the 5 remaining patients did not receive any study treatment.

A total of 50 (82%) patients completed the treatment period (full wound closure achieved) as scheduled. Eleven (11) patients discontinued treatment prematurely i.e. before full wound closure of both wound halves. Two of these patients however had full wound closure achieved for the Oleogel-S10 treated wound half (as assessed by the investigator).

Figure 7. Patient disposition in Study BBW-11



[a] Two patients discontinued prematurely with full wound closure for the Oleogel-S10 treated wound half, and nine patients had discontinued prematurely with no full wound closure for both wound halves. Note that there was one patient who had been treated for 22 days since wound closure was not achieved on Day 21. On the end of treatment page in the CRF the investigator thus ticked 'premature discontinuation (full wound closure not achieved)' and this patient is listed under disposition as premature discontinuation (T-Figure 3). However, this was not classified as 'early termination' in the scope of protocol deviations and this patient is thus not listed as 'early termination' in protocol deviation listings. This explains why there were 11 patients with premature discontinuations listed under patient disposition but only 10 patients with early termination in the protocol deviation listing (see T-Table 2).
N = number of patients.

Recruitment

First subject enrolled: 31st August 2012

Last subject completing treatment period: 17th July 2013

Conduct of the study

There were no substantial protocol amendments introduced in the study BBW-11.

Major protocol deviations are summarised in **Table 31**.

Table 31. Major Protocol Deviations in Study BBW-11(SAF, N = 61)

Deviation	Number (%)[a] of patients	Exclusion from
Total	**16 (26.2)**	
Early discontinuation[b]	10 (16.4)	Completer, PP analysis
Not treated as randomised	4 (6.6)	Completer, PP, ITT analysis
Wrong wound dressing	1 (1.6)	PP analysis
Violation of inclusion criterion 4 (wound size)	1 (1.6)	PP analysis
Macro photos lost	1 (1.6)	PP analysis
Photos judged as not evaluable by majority of readers	5 (8.2)	PP analysis

[a] Percentages are based on the total number of patients in the safety analysis set (hand-calculated).
[b] Note that there was one patient who had been treated for 22 days since wound closure was not achieved on Day 21. On the end of treatment page in the CRF the investigator thus ticked 'premature discontinuation (full wound closure not achieved)' and this patient is listed under disposition as premature discontinuation (T-Figure 3). However, this was not classified as 'early termination' in the scope of protocol deviations and this patient is thus not listed as 'early termination' in protocol deviation listings. This explains why there were 11 patients with premature discontinuations listed under patient disposition but only 10 patients with early termination in the protocol deviation listing.
Note that one patient could present with several protocol deviations.
ITT = intention-to-treat, N = number of patients in the analysis set, PP = per-protocol, SAF = safety analysis set.

Availability of wound photos for blinded evaluation

For more than half of the patients (38, 67%) one or more photos had to be excluded from the blinded read. For these patients 36% of photos had to be excluded on average, in most cases due to gel residues. As mentioned previously the CHMP requested a re-evaluation of the photo series with all photos included even if the blinding would be difficult to maintain. In addition, the applicant was requested to provide a table showing the number of excluded photos in which: a) wound on the active side was closed, b) wound on the control side was closed, c) both were closed and d) both were open. In addition, the applicant was asked to provide a statistical analysis on the difference between the two treatment groups in the proportion of patients with wound closure at the pre-specified time points. This data is presented in the "Analysis performed across trials (pooled analyses and meta-analysis)" section of this report.

Baseline data

The demographic characteristics of patients in BBW-11 can be seen in **Table 32**.

Table 32. Baseline demographics and skin characteristics in Study BBW-11 (SAF, N = 61)

Age (years)	Median (Range)	41	(18-79)
Sex			
Male	n (%)	42	(68.9)
Female	n (%)	19	(31.1)
Race			
White (Caucasian)	n (%)	51	(83.6)
Black or African American	n (%)	4	(6.6)
Asian	n (%)	5	(8.2)
Other	n (%)	1	(1.6)
Skin type Fitzpatrick			
I	n (%)	7	(11.5)
II	n (%)	30	(49.2)
III	n (%)	13	(21.3)
IV	n (%)	5	(8.2)
V	n (%)	2	(3.3)
VI	n (%)	4	(6.6)
Height (cm)			
Male	Mean (SD)	177.8	(6.9)
Female	Mean (SD)	163.2	(6.4)
Weight (kg)			
Male	Mean (SD)	88.7	(14.7)
Female	Mean (SD)	64.7	(8.2)
BMI (kg/m^2)			
Male	Mean (SD)	28.2	(4.9)
Female	Mean (SD)	24.4	(3.4)

Note: Percentages are based on the total number of patients in the safety analysis set. BMI = body mass index, n = number of patients with the respective characteristics, N = number of patients in the analysis set, SAF = safety analysis set, SD = standard deviation.

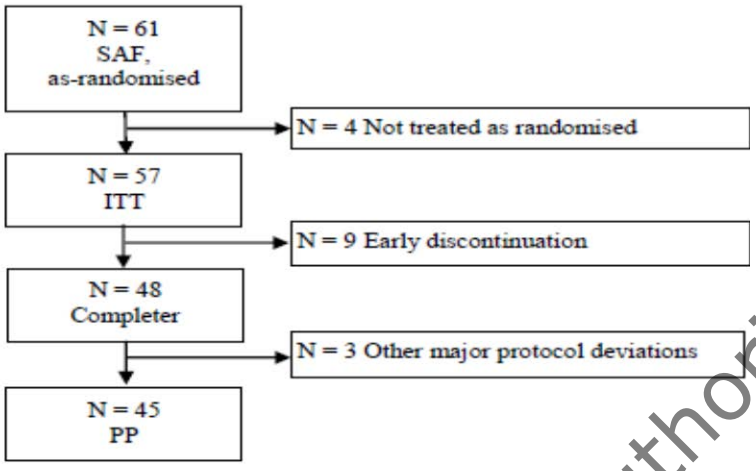
Numbers analysed

Analysis sets

The intention-to-treat (ITT) set was defined as all patients who were treated at least once, with patients whose wound halves were not treated with the intended i.e. randomised treatment regimen being excluded, was the primary confirmatory analysis. Patients for whom no treatment differences in healing were observed or for whom photographs were not evaluable were not considered in this primary analysis.
The ITT population consisted of 57 subjects, all of whom received Oleogel-S10 and Octenilin® Wound Gel applied on the respective halves of Grade 2a burn wounds.

Sensitivity analyses included analyses for the per-protocol (PP) set, completer analysis set, safety analysis set, and as randomised analysis set as well as analysis for the median between-treatment difference in time to wound closure (one-sided Sign test). These analysis sets are described in **Figure 8**.

Figure 8. Analysis sets in Study BBW-11



ITT = intention-to-treat, N = number of patients in the analysis set, PP = per-protocol, SAF = safety analysis set.

Outcomes and estimation

Primary endpoint

The results of the primary endpoint analysis based on blind photo evaluation are provided in the table below. The percentage of patients showing earlier healing of the Oleogel-S10 treated wound half compared with the Octenilin® Wound Gel treated half was higher than the percentage of patients showing the opposite result i.e. faster healing of the Octenilin® Wound Gel treated wound half (85.7% versus 14.3%). The binomial test revealed that the rate of patients with earlier healing of their Oleogel-S10 treated wound half, compared to their Octenilin® Wound Gel treated wound half, was significantly higher than 50% ($p < 0.0001$).

Table 33. Patient Rates of Earlier Healing (Oleogel-S10 vs. Control), Majority Decision of Blinded Expert Evaluation, ITT, in Study BBW-11

N=57	n	(%)	95% CI	P value[a]
Patients with a between-treatment difference in wound healing[b]	35			
Patients with earlier healing of Octenilin treated wound half	5	(14.3)	4.8, 30.	
Patients with earlier healing of Oleogel-S10 treated wound half	30	(85.7)	69.7, 95.2	<0.0001

[a] Based on one-sided, exact binomial test evaluating the rate of superiority of Oleogel-S10 being >0.5.
[b] Only patients for whom a between-treatment difference in wound healing was observed were included in this primary analysis.
CI: confidence interval, n: number of patients with the indicated 'difference' in wound healing, N: number of patients in the analysis set.

Twenty-two patients were excluded from the primary efficacy analysis because no between treatment difference was observed in the blinded read; seven had the photo series rated as 'not evaluable', seven had no complete wound closure observed in the blinded read, and eight had complete wound closure but no difference in wound healing between the Oleogel-S10 site and control site.

Supportive analyses

Results of the PP and completer analysis confirmed the findings of the primary analysis with more patients showing faster healing of Oleogel-S10 wound half than with Octenilin® Wound Gel treated wound half.

Subgroup analyses by gender and study centres

The results were consistent over gender and study centers.

Secondary variables:

Percentage of patients showing earlier wound healing with Oleogel-S10 than with Octenilin® Wound Gel based on all patients

Including patients for whom no treatment differences in healing could be observed or for whom photographs were not evaluable or for whom no majority decision could be reached in the analysis, the binomial test demonstrated that the rate of patients showing earlier healing with Oleogel-S10 treatment was no longer significantly different from 50%. According to the majority decision of the experts, 52.6% of patients showed earlier healing with Oleogel-S10 compared to 8.8% of patients with Octenilin® Wound Gel, while in 38.6% of patients no difference between the treatments was observed.

Intra-individual absolute and relative difference in time to wound closure between wound halves

Based on the mean expert evaluation, the mean differences in time to wound closure between wound sites (Oleogel-S10 treated minus Octenilin® Wound Gel treated) was approximately -1 day, i.e. smaller than zero, indicating faster wound healing with Oleogel-S10 treatment than with Octenilin® Wound Gel ($p<0.0001$, two-sided t-test).

The relative intra-patient differences in time to wound closure (i.e. time to wound closure of Oleogel-S10 treated minus Octenilin® Wound Gel treated, divided by Octenilin® Wound Gel treated wound half). The mean reader result for each patient averaged -11%, i.e. smaller than zero, also indicating faster wound healing with Oleogel-S10 treatment than with Octenilin® Wound Gel.

Time from study start after burn accident until wound closure Conservative estimation (first observation of wound closure = time of wound closure)

According to the mean expert evaluation, the mean time from the burn accident to wound closure was 7.6 days for Oleogel-S10 and 8.8 days for Octenilin® Wound Gel (**Table 34**).

Table 34. Time to wound closure (mean blinded expert evaluation, conservative estimation, ITT, N = 57)

Treatment	n [a]	Number of days from burn accident to wound closure				
		Mean	SD	Median	Min, Max	95% CI (%)
Oleogel-S10	50	7.6	3.7	6.7	2.0, 18.0	6.5, 8.6
Octenilin	50	8.8	4.3	8.0	2.0, 21.7	7.6, 10.0

[a] The seven missing patients had no evaluable photographs.
Conservative estimation means that the first observation of wound closure was taken as time of wound closure. If wound closure was not observed, it was calculated to have occurred one day after the last photograph in the series.
CI = confidence interval, ITT = intention-to-treat, Max = maximum, Min = minimum, n = number of evaluable wound sites, N = number of patients in the analysis set, SD = standard deviation.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 35. Summary of Efficacy for trial BSH-12

Title: Open, blindly evaluated, prospective, controlled, randomised, multicentre, phase III clinical trial to compare intra-individually the efficacy and tolerance of Oleogel-S10 versus standard of care in accelerating the wound healing of split-thickness skin graft donor sites			
Study identifier	BSH-12		
Design	Open, blindly evaluated, prospective, controlled, randomised, multicentre, phase III clinical trial with an intra-individual between-treatment comparison		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Up to 28 days not applicable 12-month follow-up	
Hypothesis	Superiority		
	Oleogel-S10	Oleogel-S10 gel (+non-adhesive wound dressing) applied at every change of wound dressing (every three or four days) until full wound closure or 28 days, 107 patients (pts) randomised	
	Standard of care	Non-adhesive wound dressing alone applied at every change of wound dressing (every three or four days) until full wound closure or 28 days, 107 pts randomised	
Endpoints and definitions	Primary: Intra-individual difference in time to wound closure between wound halves (ME)		Intra-individual difference in time to wound closure (at least 95% epithelialisation) between wound halves either treated with Oleogel-S10 and non-adhesive wound dressing or treated with non-adhesive wound dressing alone, based on photo evaluation by three independent, blinded experts (mean expert evaluation, ME)
	Secondary: Intra-individual difference in time to wound closure between wound halves (BE)		Intra-individual difference in time to wound closure (at least 95% epithelialisation) between wound halves either treated with Oleogel-S10 and non-adhesive wound dressing or treated with non-adhesive wound dressing alone, separately for each of the three independent, blinded experts (BE)

	Secondary: Time from surgery until wound closure (ME and BE)		Time from surgery until wound closure was achieved, separately for wound halves treated with Oleogel-S10 and non-adhesive wound dressing versus non-adhesive wound dressing alone
	Secondary: % of pts with earlier wound healing with Oleogel-S10 than standard of care		Percentage of patients with earlier wound healing with Oleogel-S10 compared to non-adhesive wound dressing alone (done for all patients and for patients in whom difference in wound healing was observed [decided cases])
	Secondary: % of pts with wound closure by time point		Percentage of patients with wound closure by time points
	Secondary: % of wound epithelialisation by time point		Percentage of wound epithelialisation by time points (study team member assessment)
	Secondary: Global assessment of efficacy		Global assessments of efficacy by investigators and patients
	Further: % of pts with earlier healing of Oleogel-S10 than standard of care (UA)		Percentage of patients with earlier healing of wound area treated with Oleogel-S10 compared to non-adhesive wound dressing alone, as evaluated by the unanimous (UA) decision of the blinded experts
	Further: Relative intra-individual difference in time to wound closure		Relative intra-individual difference in time to wound closure between wound halves
Database lock	10Feb2014		

Results and Analysis

Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat (ITT) Time of wound closure or 28 days (for some endpoints additional time points were evaluated)		
Descriptive statistics and estimate variability	Treatment group	Oleogel-S10	Standard of care
	Number of subjects (ITT)	107	107

	Secondary: Time from surgery until wound closure (mean) *(conservative estimation: first observation of wound closure = time of wound closure, only mean expert evaluation presented)*	15.5 days	17.1 days
	95% confidence interval *(t-test statistic)*	14.2 - 16.8 days	15.8 - 18.5 days
	Secondary: Time from surgery until wound closure (mean) *(mean estimation: mean between first observation of wound closure and previous photo = time of wound closure, only mean expert evaluation presented)*	14.3 days	16.5 days
	95% confidence interval *(t-test statistic)*	12.9 - 15.6 days	15.2 - 17.9 days
	Secondary: % of pts with wound closure by time points (*only Day 7, Day 14, Day 21, and Day 28 presented, only mean blinded expert evaluation presented)*	D7: 2% D14: 49% D21: 78% D28: 94%	D7: 1% D14: 37% D21: 72% D28: 90%
	95% confidence interval *(exact)*	D7: 0-7% D14: 39-59% D21: 68-85% D28: 88-98%	D7: 0-5% D14: 28-47% D21: 62-80% D28: 83-95%
	Secondary: % of wound epithelialisation by time point (mean) (*only Day 7, Day 14, Day 21, and Day 28 presented, study team member evaluation*)	D7: 37% D14: 82% D21: 92% D28: 94%	D7: 28% D14: 74% D21: 86% D28: 90%
	95% confidence interval *(t-test statistic)*	D7: 30-43% D14:77-88% D21: 89-96% D28: 91-97%	D7: 22-34% D14: 69-80% D21: 81-90% D28: 86-94%

Effect estimate per comparison	Primary: Intra-individual difference in time to wound closure between wound halves (*mean expert*	Comparison groups	Oleogel-S10 *minus* standard of care
		mean [days]	-1.4
		95% confidence interval [days]	-1.8 - -0.9

	evaluation)	P-value (2-sided paired t-test evaluating the mean difference as different from 0)	<0.0001
	Secondary: Intra-individual difference in time to wound closure between wound halves (*by expert*)	Comparison groups	Oleogel-S10 *minus* standard of care
		mean [days] (Expert 1, 2, 3)	-1.1, -1.5, -1.5
		95% confidence interval [days] (Expert 1, 2, 3)	-1.6 - -0.7, -2.2 - -0.7, -2.1 - -1.0
		P-value (2-sided paired t-test evaluating the mean difference as different from 0, Expert 1, 2, 3)	<0.0001, 0.0001, <0.0001
	Further: Relative intra-individual difference in time to wound closure (*only mean expert evaluation presented*)	Comparison groups	Oleogel-S10 *minus* standard of care
		mean	-7.9%
		95% confidence interval	-10.3 - -5.4%
	Secondary: % of pts with earlier wound healing with Oleogel-S10 than standard of care (*mean expert evaluation*) all patients *(decided cases)*	Comparison groups	Oleogel-S10 vs standard of care
		% of patients	62% *(89%)*
		95% confidence interval	52-71% *(80-95%)*
	Further: % of pts with earlier healing of Oleogel-S10 than standard of care (*unanimous decision by blinded experts*)	Comparison groups	Oleogel-S10 vs standard of care
		% of patients	15%
		95% confidence interval	9-23%
	Secondary: Global assessment of efficacy investigator assessment (*patient assessment*) *only end of treatment assessment presented*	Comparison groups	Oleogel-S10 vs standard of care
		Oleogel-S10 much more effective	
		% of patients	16% *(21%)*
		95% confidence interval	10-25% *(14-30%)*
		Oleogel-S10 more effective	
		% of patients	52% *(41%)*

		95% confidence interval	42-62% *(32-51%)*
		Same efficacy	
		% of patients	29% *(35%)*
		95% confidence interval	20-39% *(26-45%)*
		standard of care more effective	
		% of patients	2% *(3%)*
		95% confidence interval	0-7% *(1-8%)*
		standard of care much more effective	
		% of patients	1 *(0%)*
		95% confidence interval	0-5% *(-)*
Notes	Most endpoints were analysed based on mean values from or the majority decision of the three blinded experts as well as by individual expert. The analyses by expert are not presented above but show similar results as the means or majority decision across experts.		
Analysis description	Further analyses were done for the per-protocol analysis set, treatment-per-protocol analysis set, and completer analysis set.		
	The results for all endpoints were similar in all analysis sets used.		

Table 36. Summary of Efficacy for trial BSG-12

Title: Open, blindly evaluated, prospective, controlled, randomised, multicentre, phase III clinical trial to compare intra-individually the efficacy and tolerance of Oleogel-S10 versus standard of care in accelerating the wound healing of split-thickness skin graft donor sites		
Study identifier	BSG-12	
Design	Open, blindly evaluated, prospective, controlled, randomised, multicentre, phase III clinical trial with an intra-individual between-treatment comparison	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Up to 28 days not applicable 12-month follow-up
Hypothesis	Superiority	
	Oleogel-S10	Oleogel-S10 gel (+non-adhesive wound dressing) applied at every change of wound dressing (every three or four days) until full wound closure or 28 days, 112 patients (pts) randomised
	Standard of care	Non-adhesive wound dressing alone applied at every change of wound dressing (every three or four days) until full wound closure or 28 days, 112 pts randomised

Endpoints and definitions	Primary: Intra-individual difference in time to wound closure between wound halves (ME)		Intra-individual difference in time to wound closure (at least 95% epithelialisation) between wound halves either treated with Oleogel-S10 and non-adhesive wound dressing or treated with non-adhesive wound dressing alone, based on photo evaluation by three independent, blinded experts (mean expert evaluation, ME)
	Secondary: Intra-individual difference in time to wound closure between wound halves (BE)		Intra-individual difference in time to wound closure (at least 95% epithelialisation) between wound halves either treated with Oleogel-S10 and non-adhesive wound dressing or treated with non-adhesive wound dressing alone, separately for each of the three independent, blinded experts (BE)
	Secondary: Time from surgery until wound closure (ME and BE)		Time from surgery until wound closure was achieved, separately for wound halves treated with Oleogel-S10 and non-adhesive wound dressing versus non-adhesive wound dressing alone
	Secondary: % of pts with earlier wound healing with Oleogel-S10 than standard of care		Percentage of patients with earlier wound healing with Oleogel-S10 compared to non-adhesive wound dressing alone (done for all patients and for patients in whom difference in wound healing was observed [decided cases])
	Secondary: % of pts with wound closure by time point		Percentage of patients with wound closure by time points
	Secondary: % of wound epithelialisation by time point		Percentage of wound epithelialisation by time points (study team member assessment)
	Secondary: Global assessment of efficacy		Global assessments of efficacy by investigators and patients
	Further: % of pts with earlier healing of Oleogel-S10 than standard of care (UA)		Percentage of patients with earlier healing of wound area treated with Oleogel-S10 compared to non-adhesive wound dressing alone, as evaluated by the unanimous (UA) decision of the blinded experts
	Further: Relative intra-individual difference in time to wound closure		Relative intra-individual difference in time to wound closure between wound halves
Database lock	15Apr2014		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT) Time of wound closure or 28 days (for some endpoints additional time points were evaluated)		
Descriptive statistics and estimate variability	Treatment group	Oleogel-S10	Standard of care
	Number of subjects (ITT)	110	110
	Secondary: Time from surgery until wound closure (mean) *(conservative estimation: first observation of wound closure = time of wound closure, only mean expert evaluation presented)*	15.1 days	16.0 days
	95% confidence interval *(t-test statistic)*	14.1 - 16.1 days	14.8 - 17.1 days
	Secondary: Time from surgery until wound closure (mean) *(mean estimation: mean between first observation of wound closure and previous photo = time of wound closure, only mean expert evaluation presented)*	13.1 days	14.4 days
	95% confidence interval *(t-test statistic)*	12.0 - 14.1 days	13.1 - 15.6 days
	Secondary: % of pts with wound closure by time points (*only Day 7, Day 14, Day 21, and Day 28 presented, only mean blinded expert evaluation presented)*	D7: 3% D14: 48% D21: 86% D28: 96%	D7: 4% D14: 48% D21: 81% D28: 89%
	95% confidence interval *(exact)*	D7: 1-8% D14: 38-58% D21: 78-92% D28: 91-99%	D7: 1-9% D14: 38-58% D21: 72-88% D28: 85-96%
	Secondary: % of wound epithelialisation by time point (mean) (*only Day 7, Day 14, Day 21, and Day 28 presented, study team member evaluation*)	D7: 27% D14: 81% D21: 94% D28: 96%	D7: 21% D14: 75% D21: 89% D28: 93%

	95% confidence interval *(t-test statistic)*		D7: 22-33% D14:75-86% D21: 91-97% D28: 94-99%	D7: 16-26% D14: 69-81% D21: 84-93% D28: 89-96%
Effect estimate per comparison	Primary: Intra-individual difference in time to wound closure between wound halves (*mean expert evaluation*)	Comparison groups		Oleogel-S10 *minus* standard of care
		mean [days]		-0.8
		95% confidence interval [days]		-1.5 - -0.1
		P-value (2-sided paired t-test evaluating the mean difference as different from 0)		0.0232
	Secondary: Intra-individual difference in time to wound closure between wound halves (*by expert*)	Comparison groups		Oleogel-S10 *minus* standard of care
		mean [days] (Expert 1, 2, 3)		-0.7, -0.7, -1.0
		95% confidence interval [days] (Expert 1, 2, 3)		-1.5 - 0.1, -1.5 - 0.1, -1.8 - -0.2
		P-value (2-sided paired t-test evaluating the mean difference as different from 0, Expert 1, 2, 3)		0.0797, 0.0828, 0.0150
	Further: Relative intra-individual difference in time to wound closure (*only mean expert evaluation presented*)	Comparison groups		Oleogel-S10 *minus* standard of care
		mean		-1.3%
		95% confidence interval		-5.5 - 2.8%
	Secondary: % of pts with earlier wound healing with Oleogel-S10 than standard of care (*mean expert evaluation*) all patients (*decided cases*)	Comparison groups		Oleogel-S10 vs standard of care
		% of patients		46% (*60%*)
		95% confidence interval		36-55% (*49-71%*)
	Further: % of pts with earlier healing of Oleogel-S10 than standard of care (*unanimous decision by blinded experts*)	Comparison groups		Oleogel-S10 vs standard of care
		% of patients		13%
		95% confidence interval		7-20%

	Secondary: Global assessment of efficacy investigator assessment (*patient assessment*) *only end of treatment assessment presented*	Comparison groups	Oleogel-S10 vs standard of care
		Oleogel-S10 much more effective	
		% of patients	17% *(15%)*
		95% confidence interval	11-26% *(9-23%)*
		Oleogel-S10 more effective	
		% of patients	35% *(36%)*
		95% confidence interval	26-45% *(27-46%)*
		Same efficacy	
		% of patients	37% *(39%)*
		95% confidence interval	28-47% *(30-49%)*
		standard of care more effective	
		% of patients	10% *(8%)*
		95% confidence interval	5-17% *(3-15%)*
		standard of care much more effective	
		% of patients	1 *(2%)*
		95% confidence interval	0-5% *(0-7%)*
Notes	Most endpoints were analysed based on mean values from or the majority decision of the three blinded experts as well as by individual expert. The analyses by expert are not presented above but show similar results as the means or majority decision across experts.		
Analysis description	**Further analyses were done for the per-protocol analysis set, treatment-per-protocol analysis set, and completer analysis set.**		
	The results for all endpoints were similar in all analysis sets used.		

Table 37. Summary of Efficacy for trial BBW-11

Title: Open, blindly evaluated, prospective, controlled, randomised, multicentre, phase III clinical trial to compare intra-individually the efficacy and tolerance of Oleogel-S10 versus standard of care in accelerating the healing of Grade 2a partial thickness burn wounds		
Study identifier	BBW-11	
Design	Open, blindly evaluated, prospective, controlled, randomised, multicentre, phase III clinical trial with an intra-individual between-treatment comparison	
	Duration of main phase:	Up to 21 days
	Duration of Run-in phase:	not applicable

	Duration of Extension phase:		12-month follow-up
Hypothesis	Superiority		
Treatments groups	Oleogel-S10		Oleogel-S10 gel (+fatty gauze) applied at every change of wound dressing (latest every second day) until full wound closure or 21 days, 61 patients randomized
	Octenilin		Octenilin Wound Gel (+fatty gauze), topical hydrogel applied at every change of wound dressing (latest every second day) until full wound closure or 21 days, 61 patients randomized
Endpoints and definitions	Primary: % of pts with faster wound healing with Oleogel-S10 than Octenilin (MD)		Percentage of patients with earlier healing (at least 95% epithelialisation) of the wound half treated with Oleogel-S10 compared to Octenilin, as evaluated by the majority decision (MD) of three independent, blinded experts (only patients for whom difference in wound healing was observed included)
	Secondary: % of pts with faster wound healing with Oleogel-S10 than Octenilin (BE)		Percentage of patients with earlier healing of wound half treated with Oleogel-S10 compared to Octenilin, evaluated separately for each of the three independent, blinded expert (BE)
	Secondary: % of pts with faster wound healing with Oleogel-S10 than Octenilin (MD and BE, all pts)		Percentage of patients with earlier healing of wound half treated with Oleogel-S10 compared to all other patients (earlier healing of wound half treated with Octenilin or no difference between treatment regimens)
	Secondary: Intra-individual difference in time to wound closure		Intra-individual difference in time to wound closure between wound halves, either treated with Oleogel-S10 or Octenilin
	Secondary: Time to wound closure		Time from study start after burn accident until wound closure achieved separately for wound halves treated with Oleogel-S10 versus Octenilin
	Secondary: % of pts with wound closure by time point		Percentage of patients with wound closure at different time points
	Secondary: % of epithel-ialisation by time point		Percentage of wound epithelialisation at different time points as assessed by the investigator

	Secondary: Assessment of efficacy		Assessment of efficacy (evaluated by both the investigators and patients) using a questionnaire
	Further: % of pts with faster wound healing with Oleogel-S10 than Octenilin (UA)		Percentage of patients with earlier healing of wound half treated with Oleogel-S10 compared to Octenilin, as evaluated by the unanimous decision (UA) of 3 independent, blinded experts
	Further: Relative intra-individual difference in time to wound closure		Relative intra-individual difference in time to wound halves either treated with Oleogel-S10 or Octenilin
Database lock	04Dec2013		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT) Time of wound closure or 21 days (for some endpoints additional time points evaluated)		
Descriptive statistics and estimate variability	Treatment group	Oleogel-S10	Octenilin
	Number of subject (ITT)	57	57
	Secondary: Time to wound closure (mean) *(conservative estimation: first observation of wound closure = time of wound closure, only mean expert evaluation presented)*	7.6 days	8.8 days
	95% confidence interval *(t-test statistic)*	6.5 - 8.6 days	7.6 - 10.0 days
	Secondary: Time to wound closure (mean) *(mean estimation: mean between first observation of wound closure and previous = time of wound closure, only mean expert evaluation presented)*	6.4 days	7.9 days
	95% confidence interval *(t-test statistic)*	5.4 - 7.5 days	6.7 - 9.1 days

	Secondary: % of pts with wound closure by time point *(only Day 7, Day 14, Day 21 presented, only majority decision of blinded expert evaluation presented*)	D7: 56% D14: 92% D21: 100%	D7: 38% D14: 84% D21: 98%
	95% confidence interval *(exact)*	D7: 41-70% D14: 81-98% D21: 93-100%	D7: 25-53% D14: 71-93% D21:89-100%
	Secondary: % of epithelialisation by time point (mean) *(only Day 7, Day 14, Day 21 presented, investigator evaluation)*	D7:72% D14: 88% D21: 90%	D7: 56% D14: 82% D21: 87%
	95% confidence interval *(t-test statistic)*	D7:62-82% D14: 80-96% D21: 82-98%	D7: 45-66% D14: 73-91% D21: 78-95%

Effect estimate per comparison	Primary: % of pts with faster wound healing with Oleogel-S10 than Octenilin (MD) *(majority decision of blinded expert evaluation)*	Comparison groups	Oleogel-S10 vs Octenilin
		% of patients	86%
		95% confidence interval	70-95%
		P-value (1-sided, exact binomial test, alternative hypothesis: rate of superiority of Oleogel-S10 >0.5)	<0.0001
	Secondary: % of pts with faster wound healing with Oleogel-S10 than Octenilin (*by expert*)	Comparison groups	Oleogel-S10 vs Octenilin
		% of patients (Expert 1, 2, 3)	79%, 82%, 89%
		95% confidence interval (Expert 1, 2, 3)	61-91%, 62-94%, 74-97%
		P-value (2-sided, exact binomial test, alternative hypothesis: rate of superiority of Oleogel-S10 is different from 0.5, Expert 1, 2, 3)	0.0013, 0.0015, <0.0001
	Secondary: % of pts with faster wound healing with Oleogel-S10 than Octenilin (*only majority decision of blinded expert evaluation presented*, all pts)	Comparison groups	Oleogel-S10 vs Octenilin
		% of patients	53%
		95% confidence interval	39-66%
		P-value (2-sided, exact binomial test, alternative hypothesis: rate of superiority of Oleogel-S10 is different from 0.5)	0.7914

	Secondary: Intra-individual difference in time to wound closure *(only mean expert evaluation presented)*	Comparison groups	Oleogel-S10 - Octenilin
		Mean	-1.0 days
		95% confidence interval	-1.4- -0.6 days
		P-value (2-sided paired t-test evaluating the mean difference being different from 0)	<0.0001
	Further: Relative intra-individual difference in time to wound closure *(only mean expert evaluation presented)*	Comparison groups	Oleogel-S10 - Octenilin
		Mean	-11%
		95% confidence interval	-61- 26%
	Secondary: % of epithelialisation by time point (difference in % of epithelialisation, assessed by investigator)	Comparison groups	Oleogel-S10 - Octenilin
		Mean *(only Day 7, Day 14, Day 21 presented)*	D7: 17%, D14: 6%, D21: 3%
		95% confidence interval *(only Day7, Day 14, Day 21 presented)*	D7: 10-23%, D14: 2-11%, D21: 0-6%
		P-value (2-sided, paired t-test evaluating the mean difference being different from 0) *(only Day 7, Day 14, Day 21 presented)*	D7: <0.0001, D14: 0.0092, D21: 0.0310
	Further: % of pts with faster wound healing with Oleogel-S10 than Octenilin *(unanimous decision of blinded experts)*	Comparison groups	Oleogel-S10 vs Octenilin
		% of patients	92%
		95% confidence interval	64-100%
		P-value (2-sided, exact binomial test, alternative hypothesis: rate of superiority of Oleogel-S10 is different from 0.5)	0.0034
	Secondary: Assessment of efficacy investigator assessment *(patient assessment) only end of treatment assessment presented.*	Comparison groups	Oleogel-S10 vs Octenilin
		Oleogel-S10 much more effective	
		% of patients	50% *(56%)*
		95% confidence interval	35-65% *(41-71%)*
		Oleogel-S10 more effective	
		% of patients	38% *(29%)*

		95% confidence interval	24-53% *(17-44%)*
		Same efficacy	
		% of patients	10% *(15%)*
		95% confidence interval	4-23% *(6-28%)*
		Octenilin more effective	
		% of patients	0% *(0%)*
		95% confidence interval	- *(-)*
		Octenilin much more effective	
		% of patients	2 *(0%)*
		95% confidence interval	0-11 *(-)*
Notes	Most endpoints were analysed based on mean values from or the majority decision of the three blinded experts as well as by individual expert. The analyses by expert are not presented above but show similar results as the means or majority decision across experts.		
Analysis description	**Further analyses were done for the per-protocol analysis set, as randomised analysis set, safety analysis set, and completer analysis set.**		
	The results for all endpoints were similar in all analysis sets used.		

Analysis performed across trials (pooled analyses and meta-analysis)

Pooled data were presented for studies BSH-12 and BSG-12, which were almost identical with regards to study design. The populations studied in this analysis are described in **Table 38**.

Table 38. Analysis Sets, BSH-12 and BSG-12 Pooled Analysis

	ITT		Completer		TPP		PP	
	n	(%)[a]	n	(%)[a]	n	(%)[a]	n	(%)[a]
BSH-12	107	(100)	97	(90.7)	93	(86.9)	31	(29.0)
BSG-12	110	(100)	104	(94.5)	98	(89.1)	37	(33.6)
Pooled	217	(100)	201	(92.6)	191	(88.0)	68	(31.3)

[a] Percentages are based on the total number of patients in the intention to treat set.

n: number of patients in the analysis set

Intention to treat (ITT): All patients with correctly signed informed consent who received at least one dose of Oleogel-S10, analysed 'as randomised'.

Completer analysis set: All patients in the ITT who did not prematurely discontinue the study for any reason.

Treatment per protocol set (TPP): All patients in the ITT without any major protocol deviations (without consideration of photographs for the blinded read).

Per protocol set (PP): All patients of the TPP with 'valid' blinded read assessments as defined by the BDRM.

The results from the primary endpoint in the pooled analysis across the two trials is presented in **Table 39.**

Table 39. Primary Analysis, ITT, BSH-12 and BSG-12 Pooled Analysis

	N	Difference in time to wound closure (days), primary analysis (Oleogel-S10 and wound dressing *minus* standard of care)[a]					
		Mean	SD	Median	Min, Max	95% CI	P value[b]
BSH-12	107	-1.4	2.3	-0.3	-10.0, 2.3	-1.8, -0.9	<0.0001
BSG-12	110	-0.8	3.6	0.0	-18.3, 12.3	-1.5,-0.1	0.0232
Pooled	217	-1.1	3.1	-0.3	-18.3, 12.3	-1.5, -0.7	<0.0001

[a] Difference in time to wound closure was set to 0 for photo series rated as 'not evaluable'. If wound closure was not observed, it was calculated to have occurred one day after the last photograph in the series.
[b] Based on a two-sided paired t-test evaluating the mean difference as different from 0.
CI: confidence interval, ITT: intention-to-treat, Max: maximum, Min: minimum, N: number of patients in the analysis set, SD: standard deviation.

Blinded re-evaluation with all photos included

Results of secondary blinded read in Studies BSH-12 and BSG-12 and BBW-11

To further investigate the impact of excluded photographs, the blinded photo evaluation was repeated with all photos included. The same experts as in the primary evaluation also conducted this secondary blinded read. The results showed a larger effect size compared to the primary evaluation (**Tables 40 and 41**).

Table 40: Mean intra-patient difference in time to wound closure, +1 day censoring convention, mean blinded experts result, ITT from studies BSH-12 and BSG-12

			Difference in time to wound closure (days), primary analysis (Oleogel-S10 and wound dressing *minus* standard of care)[a]					
Study	N	Blinded read	Mean	SD	Median	Min, Max	95% CI	P value[b]
BSH-12	107	Primary	-1.4	2.3	-0.3	-10.0, 2.3	-1.8, -0.9	<0.0001
		Secondary	-2.0	3.3	-0.7	-14.0, 4.3	-2.7, -1.4	<0.0001
BSG-12	110	Primary	-0.8	3.6	0.0	-18.3, 12.3	-1.5, -0.1	0.0232
		Secondary	-1.4	4.0	-0.7	-14.7, 10.0	-2.1, -0.6	0.0005
Pooled	217	Primary	-1.1	3.1	-0.3	-18.3, 12.3	-1.5, -0.7	<0.0001
		Secondary	-1.7	3.7	-0.7	-14.7, 10.0	-2.2, -1.2	<0.0001

[a] Difference in time to wound closure was set to 0 for photo series rated as 'not evaluable'. If wound closure was not observed, it was calculated to have occurred one day after the last photograph in the series.
[b] Based on a two-sided paired t-test evaluating the mean difference as different from 0.
CI: confidence interval, ITT: intention-to-treat, Max: maximum, Min: minimum, N: number of patients in the analysis set, SD: standard deviation.

Table 41: Mean intra-patient difference in time to wound closure, mean blinded experts result, ITT from study BBW-11

		Difference in time to wound closure (days) [a, b] (Oleogel-S10 and wound dressing *minus* standard of care)					
N	**Blinded read**	**Mean**	**SD**	**Median**	**Min, Max**	**95% CI**	**P value[c]**
57	Primary	-1.0	1.5	-0.7	-5.0, 2.0	-1.4, -0.6	<0.0001
	Secondary	-1.3	1.6	-1.0	-6.3, 1.3	-1.8, -0.9	<0.0001

[a] Conservative estimation, which means that the first observation of wound closure was taken as time of wound closure.

[b] Difference in time to wound closure was set to 0 for two photo series with only Day 0 photo available. If wound closure was not observed, it was calculated to have occurred one day after the last photograph in the series.

[c] Based on a two-sided paired t-test evaluating the mean difference as different from 0.

CI: confidence interval, ITT: intention-to-treat, Max: maximum, Min: minimum, SD: standard deviation.

Statistical analysis on the difference between the two treatment groups in the proportion of patients with wound closure at pre-specified time points.

A statistical analysis on the difference between the two treatment groups was conducted using Fisher's exact test following a request from the CHMP.

The number of wound halves with wound closure was higher for the Episalvan gel-treated wound half compared to the standard of care treated wound half in the overall expert evaluation based on the majority of the three blinded experts (**Table 42**). This was the case for all three studies at all-time points. For burn wound study BBW-11, the differences were most pronounced at the first pre-specified time point day 7. For the STSG studies, the differences between groups increased with time and reached statistical significance for day 10 through day 28 for study BSH-12 as well as for the pooled analysis of studies BSH-12 and BSG-12.

Wound closure status and relevance of excluded photos using secondary blinded read data

The observations of the secondary blinded reads were directly compared for several relevant groups of excluded photos. In this new analysis the wound closure status was derived from observation in the secondary blinded read, comparing the results for

- all excluded photographs (**Table 43**),
- 'relevant' excluded photographs with possible impact on the result (**Table 44**) and
- 'relevant' excluded photographs with definite impact on the result (**Table 45**).

Table 42: Statistical analysis on the difference between the two treatment groups in the proportion of patients with wound closure at pre-specified time points.

	Wound closure achieved: Oleogel-S10 vs. standard of care						
Overall expert evaluation	Oleogel-S10			Standard of Care			Fisher's exact test, p-value (two-sided)
	Yes	No	Missing	Yes	No	Missing	
	N	N	N	N	N	N	
BSH-12							
Day 7	2	99	6	0	101	6	0.5652
Day 10	19	77	11	8	85	14	0.0756
Day 14	46	47	14	17	63	27	<0.0001
Day 18	55	30	22	22	40	45	<0.0001
Day 21	59	23	25	25	30	52	<0.0001
Day 28	66	9	32	29	12	66	<0.0001
BSG-12							
Day 7	4	101	5	1	104	5	0.5787
Day 10	12	92	6	11	92	7	1.0000
Day 14	45	51	14	41	54	15	0.8959
Day 18	68	22	20	54	30	26	0.1785
Day 21	73	14	23	59	22	29	0.1325
Day 28	79	6	25	65	7	38	0.1201
Pooled							
Day 7	6	200	11	1	205	11	0.1882
Day 10	31	169	17	19	177	21	0.1806
Day 14	91	98	28	58	117	42	0.0027
Day 18	123	52	42	76	70	71	<0.0001
Day 21	132	37	48	84	52	81	<0.0001
Day 28	145	15	57	94	19	104	<0.0001
BBW-11							
Day 7	28	22	7	19	31	7	0.1940
Day 10	40	10	7	37	13	7	0.7793
Day 14	46	4	7	42	8	7	0.5526
Day 18	50	0	7	48	2	7	0.5719
Day 21	50	0	7	49	1	7	1.0000

Intent-to-treat analysis set. N refers to the number of patients assessed to have achieved wound closure of the respective wound half at the indicated time point, based on the majority decision of the three blinded readers. In case of achievement of full wound closure, time to wound closure is the median value of time to wound closure for the three experts and wound closure is present for all time points greater than or equal to this median value.

The relevance classification of excluded photograph(s) ('relevant' vs. 'not relevant' exclusion, 'possible impact' vs. 'definite impact') was again carried forward from the primary blinded read to allow comparison of results within the identical sample of photographs.

Table 43. All excluded photographs: Comparison of wound closure status in primary and secondary blinded read

	Wound dressing changes (visits) with excluded photo(s)			
	Primary blinded read – wound closure status carried forward from preceding presented photograph(s)		Secondary blinded read – wound closure status at wound dressing change with previously excluded photograph(s)	
Wound closure status	N	%	N	%
BSH-12	**166**[1]	100.0	**166**	100.0
Missing	14	8.4	1	0.6
Both wound halves open	139[1]	83.7	128	77.1
Wound closed on Oleogel-S10 side only	12	7.2	31	18.7
Wound closed on standard of care side only	1	0.6	3	1.8
Both wound halves closed	0	0.0	3	1.8
BSG-12	**169**	100.0	**169**	100.0
Missing	8	4.7	0	0.0
Both wound halves open	148	87.6	126	74.6
Wound closed on Oleogel-S10 side only	8	4.7	17	10.1
Wound closed on standard of care side only	4	2.4	8	4.7
Both wound halves closed	1	0.6	18	10.7
BBW-11	**69**	100.0	**69**	100.0
Missing	15	21.7	0	0.0
Both wound halves open	41	59.4	50	72.5
Wound closed on Oleogel-S10 side only	7	10.1	14	20.3
Wound closed on standard of care side only	1	1.4	0	0.0
Both wound halves closed	5	7.2	5	7.2

Intent-to-treat analysis set. N and % refer to the number and percentage of wound dressing changes (visits) with excluded photo(s). Derivation of wound closure status was based on time to wound closure (conservative estimation) and the corresponding censoring indicator (indicating whether wound closure was observed or not), based on the overall expert evaluation.

Table 44. Relevant excluded photos with possible impact on result: Comparison of wound closure status in primary and secondary blinded read

	Wound dressing changes (visits) with relevant excluded photo(s)			
	Primary blinded read – wound closure status carried forward from preceding presented photograph(s)		Secondary blinded read – wound closure status at wound dressing change with previously excluded photograph(s)	
Wound closure status	N	%	N	%
BSH-12	46[1]	100.0	46	100.0
Both wound halves open	36[1]	78.3	22	47.8
Wound closed on Oleogel-S10 side only	9	19.6	19	41.3
Wound closed on standard of care side only	1	2.2	2	4.3
Both wound halves closed	0	0.0	3	6.5
BSG-12	90	100.0	90	100.0
Both wound halves open	80	88.9	57	63.3
Wound closed on Oleogel-S10 side only	6	6.7	13	14.4
Wound closed on standard of care side only	4	4.4	8	8.9
Both wound halves closed	0	0.0	12	13.3
BBW-11	28	100.0	28	100.0
Both wound halves open	24	85.7	21	75.0
Wound closed on Oleogel-S10 side only	3	10.7	3	10.7
Wound closed on standard of care side only	1	3.6	0	0.0
Both wound halves closed	0	0.0	4	14.3

Intent-to-treat analysis set. N and % refer to the number and percentage of wound dressing changes (visits) with relevant excluded photo(s). Relevance of excluded photos was directly adopted from the primary blinded read. Derivation of wound closure status was based on time to wound closure (conservative estimation) and the corresponding censoring indicator (indicating whether wound closure was observed or not), based on the overall expert evaluation.

Table 45. Relevant excluded photos with definite impact on result: Comparison of wound closure status in primary and secondary blinded read

	Excluded photo(s) at last wound dressing change			
	Primary blinded read – carried forward from preceding presented photograph		Secondary blinded read – observation of previously excluded photograph	
Wound closure status	N	%	N	%
BSH-12	**20**	**100.0**	**20**	**100.0**
Missing	3	15.0	1	5.0
Both wound halves open	9	45.0	5	25.0
Wound closed on Oleogel-S10 side only (impact of exclusion: advantage SOC control)	7	35.0	11	55.0
Wound closed on standard of care side only (impact of exclusion: advantage Oleogel-S10)	1	5.0	0	0.0
Both wound halves closed	0	0.0	3	15.0
BSG-12	**20**	**100.0**	**20**	**100.0**
Missing	2	10.0	0	0.0
Both wound halves open	11	55.0	2	10.0
Wound closed on Oleogel-S10 side only (impact of exclusion: advantage SOC control)	4	20.0	6	30.0
Wound closed on standard of care side only (impact of exclusion: advantage Oleogel-S10)	2	10.0	2	10.0
Both wound halves closed	1	5.0	10	50.0
BBW-11	**13**	**100.0**	**13**	**100.0**
Missing	5	38.5	0	0.0
Both wound halves open	3	23.1	2	15.4
Wound closed on Oleogel-S10 side only (impact of exclusion: advantage SOC control)	1	7.7	8	61.5
Wound closed on standard of care side only (impact of exclusion: advantage Oleogel-S10)	1	7.7	0	0.0
Both wound halves closed	3	23.1	3	23.1

Intent-to-treat analysis set. N and % refer to the number and percentage of wound dressing changes (visits) with uploaded photo(s). Derivation of wound closure status was based on time to wound closure (conservative estimation) and the corresponding censoring indicator (indicating whether wound closure was observed or not) for the preceding photograph, based on the majority decision of the three blinded readers.
SOC: Standard of care.

Clinical studies in special populations

No clinical studies in special populations were conducted which was considered acceptable due to the low systemic exposure following Episalvan gel application.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of Episalvan gel is mainly supported by three clinical studies; two phase 3 studies (BSH-12 and BSG-12) performed in patients with split-thickness skin graft (STSG) donor sites wounds and one phase 3 study (BBW-11) performed in patients with Grade 2a burn wounds. The studies are open, blindly evaluated, prospective, intra-individually controlled and randomised. The three pivotal phase 3 studies were performed in Europe.

The phase 3 studies enrolled male and female patients 18 years of age or above presenting an STSG donor site wound or acute Grade 2a burn wounds of certain sizes. There is no European guideline available for products indicated for treatment of wounds. Hence, efficacy end-points to be used are not clearly established. The primary efficacy end-point in the two pivotal studies BSH-12 and BSG-12 was the intra-individual difference in time to wound closure (at least 95% epithelialisation) between wound halves, either treated with Episalvan gel and non-adhesive wound dressing, or with non-adhesive wound dressing alone.

In study BBW-11, the primary efficacy end-point was percentage of patients with earlier healing (at least 95% epithelialisation) of the wound half treated with Episalvan gel compared to standard of care (Octenilin® Wound Gel), as evaluated by the majority decision of three independent, blinded experts.

Secondary and further efficacy end-points in studies BSH-12 and BSG-12 addressed intra-individual difference in time to wound closure, time from surgery until wound closure, percentage of patients with earlier healing of wound area treated with Episalvan gel compared to non-adhesive wound dressing alone and percentage of patients with earlier healing of wound half treated with Episalvan gel compared to non-adhesive wound dressing alone, as evaluated by the unanimous decision and relative intra-individual difference in time to wound closure between wound halves.

In study BBW-11, secondary and further efficacy end-points addressed percentage of patients with earlier healing of wound half treated with Episalvan gel compared to Octenilin® Wound Gel, intra-individual difference in time to wound closure between wound halves and percentage of patients with earlier healing of wound half treated with Episalvan gel compared to Octenilin® Wound Gel, as evaluated by the unanimous decision of the three independent, blinded experts.

Overall, the end-points used in the phase 3 studies were considered relevant.

During the randomisation process, the wound was divided into two halves, one to be treated with Episalvan gel and one with standard dressing (BSH-12 and BSG-12) or with Episalvan gel and Octenilin treated wound half (BBW-11). The posology of Episalvan gel in studies BSH-12 and BSG-12 were 1 cm Episalvan gel (approximately 100 mg) per cm^2 (i.e. approximately 1 mm thick) which was applied to one half of STSG donor site by applying it onto the wound-facing side of the wound dressing. Since the design is intra-individual, the possibility of spill-over of active between the treatment halves could be of concern. However in these studies, where Episalvan gel was administered to the wound dressing and moreover, the allowance of a 1 cm wide middle section to provide separate images per wound half, spill-over was not considered to be a concern in assessing efficacy.

Episalvan gel was applied at every change of wound dressing, approximately every third day. The duration of treatment period was until full wound closure of both wound halves, but no longer than 28 days after the start of study treatment. In study BBW-11, after cleansing of the wound, about 1 cm of Episalvan gel (approximately 100 mg) per cm^2 was applied to one half of the burn at every change of wound dressing. The

other half of the wound was covered with Octenilin® Wound Gel and fatty gauze as wound dressing. The duration of treatment period was until full wound closure of both wound halves, but no longer than 21 days after the start of study treatment.

Although the treatment was open to patients and investigators, the evaluation of the clinical efficacy was performed in a blinded manner. Photographs of the treated wound halves taken by the site staff were evaluated by three independent wound healing experts having no information about the treatment regimen of any of the photographed wounds for an unbiased, blinded judgement. To ensure that the blinding procedure was maintained, a large proportion of the patients had one or more photos excluded from the blinded read in cases where there is residue of the gel in the active treated part of the wound. As a consequence, 65% of patients in study BSH-12 and 67% of patients in study BSG-12 had one or more photos excluded. For the ITT analysis, those patients were included with the remaining photos. However, those patients were completely excluded from the PP population. Therefore, the PP analysis set included only 31 and 37 subjects in studies BSH-12 and BSG-12, respectively. However, not all of the photos removed in the quality check were critical for the evaluation of the primary endpoint, e.g. if they affected photos early on. The removal of a photo would cause a blinded read evaluation to be not 'valid' according to the Blind data review meeting if a photo directly prior to the observed time point of wound closure was excluded, or if the last photo was excluded, and no wound healing was observed.

Since gel residue was the main reason for exclusion of photos, there was a concern that wounds not closed on the side of active treatment could have been more difficult to clean and hence more likely to include gel residue and therefore to be excluded. If this had been the case, the bias introduced would favour Episalvan gel.

To further investigate the impact of excluded photographs, the blinded photo evaluation was repeated with all photos included. The same experts as in the primary evaluation also conducted this secondary blinded read. These analyses showed a slightly larger effect size compared to the primary evaluation. The applicant also provided information on wound closure status for the excluded photos based on this secondary evaluation, showing that wounds not closed on the side of active treatment were not more likely to be excluded. Therefore, the CHMP agreed that no significant bias favouring Episalvan gel was introduced by the exclusion of these photos to maintain the blinding of the evaluators.

The statistical methods used in the phase 3 studies were considered adequate for the study design and endpoints.

Efficacy data and additional analyses

Treatment of split-thickness skin graft donor site wounds (study BSH-12 and BSG-12)

The majority of STSG donor sites were located on the legs. The median wound size was 58 cm^2 in study BSH-12 and 76 cm^2 in study BDG-12.

In both pivotal studies, Episalvan gel met the primary end-point and was significantly superior ($p<0.0001$ study BSH-12; $p<0.00232$ study BSG-12) compared to standard dressing. In study BSH-12, the mean time from surgery to wound closure was 17.1 days with standard of care treatment and 15.5 days when the wound was treated with Oloegel-S10. The mean intra-individual difference in time to wound closure between the wound halves was -1.4 days, and this difference was statistically significant. The result in study BSG-12 is consistent with that of study BSH-12 albeit smaller. The mean time from surgery to wound closure is 16.0 days with standard dressing and 15.1 days when the wound was treated with Episalvan gel. The mean intra-individual difference in time to wound closure between the wound halves was -0.8 days.

The CHMP noted that the effect size of Episalvan gel treatment appeared to be small, however also acknowledged that Episalvan gel has been developed for severe partial thickness wounds that require hospital treatment and that the length of hospitalisation is influenced by the progression of healing. The risk of healing delays and complications is directly correlated with time to wound closure. Therefore a difference of 1-2 days in the reduction of the wound closure which may appear small, could potentially determine the decision for or against a surgical procedure. Therefore any acceleration of wound healing of severe partial thickness wounds treated in the hospital should be considered as clinically relevant. The CHMP therefore considered that the clinical relevance of the observed effects had been adequately justified.

Wound closure could not be determined for all photo series by the blinded experts. If wound closure was not observed in one or both photo series for a patient, no definite time to calculate a difference in wound healing time was available ('censored values') and certain assumptions had to be made to calculate the intra-individual difference in time to wound closure. If wound closure had not been observed for one of the two wound halves, the time to wound closure for the unknown half was set to the day of the last photo +1 day. As substantially more wounds were closed in the Episalvan gel group, this provided reassurance to the CHMP that the proposed method of analysis was not biased in favour of Episalvan gel, the time difference to wound closure of the other wound half, and thus the treatment effect size, was likely underestimated.

Because of the high proportion of censored values in the calculation of the primary endpoint, sensitivity analyses were done to assess whether the size of treatment effect is truly reflected in the primary endpoint. However, as wound dressings were changed every three to four days, three to four days would be the minimal duration for which healing would have been observed in the study, a much longer interval than one day used in the primary analysis. Thus in the sensitivity analysis, different intervals (+2 days, +3 days, +4 days, +7 days, and +MTWDC) were added to the last day for which a photo was available.

Of these MTWDC (mean time to wound dressing change), which is considered most relevant, indicated that Episalvan gel reduced time to healing with 2.0 and 1.1 days, respectively. Even if this analysis was conducted post-hoc, the CHMP agreed that the +1 assumption which was used probably underestimates the efficacy of Episalvan gel.

Treatment of Grade 2a partial thickness burn wounds (study BBW-11)

The study performed in patients with Grade 2a partial thickness burn wounds (BBW-11) enrolled 66 patients at 10 centres. The ITT group constituted of 57 patients and the PP group of 45 patients.

The primary endpoint was percentage of patients showing earlier healing of the Oleogel-S10 treated wound half compared with the Octenilin® Wound Gel treated half. 85.7% of patients showing a between-treatment difference in time to healing had faster healing with Oleogel-S10 ($p<0.0001$). However, since 22/57 patients (39%) had no between-treatment difference, only 53% of all treated patients had faster healing with Oleogel-S10. Results of the PP and completer analysis confirmed the findings of the primary analysis with more patients showing faster healing of Episalvan gel wound half than with Octenilin® Wound Gel treated wound half.

The target population as specified by the proposed indication would include Grade 2b (deep partial thickness extending to dermis) which however were not studied in the clinical development program. The CHMP acknowledged that most patients from the Episalvan gel studies had superficial partial thickness wounds. However, deep partial thickness wounds were also present. In study BBW-11 in grade 2a burn wounds, 3 patients were enrolled with initial diagnosis of grade 2a that later were assessed as grade 2b and received STSG surgery. This was considered reflective of the difficulty to distinguish between 'superficial' and 'deep' partial thickness at initial wound diagnosis.

Partial thickness burns (grade 2) often present with a continuum of different wound depths, changing gradually from grade 2a into grade 2b, and there may also be mixtures of different depths within the same wound. In clinical practice, the initial diagnosis of a grade 2a or 2b burn depth will frequently require revision as time progresses and repeated critical assessment of burn depth and healing progression is indicated (Papini, 2004). After 3 to 7 days post-injury, the assessment and estimate of wound healing time becomes more precise. Wounds judged to take more than 3 weeks to heal are indicated for transplantation with a STSG to reduce the risk of hypertrophic scarring. For grade 2b wounds, decision to transplant is typically taken one to two weeks post-injury.

Accidental wounds

Accidental wounds are often of mixed depth, presenting a continuum of varying wound depths within the injured skin area. It is a treatment goal to preserve as much viable tissue as possible to reduce the need and the area for skin transplantation. Grade 2a burns represent accidental wounds and Episalvan gel showed efficacy in this wound type. For accidental wounds of other origins, after wound cleaning the STSG donor site wound is considered representative.

Therefore the CHMP agreed that the proposed indication for Episalvan gel in the treatment of partial thickness wounds in adults adult was appropriate.

The SmPC states that there is no clinical experience from use of Episalvan for the treatment of chronic wounds, e.g. diabetic foot ulcers, venous leg ulcers or wounds in patients with Epidermolysis bullosa and that there is no information available on clinical use of Episalvan for more than 4 weeks.

2.5.4. Conclusions on the clinical efficacy

In clinical trials Episalvan gel was associated with faster healing in the order of 1-2 days out of 17 days associated with standard treatment in patients in healing of split-thickness wounds and by 1 day out of 9 days Grade 2a burn wounds. The secondary efficacy end-points and other endpoints supported the efficacy of Episalvan gel. These effects are considered to be of clinical relevance in conditions with limited treatment options.

2.6. Clinical safety

Patient exposure

In order to evaluate the safety of Episalvan gel, the Applicant conducted a pooled analysis of safety data which included patients from the Phase III studies BSG-12, BSH-12 and BBW-11. For this pooled analysis different conventions were used in the statistical analysis, compared to the analysis of the individual studies:

- Only treatment-emergent AEs were considered in the pooled analysis whereas also AEs occurring outside the treatment period were considered in the analysis of the individual studies.
- The classification of patients as “completers”, “premature discontinuations due to AE” and “premature discontinuations not due to AE” was only used in the pooled analysis, but not in the individual studies.

As a consequence of these different conventions discrepancies can be seen e.g. in the total numbers of AEs or the numbers of AEs leading to discontinuation between the pooled analysis and the individual studies.

A total of 280 patients were included in the safety population for the Phase III studies BSG-12 and BSH-12 and BBW-11, and 253 (90.4%) patients completed the study. A total of 27 (9.6%) patients prematurely discontinued treatment, and for 10 (3.6%) of these patients, the primary reason for premature discontinuation was an AE (**Table 46**).

The planned treatment was until wound closure or up to 28 days for the two skin graft wound studies (and until wound closure up to 21 days for the Grade 2a burn. The number of days on drug exposure is summarised in **Table 47**.

The median size (range) of the treatment area was 33.8 cm^2 for studies BSG-12 and BSH-12 and 84.5 cm^2 for BBW-11, with an overall median (range) treatment area of 40 cm^2. In study BBW-11, the large majority of patients (54, 88.5%) had one coherent wound area, whereas seven (11.5%) patients had two comparable separate wounds (**Table 48**).

Table 46. Patient disposition, pooled analysis of safety

		Completed	Discontinued treatment [b]	Discontinued treatment due to an AE [a]
	N	n (%)	n (%)	n (%)
Overall	280	253 (90.4)	27 (9.6)	10 (3.6)
Skin graft wound subpopulation	219	202 (92.2)	17 (7.8)	5 (2.3)
Grade 2a burn wound subpopulation	61	51 (83.6)	10 (16.4)	5 (8.2)

Patient base: Safety Analysis Set (all patients who received at least a single application of Oleogel-S10 in the skin graft studies BSG-12 and BSH-12 or Grade 2a burn wound study BBW-11).

[a] *Patients for whom the primary reason for discontinuation was "AEs or other safety reasons that do not allow continuation", as indicated on the withdrawal page of the CRF.*

[b] *Numbers were obtained by subtracting completers from total number of patients.*

Table 47. Number of days of study drug exposure, pooled analyses of safety

	N	Mean ± SD	Median	Range
Overall	280	16.7 ± 7.2	15.0	2-34
Skin graft wound subpopulation	219	18.5 ± 6.8	16.0	3-34
Grade 2a burn wound subpopulation	61	10.4 ± 4.9	9.0	2-23

Patient base: Safety Analysis Set (all patients who received at least a single application of Episalvan gel in the skin graft studies BSG-12 and BSH-12 or Grade 2a burn wound study BBW-11).

Table 48. Size of treatment area (cm^2), pooled analyses of safety

	N	Mean ± SD	Median	Range
Overall	280	55.5 ± 53.8	40.0	7.5-395
Skin graft wound subpopulation	219	40.9 ± 33.1	33.8	7.5-300
Grade 2a burn wound subpopulation	61	108.2 ± 76.5	84.5	22.5-395

Patient base: Safety Analysis Set (all patients who received at least a single application of Episalvan gel in the skin graft studies BSG-12 and BSH-12 or Grade 2a burn wound study BBW-11).

Other Studies with Clinical Safety Data

In other studies which were not included in the pooled analysis of safety, 260 patients received at least one application of Episalvan gel (TE 10%) or TE 4%, and the study was completed by 249 (95.8%) patients. Two discontinuations were attributed to AEs, one in the actinic keratosis study BAK-08 and one in the psoriasis study BC-002.

The CHMP considered that the safety assessment should be focused on the pooled analysis of data, as information from the studies would be of limited relevance as they concerned other types of lesions and/or used other treatment schedules and formulations/strengths of Episalvan gel.

Demographic and Baseline Characteristics

In the pooled analysis of safety, the majority (65%) were male patients, most patients (91%) were white, and most patients had a Fitzpatrick skin type of Grade II or III (77%). The mean age was around 50 years and approximately 25% of the patients were aged ≥ 65 years. The mean age in the burn wound study was lower compared with the STSG studies with only around 10% above 65 years (**Table 49**).

Adverse events

For patients in the pooled analysis of safety, AEs were reported for 98 (35.0%) patients, related AEs were reported for 25 (8.9%) of patients, SAEs for 15 (5.4%) patients, and a related SAE for 1 (0.4%) patient (**Table 53**). AEs that led to discontinuation were reported for 7 (2.5%) patients, and 1 (0.4%) patient had a related AE that led to discontinuation. In the analysis of adverse events, relationship was reported as related to study drug if it was assessed by investigator as remote/ unlikely, possible, probable or unknown.

Common Adverse Events

One or more AEs were reported for a total of 35% of patients. SOCs with highest incidence were infections and infestations (11.4%), injury, poisoning and procedural complications (8.2%) and skin and subcutaneous tissue disorders (10.4%). Most frequent AEs (by preferred term) comprised pyrexia and wound infection (3.9% of patients), skin infection (4.6%), pain of skin (5.4%) and pruritus (4.6%). Adverse events reported in at least two patients are summarised in **Table 50**.

Table 49. Patient demographic and baseline characteristics, pooled analysis of safety

		Overall	Skin graft wound	Grade 2a burn wound
		N=280	N=219	N=61
Age, years	Mean ± SD	49.8 ± 17.9	52.5 ± 17.7	40.1 ± 15.3
	18 to <65, n (%)	211 (75.4)	156 (71.2)	55 (90.2)
	≥ 65 years, n (%)	69 (24.6)	63 (28.8)	6 (9.8)
Sex, n (%)	Male	183 (65.4)	141 (64.4)	42 (68.9)
	Female	97 (34.6)	78 (35.6)	19 (31.1)
Race, mean ± SD	White	256 (91.4)	205 (93.6)	51 (83.6)
	Other	24 (8.6)	14 (6.4)	10 (16.4)
Fitzpatrick skin type, No. Patients (%)	I	11 (3.9)	4 (1.8)	7 (11.5)
	II	144 (51.4)	114 (52.1)	30 (49.2)
	III	72 (25.7)	59 (26.9)	13 (21.3)
	IV	27 (9.6)	22 (10.0)	5 (8.2)
	V	22 (7.9)	20 (9.1)	2 (3.3)
	VI	4 (1.4)	0	4 (6.6)

Patient base: Safety Analysis Set (all patients who received at least a single application of Oleogel-S10 in the skin graft studies BSG-12 and BSH-12 or Grade 2a burn wound study BBW-11).

Table 50. Overview of adverse events, pooled analysis of safety

	Overall	Skin graft wound	Grade 2a burn wound
	N =280	N =219	N =61
No. Patients (%)			
Overall	98 (35.0)	78 (35.6)	20 (32.8)
Related	25 (8.9)	19 (8.7)	6 (9.8)
Serious	15 (5.4)	7 (3.2)	8 (13.1)
Serious related	1 (0.4)	0	1 (1.6)
Led to discontinuation[a]	7 (2.5)	4 (1.8)	3 (4.9)
Led to discontinuation, related	1 (0.4)	0	1 (1.6)

Patient base: Safety Analysis Set (all patients who received at least a single application of Episalvan gel in the skin graft studies BSG-12 and BSH-12 or Grade 2a burn wound study BBW-11).

[a] *Events leading to discontinuation were defined as AEs with "action taken regarding study medication= discontinued", as documented on the AE pages of the CRF, for patients who prematurely discontinued due to AE (as indicated on the withdrawal page of the CRF).*

Table 51. Incidence of adverse events (reported in 2 [0.7%] or more patients overall) by MedDRA system organ class and preferred term, pooled analysis of safety

MedDRA Version 16.0 System Organ Class Preferred Term	Overall N=280	Skin graft wound N=219	Burn wound N=61
No. Patients (%)	98 (35.0)	78 (35.6)	20 (32.8)
Blood and lymphatic system disorders	7 (2.5)	7 (3.2)	0
Anaemia	7 (2.5)	7 (3.2)	0
Leukocytosis	2 (0.7)	2 (0.9)	0
Gastrointestinal disorders	15 (5.4)	14 (6.4)	1 (1.6)
Diarrhoea	3 (1.1)	3 (1.4)	0
Constipation	7 (2.5)	7 (3.2)	0
Nausea	4 (1.4)	3 (1.4)	1 (1.6)
Vomiting	3 (1.1)	3 (1.4)	0
General disorders and administration site conditions	24 (8.6)	20 (9.1)	4 (6.6)
Pyrexia	11 (3.9)	10 (4.6)	1 (1.6)
Chills	2 (0.7)	2 (0.9)	0
Condition aggravated	2 (0.7)	0	2 (3.3)
Infusion site extravasation	4 (1.4)	4 (1.8)	0
Injection site reaction	2 (0.7)	2 (0.9)	0
Oedema peripheral	3 (1.1)	3 (1.4)	0
Pain	6 (2.1)	5 (2.3)	1 (1.6)
Infections and infestations	32 (11.4)	26 (11.9)	6 (9.8)
Wound infection	11 (3.9)	7 (3.2)	4 (6.6)
Skin infection	13 (4.6)	13 (5.9)	0
Urinary tract infection	3 (1.1)	2 (0.9)	1 (1.6)
Injury, poisoning and procedural complications	23 (8.2)	19 (8.7)	4 (6.6)
Wound complication	4 (1.4)	2 (0.9)	2 (3.3)
Wound haematoma	3 (1.1)	3 (1.4)	0
Wound haemorrhage	3 (1.1)	3 (1.4)	0
Post procedural complication	5 (1.8)	5 (2.3)	0
Procedural pain	2 (0.7)	2 (0.9)	0
Wound dehiscence	2 (0.7)	2 (0.9)	0
Investigations	4 (1.4)	4 (1.8)	0
Transaminases increased	2 (0.7)	2 (0.9)	0
Metabolism and nutrition disorders	2 (0.7)	2 (0.9)	0
Hyperglycaemia	2 (0.7)	2 (0.9)	0
Skin and subcutaneous tissue disorders	29 (10.4)	23 (10.5)	6 (9.8)
Pain of skin	15 (5.4)	12 (5.5)	3 (4.9)
Pruritus	13 (4.6)	10 (4.6)	3 (4.9)
Excessive granulation tissue	3 (1.1)	3 (1.4)	0
Vascular disorders	8 (2.9)	8 (3.7)	0
Hypertension	4 (1.4)	4 (1.8)	0
Hypotension	2 (0.7)	2 (0.9)	0

Patient base: Safety Analysis Set (all patients who received at least a single application of Oleogel-S10 in the skin graft studies BSG-12 and BSH-12 or Grade 2a burn wound, study BBW-11).

Numbers in column skin graft wound were obtained by adding numbers for study BSG-12 and BSH-12.

AEs for which a relationship to treatment could not be ruled out were reported for a total of 25 (8.9%) patients (N=280) (**Table 52**). These comprised 8 (2.9%) patients with pain of skin, 4 (1.4%) patients with pruritus, 3 (1.1%) patients each with wound complication and post procedural complication, 2 (0.7%) patients with pain, and 1 (0.4%) patient each with impaired healing, mucosal induration, hypersensitivity, wound infection, inflammation of wound, wound necrosis, wound secretion, cough, dermatitis, rash pruritic, purpura and excessive granulation tissue.

Table 52. Incidence of related adverse events by MedDRA system organ class, high level term and preferred term, pooled analysis of safety

MedDRA Version 16.0 System Organ Class Preferred Term	**Overall**	**Skin graft wound**	**Grade 2a burn wound**
	N=280	**N=219**	**N=61**
No. Patients (%)			
Any	25 (8.9)	19 (8.7)	6 (9.8)
General disorders and administration site conditions	4 (1.4)	4 (1.8)	0
Impaired healing	1 (0.4)	1 (0.5)	0
Mucosal induration	1 (0.4)	1 (0.5)	0
Pain	2 (0.7)	2 (0.9)	0
Immune system disorders	1 (0.4)	1 (0.5)	0
Hypersensitivity	1 (0.4)	1 (0.5)	0
Infections and infestations	1 (0.4)	1 (0.5)	0
Wound infection	1 (0.4)	1 (0.5)	0
Injury, poisoning and procedural complications	8 (2.9)	5 (2.3)	3 (4.9)
Inflammation of wound	1 (0.4)	0	1 (1.6)
Wound complication	3 (1.1)	2 (0.9)	1 (1.6)
Wound necrosis	1 (0.4)	0	1 (1.6)
Wound secretion	1 (0.4)	1 (0.5)	0
Post procedural complication	3 (1.1)	3 (1.4)	0
Respiratory, thoracic and mediastinal disorders	1 (0.4)	1 (0.5)	0
Cough	1 (0.4)	1 (0.5)	0
Skin and subcutaneous tissue disorders	13 (4.6)	10 (4.6)	3 (4.9)
Pain of skin	8 (2.9)	6 (2.7)	2 (3.3)
Dermatitis	1 (0.4)	1 (0.5)	0
Pruritus	4 (1.4)	4 (1.8)	0
Rash pruritic	1 (0.4)	0	1 (1.6)
Purpura	1 (0.4)	0	1 (1.6)
Excessive granulation tissue	1 (0.4)	1 (0.5)	0

Patient base: Safety Analysis Set (all patients who received at least a single application of Oleogel-S10 in the skin graft studies BSG-12 and BSH-12 or Grade 2a burn wound study BBW-11).

Numbers in column skin graft wound were obtained by adding numbers for study BSG-12 and BSH-12.

Application-site AEs were reported for the Episalvan gel treatment site for a total of 4 (1.4%) patients, the control (STC) site for 15 (5.4%) patients, and both treatment halves (meaning that the location of the AE could not be further differentiated ("location not further differentiated") for 36 (12.9%) patients (N=280) (**Table 53**).

If only the Episalvan gel treatment sites and the sites with "location not further differentiated" were considered, a total of 40 (14.3%) patients had one or more application site AEs. Application site AEs reported for 2 (0.7%) or more patients in this category (Episalvan gel sites combined with the sites with "location not further differentiated") comprised pain of skin (6 patients, 2.1%), wound infection (7 patients, 2.5%), skin infection (6 patients, 2.1%) and pruritus (6 patients, 2.1%); post procedural complication and wound

complication for 3 (1.1%) patients each; and 2 (0.7%) patients each with condition aggravated, procedural pain, wound haematoma and wound haemorrhage.

Table 53. Incidence of application-site adverse events by system organ class and preferred term and treatment, pooled analysis of safety

MedDRA Version 16.0 System Organ Class Preferred Term	Treatment allocated to wound half:			Subtotal:	TOTAL
	Episalvan gel	Standard of care	Location not further differentiated	Episalvan gel *or* location not further differentiated	
	N=280	N=280	N=280	N=280	N=280
No. Patients (%)	4 (1.4)	15 (5.4)	36 (12.9)	40 (14.3)	55 (19.6)
General disorders and administration site conditions			3 (1.1)	3 (1.1)	3 (1.1)
Condition aggravated			2 (0.7)	2 (0.7)	2 (0.7)
Infections and infestations	1 (0.4)	1 (0.4)	12 (4.3)	13 (4.6)	14 (5.0)
Wound infection		1 (0.4)	7 (2.5)	7 (2.5)	8 (2.9)
Skin infection	1 (0.4)	4 (1.4)	5 (1.8)	6 (2.1)	10 (3.6)
Injury, poisoning and procedural complications	1 (0.4)	4 (1.4)	12 (4.3)	13 (4.6)	17 (6.1)
Post procedural complication			3 (1.1)	3 (1.1)	3 (1.1)
Procedural pain			2 (0.7)	2 (0.7)	2 (0.7)
Wound complication		1 (0.4)	3 (1.1)	3 (1.1)	4 (1.4)
Wound haematoma			2 (0.7)	2 (0.7)	2 (0.7)
Wound haemorrhage		1 (0.4)	2 (0.7)	2 (0.7)	3 (1.1)
Skin and subcutaneous tissue disorders	2 (0.7)	5 (1.8)	11 (3.9)	13 (4.6)	18 (6.4)
Pain of skin		4 (1.4)	6 (2.1)	6 (2.1)	10 (3.6)
Pruritus	1 (0.4)		5 (1.8)	6 (2.1)	6 (2.1)

Patient base: Safety Analysis Set (all patients who received at least a single application of Oleogel-S10 in the skin graft studies BSG-12 and BSH-12 or Grade 2a burn wound study BBW-11).

Frequently reported: 2 (0.7%) or more patients (preferred term) in the overall pooled analysis of safety in wound halves treated with Oleogel-S10 (N=280).Wound half: Each patient received both Oleogel-S10 and standard of care. The two different treatments were applied either to two halves of the same wound (BBW-11, BSH-12 and BSG-12) or to two non-contiguous wounds with equal treatment areas (BBW-11 only).

Numbers in columns "Oleogel-S10 or location not further differentiated" and column "total" were obtained by adding numbers from relevant columns.

Application-site AEs for which a relationship to treatment could not be ruled out were reported for the Episalvan gel treatment site for a total of 3 (1.1%) patients, the STC site for 6 (2.1%) patients, and both treatment halves ("location not further differentiated") for 16 (5.7%) patients (**Table 54**).

If only the Episalvan gel treatment sites and the sites with "location not further differentiated" are considered, a total of 19 (6.8%) patients had one or more application site AEs. Related application site AEs reported for 2 (0.7%) or more patients in this category (Oleogel-S10 sites combined with the sites with "location not further differentiated") comprised pain of skin (1.8% of patients), pruritus (1.4% of patients), post procedural complication (1.1%), and wound complication (1.1%).

Table 54. Incidence of related application-site adverse events by system organ class and preferred term and treatment, pooled analysis of safety

MedDRA Version 16.0 System Organ Class Preferred Term	Treatment allocated to wound half:			Subtotal:	TOTAL
	Episalvan gel	Standard of care	Location not further differentiated	Episalvan gel *or* location not further differentiated	
	N=280	N=280	N=280	N=280	N=280
No. Patients (%)	3 (1.1)	6 (2.1)	16 (5.7)	19 (6.8)	25 (8.9)
General disorders and administration site conditions			1 (0.4)	1 (0.4)	1 (0.4)
Impaired healing			1 (0.4)	1 (0.4)	1 (0.4)
Immune system disorders			1 (0.4)	1 (0.4)	1 (0.4)
Hypersensitivity			1 (0.4)	1 (0.4)	1 (0.4)
Infections and infestations		1 (0.4)			1 (0.4)
Wound infection		1 (0.4)			1 (0.4)
Injury, poisoning and procedural complications	1 (0.4)	1 (0.4)	6 (2.1)	7 (2.5)	8 (2.9)
Inflammation of wound		1 (0.4)			1 (0.4)
Post procedural complication			3 (1.1)	3 (1.1)	3 (1.1)
Wound complication			3 (1.1)	3 (1.1)	3 (1.1)
Wound necrosis	1 (0.4)			1 (0.4)	1 (0.4)
Wound secretion			1 (0.4)	1 (0.4)	1 (0.4)
Skin and subcutaneous tissue disorders	2 (0.7)	4 (1.4)	9 (3.2)	11 (3.9)	15 (5.4)
Dermatitis		1 (0.4)			1 (0.4)
Pain of skin		3 (1.1)	5 (1.8)	5 (1.8)	8 (2.9)
Pruritus	1 (0.4)		3 (1.1)	4 (1.4)	4 (1.4)
Rash pruritic	1 (0.4)			1 (0.4)	1 (0.4)
Purpura			1 (0.4)	1 (0.4)	1 (0.4)
Excessive granulation tissue			1 (0.4)	1 (0.4)	1 (0.4)

Patient base: Safety Analysis Set (all patients who received at least a single application of Oleogel-S10 in the skin graft studies BSG-12 and BSH-12 or Grade 2a burn wound study BBW-11).

Frequently reported: 2 (0.7%) or more patients (preferred term) in the overall pooled analysis of safety in wound halves treated with Oleogel-S10 (N=280).

Wound half: Each patient received both Episalvan gel and standard of care. The two different treatments were applied either to two halves of the same wound (BBW-11, BSH-12 and BSG-12) or to two non-contiguous wounds with equal treatment areas (BBW-11 only). Numbers in columns "Episalvan gel" or location not further differentiated" and column "total" were obtained by adding numbers from relevant columns.

Several terms in the previous table of adverse reactions related to complications, namely 'wound complication', 'post-procedural complication', 'wound secretion', 'impaired healing', or 'inflammation of wound'. The Applicant considered that these different terms represented the same phenomenon, and therefore proposed to group these in Section 4.8 of the SmPC as "Wound complication", and this was considered acceptable by the CHMP.

Serious adverse event/deaths/other significant events

There were no deaths in the pooled analysis (study BSH-12, BSG-12 or BBW-12).

There were two deaths (0.8%) in the clinical studies not included in the pooled analysis (N=260). Neither death was considered to be related to treatment. In BSH-10, one patient died from progression of cancer

nearly 5 weeks after the 14-day treatment period. In the actinic keratosis study BAK-08, one patient died from cholangiocarcinoma 6 weeks after the last application of study medication.

There were a total of 15 (5.4%) patients who experienced one or more SAEs (**Table 55**). The most frequently reported SAEs were wound infection, reported for 4 (1.4%) patients, and condition aggravated, reported for 2 (0.7%) patients (see table below). All other SAEs were reported for 1 (0.4%) patient each: pyrexia, bacteraemia, sepsis, soft tissue infection, postoperative wound complication, wound necrosis, tonsil cancer, mania, bronchospasm and diabetic foot.

Table 55. Incidence of serious adverse events by MedDRA system organ class and preferred term, pooled analysis of safety

MedDRA Version 16.0 **System Organ Class** **Preferred Term**	**Overall** **N=280**	**Skin graft wound** **N=219**	**Burn wound** **N=61**
No. Patients (%)			
Overall	15 (5.4)	7 (3.2)	8 (13.1)
General disorders and administration site conditions	3 (1.1)	0	3 (4.9)
Condition aggravated	2 (0.7)	0	2 (3.3)
Pyrexia	1 (0.4)	0	1 (1.6)
Infections and infestations	7 (2.5)	4 (1.8)	3 (4.9)
Wound infection	4 (1.4)	2 (0.9)	2 (3.3)
Bacteraemia	1 (0.4)	1 (0.5)	0
Sepsis	1 (0.4)	1 (0.5)	0
Soft tissue infection	1 (0.4)		1 (1.6)
Injury, poisoning and procedural complications	2 (0.7)	1 (0.5)	1 (1.6)
Postoperative wound complication	1 (0.4)	1 (0.5)	0
Wound necrosis	1 (0.4)	0	1 (1.6)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.4)	0	1 (1.6)
Tonsil cancer	1 (0.4)	0	1 (1.6)
Psychiatric disorders	1 (0.4)	1 (0.5)	
Mania	1 (0.4)	1 (0.5)	
Respiratory, thoracic and mediastinal disorders	1 (0.4)	1 (0.5)	0
Bronchospasm	1 (0.4)	1 (0.5)	0
Skin and subcutaneous tissue disorders	1 (0.4)	1 (0.5)	0
Diabetic foot	1 (0.4)	1 (0.5)	0

Patient base: Safety Analysis Set (all patients who received at least a single application of Oleogel-S10 in the skin graft studies BSG-12 and BSH-12 or Grade 2a burn wound study BBW-11).

Frequently reported: 2 (0.7%) or more patients (preferred term) in the overall pooled analysis of safety (N=280).

There was one related (relationship reported as unknown) SAE in the pooled analysis (0.4%, N=280) for "wound necrosis" which was experienced by a 79-year-old male patient in the Grade 2a burn wound study BBW-11. The patient's hospital stay was prolonged because skin graft surgery was necessary. Both the wound half treated with Oleogel-S10 and STD alone had changed to Grade 2b and required skin grafting. The patient was prematurely discontinued from the study on Day 8 due to the SAE, two days after the last treatment with study medication.

A change in burn wound depth from Grade 2a to Grade 2b is expected for up to 30% of patients in the study and skin grafting is the standard treatment for Grade 2b burn wounds. Based on the available information, the Applicant did not propose to include wound necrosis in the SmPC, and the CHMP agreed with this.

In the studies not included in the pooled analysis (N=260), there were a total of 5 (1.9%) patients for whom SAEs were reported, none of which was considered related to study drug. All SAEs occurred in elderly individuals >65 years of age in the actinic keratosis study BAK-08.

Laboratory findings

Routine clinical laboratory assessments and measurement of vital signs were not done in the studies performed within the Episalvan gel clinical development program.

In study BBW-11 microbial colonisation of the wound halves treated with Oleogel-S10 or Octenilin was assessed by a local laboratory. This was done at Days 7 (±1 day), 14 (±1 day) and EoT. The difference in microbial colonisation of the two wound halves was assessed. If a clinically significant difference in microbial colonisation was found, the wound half showing more microbial colonisation was noted, as was the name of the germ mainly causing the difference and additional medical intervention required due to this microbial colonisation.

For the majority of patients, no difference in microbial colonisation was noted between wound halves treated with the antiseptic Octenilin and Episalvan gel.

Safety in special populations

Adverse events by age group

The nature and incidence of AEs for patients 18 to <65 years of age compared to older patients (**Table 56**), did not reveal any significant differences between the two groups.

Table 56. Incidence of adverse events experienced by 3% or more of patients overall by age, pooled analysis of safety

MedDRA Version 16.0 System Organ Class Preferred Term	Overall N=280	18 to <65 years N=211	≥ 65 years N=69
No. Patients (%)	98 (35.0)	73 (34.6)	25 (36.2)
General disorders and administration site conditions	24 (8.6)	21 (10.0)	3 (4.3)
Pyrexia	11 (3.9)	9 (4.3)	2 (2.9)
Infections and infestations	32 (11.4)	21 (10.0)	11 (15.9)
Wound infection	11 (3.9)	7 (3.3)	4 (5.8)
Skin infection	13 (4.6)	7 (3.3)	6 (8.7)
Skin and subcutaneous tissue disorders	29 (10.4)	26 (12.3)	3 (4.3)
Pain of skin	15 (5.4)	12 (5.7)	3 (4.3)
Pruritus	13 (4.6)	13 (6.2)	0

Safety Analysis Set: all patients who received at least a single application of Oleogel-S10.

Use in Pregnancy and Lactation

There is no clinical experience of Episalvan gel in pregnant or lactating women. No effects during pregnancy are anticipated, since systemic exposure to Episalvan is negligible

Immunological events

There were reports of allergic-like reactions, hypersensitivity, asthma and contact dermatitis reported in one patient each.

The case of asthma was reported in one the studies in AK. This case was considered to be unlikely related to treatment, as the risk for IgE mediated allergies due to Episalvan gel was deemed small.

The case of contact dermatitis originated from a publication (Meyer-Hoffert and Brasch, 2013), in which a 51-year old male developed itchy erythema and papules on his hands and face 4 months after starting to use Imlan® Creme Pur cream (containing birch bark extract, jojoba oil, and water). It was later confirmed via patch tests that 10% birch bark extract in jojoba oil resulted in mild to moderate allergic reactions while 100% jojoba oil was negative. The authors concluded that as betulin is the major triterpene in Imlan® Creme Pur cream, it was suspected as the relevant allergen in this case, however, it cannot be excluded that another triterpene could have been the causative agent.

Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies were included in the development program, due to the low systemic exposure, and no AEs related to interactions have been reported.

Discontinuation due to adverse events

There were 10 patients (3.6%) in the pooled safety database who discontinued the study due to AEs (**Table 57**).

The most frequently reported AE which led to discontinuation of treatment was wound infection (n=3; 1.1% of patients) (Table). All other AEs that led to discontinuation were reported for one (0.4%) patient each (soft tissue infection, post procedural complication, wound necrosis, and mania).

Table 57. Incidence of adverse events that led to discontinuation by MedDRA system organ class and preferred term, pooled analysis of safety

MedDRA Version 16.0 **System Organ Class** **Preferred Term**	**Overall** N=280	**Skin graft wound** N=219	**Burn wound** N=61
No. Patients (%)			
Overall	7 (2.5)	4 (1.8)	3 (4.9)
Infections and infestations	4 (1.4)	2 (0.9)	2 (3.3)
Wound infection	3 (1.1)	2 (0.9)	1 (1.6)
Soft tissue infection	1 (0.4)	0	1 (1.6)
Injury, poisoning and procedural complications	2 (0.7)	1 (0.5)	1 (1.6)
Post procedural complication	1 (0.4)	1 (0.5)	0
Wound necrosis	1 (0.4)	0	1 (1.6)
Psychiatric disorders	1 (0.4)	1 (0.5)	0
Mania	1 (0.4)	1 (0.5)	0

Patient base: Safety Analysis Set (all patients who received at least a single application of Oleogel-S10 in the skin graft studies BSG-12 and BSH-12 or Grade 2a burn wound study BBW-11).

AEs leading to discontinuation are defined as AEs with "action taken regarding study medication = discontinued" on the AE pages of the CRF.

Post marketing experience

There is no post marketing experience with Episalvan gel.

2.6.1. Discussion on clinical safety

The pooled safety data base for Episalvan gel consists of 280 patients in total, with the majority from the two STSG studies (n=219) and a smaller proportion from the Grade 2a burn wound study (n=61). The treatment duration differed for the different wound types with a mean ± SD treatment period of 18.5 ± 6.8 days for STSG and 10.4 ± 4.9 days for study BBW-11. The median size of the treatment area was smaller for studies BSG-12 and BSH-12 (34 cm2) in comparison with the burn wound study BBW-11 (85 cm2). Thus, even if it is agreed that the three studies may be combined, there are differences in duration and treated wound area. In order to address this, the Applicant presented the STSG and burn wound study results both combined and separately, which was considered acceptable by the CHMP.

In the studies not included in the pooled analysis of safety, 260 patients received at least one application of Episalvan gel (TE 10%) or TE 4%. The CHMP considered that data from these studies could only contribute supportive information, since they relate to other indications, other treatment schedules and other concentrations and formulations of Episalvan gel.

In the pooled analysis of safety, one or more AEs were reported for a total of 35% of patients. The SOCs with highest incidence were infections and infestations (11%), injury, poisoning and procedural complications (8%) and skin and subcutaneous tissue disorders (10%). Most frequent AEs (by preferred term) comprised pyrexia and wound infection, skin infection, pain of skin and pruritus, each reported at a rate of 4 6%.

Regarding AEs classified as related, this concerns a total of 25 (9%) patients, comprising pain of skin (2.9%), pruritus (1.4%), and a few patients with other AEs, e.g. wound complication and post procedural complications.

Application-site AEs were reported separately for the Episalvan gel treatment site and the control (STC) site, however, in many cases it was classified as “location not further differentiated”. Analyses have been presented for these separate categories as well as for the combined category “Episalvan gel or location not further differentiated”. This was considered acceptable by the CHMP as it was expected that it would be difficult to distinguish between application-site adverse events for a wound divided in two halves, unless the effect was very pronounced. The rates of application-site adverse events were overall low and are adequately reflected in the SmPC.

Regarding serious adverse events, the overall number of patients who experienced one or more SAEs in the pooled analysis of safety was low (15 or 5.4% of the patients). Wound infections were observed, however, none considered related to treatment. For one of the SAE (wound necrosis) causality between treatment and event was reported as unknown by the investigator. The CHMP agreed with the Applicant’s response that the relationship between Episalvan and the reported event was not established based on the available information.

No deaths were reported in the studies in the pooled analysis and two deaths in the other clinical studies which however were considered not related to the treatment.

The number of patients in the pooled safety database who discontinued the study due to AEs was low (10 patients, 3.6%) and with the exception of the wound necrosis case, none of these was considered as related to treatment.

With respect to immunological adverse events, the medicinal product contains an extract and not a single, defined active substance. Therefore, the possibility that the product does not contain constituents that may induce hypersensitivity reactions is difficult to be categorically excluded. Single cases of hypersensitivity, contact dermatitis and asthma have been reported with Episalvan gel.

Hypersensitivity to the active substance or to the excipient contained in the product are a contraindication for the use of Episalvan gel. In addtion, hypersensitivity and dermatitis are listed in Section 4.8 of the SmPC. It was considered however unlikely that Episalvan could have contributed to the single case of asthma case which has been reported.

Episalvan gel is a locally applied, locally acting product with limited systemic absorption. Hence, no drug-drug interactions are expected. There is no information on the potential for interactions with other topically applied products and this is reflected in the SmPC.

There were no major differences in the nature and incidence of AEs for patients aged less than 65 years compared with older patients, however, the number of patients aged 65 years and above was rather small (n=69). Even if slightly higher incidences of AEs were sometimes observed in elderly patients, the data gave no cause for concern, and no dose adjustment is required for use of Episalvan in the elderly.

2.6.2. Conclusions on the clinical safety

Three studies are pivotal for assessment of the safety of Episalvan gel; all using an intra-individual, comparative design with the target wound area of each patient divided into two treatment areas or by selection of two comparable wounds (in the burn wound study only).

The safety data presented did not give any major cause for concern with respect to all AEs, related AEs, SAEs, application site AEs or discontinuation due to AEs. Related AEs were reported in 9% of patients, with pain of skin (2.9%) and pruritus (1.4%) being the most common. Very few systemic AEs were reported, indicating a low risk for safety issues related to systemic absorption and causality in these reports was considered to be unlikely.

Episalvan gel is not intended for long-term treatment and the recommended maximum treatment duration is 4 weeks. Therefore no long-term safety studies are required.

Since the intended action of Episalvan gel is to promote wound healing, there is a potential proliferative and/or carcinogenic effect of the product, even if there is no evidence of such effects from the currently available data. However, as the product is only intended for short-term use, a proliferative effect is likely not to be an issue of clinical relevance.

The safety profile of Episalvan gel is considered manageable, with the risk minimisation measures included in the SmPC and the RMP of the product.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.2 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Summary of the safety concerns.

Summary of safety concerns	
Important identified risks	Allergic reaction / Hypersensitivity
Important potential risks	Wound infection Use in patients with epidermolysis bullosa Prolonged healing of burn wounds and risk of hypertrophic scarring if surgery is delayed
Missing information	Interaction with other topical applied medicinal products Use in patients with multiple allergic disorder Use in patients with different skin types regarding ethnic origin / Fitzpatrick skin types Long term / repeated use Sensitisation Use in paediatric patients

The PRAC agreed.

Pharmacovigilance plan

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Allergic reaction / Hypersensitivity	Listed as contraindication in section 4.3 of the SmPC and section 2 of the PIL. Listed as undesirable effect in section 4.8 of the SmPC and section 4 of the PIL	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Wound infection	Listed as undesirable effect in section 4.8 of the SmPC and in section 4 of the PIL. A note is placed in section 4.2 of the SmPC. A warning is placed in section 4.4 of the SmPC: A warning is placed in section 2 of the PIL:	None
Use in patients with epidermolysis bullosa	Warning in section 4.4 of the SmPC Follow up with reporter on an individual bases based on medical considerations.	None
Prolonged healing of burn wounds and risk of hypertrophic scarring if surgery is delayed	Warning in section 4.4 of the SmPC	None
Interaction with other topical applied medicinal	A warning is placed in section 4.5 of the SmPC A warning is placed in section 2 of the PIL	None
Use in patients with multiple allergic disorder	None	None
Use in patients with different skin types regarding ethnic origin / Fitzpatrick skin types	None	None
Long term / repeated use	A note is placed in section 4.2 of the SmPC: … until the wound is healed, for up to 4 weeks. A warning is placed in section 4.4 of the SmPC: There is no information available on clinical use of Episalvan for more than 4 weeks.	None
Sensitisation	A warning is placed in section 4.4 of the SmPC: There is no information available on clinical use of Episalvan for more than 4 weeks.	None
Use in paediatric patients	Warning in section 4.2 of the SmPC Warning in section 2 of the PIL	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Episalvan gel is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The aim of Episalvan gel treatment is the healing of partial thickness wounds of different origin. The pivotal clinical studies were performed in patients with split-thickness skin graft (STSG) donor sites wounds and in patients with Grade 2a burn wounds.

The primary efficacy end-point in the two pivotal studies on STSG donor sites wounds were intra-individual difference in time to wound closure (at least 95% epithelialisation) between wound halves, either treated with Episalvan gel and non-adhesive wound dressing, or with non-adhesive wound dressing alone. In both pivotal studies, Episalvan gel met the primary end-point and was significantly superior in both studies compared to standard dressing. In the first study, the mean time from surgery to wound closure was 17.1 days with standard of care treatment and 15.5 days when the wound was treated with Episalvan gel. The mean intra-individual difference in time to wound closure between the wound halves was -1.4 days. The difference was highly statistically significant ($p<0.0001$). The results in the second study were consistent with the first study. The mean time from surgery to wound closure was 16.0 days with standard dressing and 15.1 days when the wound was treated with Episalvan gel The mean intra-individual difference in time to wound closure between the wound halves was -0.8 days and again statistically significant ($p<0.0232$).

In the pivotal study performed in patients with Grade 2a partial thickness burn wounds, the primary endpoint was percentage of patients showing earlier healing of the Episalvan gel treated wound half compared with the Octenilin® Wound Gel treated half. 53% of all treated patients had faster healing with Episalvan gel. According to the mean expert evaluation, the mean time from the burn accident to wound closure was 7.6 days for Episalvan gel and 8.8 days for Octenilin® Wound Gel. According to the mean expert evaluation, the mean time from the burn accident to wound closure was 7.6 days for Episalvan gel and 8.8 days for Octenilin® Wound Gel.

Uncertainty in the knowledge about the beneficial effects

Methodological problems were encountered in evaluating efficacy in the STSG donor sites studies. Many of the photographs of the treated wound halves taken by the site staff were excluded from the PP population in order to maintain the blinded read.

Therefore, in some cases no definite time to calculate a difference in wound healing time was available if wound closure was not observed in one or both photo series for a patient. Consequently, certain assumptions had to be made to calculate the intra-individual difference in time to wound closure. If wound closure had not been observed for one of the two wound halves, the time to wound closure for the unknown half was set to the day of the last photo +1 day. The CHMP agreed that this method of evaluation is likely to underestimate the effect size of the active treatment.

Episalvan gel has not been used for more than 28 days, thus, the clinical efficacy beyond this time frame is uncertain, which is clearly stated in the SmPC.

Risks

Unfavourable effects

The most common adverse events which were considered as related to Episalvan gel concerned a total of 25 (9%) patients, comprising pain of skin (2.9%), pruritus (1.4%), and a few patients with other AEs, e.g. wound complication and post procedural complications.

The safety profile of Episalvan gel was considered manageable, with the risk minimisation measures included in the SmPC and the RMP of the product.

Due to the design of the studies was intra-individual, it was expected that it would be difficult to distinguish between application-site adverse events for a wound divided in two halves, unless the effect was very pronounced. However, the rates of application-site adverse events are overall low and did not appear to be of concern.

Uncertainty in the knowledge about the unfavourable effects

Although Episalvan gel is a local treatment and the systemic absorption is limited, systemic effects may not be completely ruled out. However, very few systemic AEs in the clinical program were reported and these were not considered related to the treatment. Furthermore, from available pharmacokinetic data it was concluded that betulin plasma levels resulting from topical treatment were not higher than natural background levels originating from nutritional sources. Although it cannot be excluded that treatment of larger wounds may result in higher systemic uptake of betulin, it seems unlikely that the plasma concentrations would reach levels with risk for systemic toxicity.

Due to the design of the studies was intra-individual, it was expected that it would be difficult to distinguish between application-site adverse events for a wound divided in two halves, unless the effect was very pronounced. However, the rates of application-site adverse events are overall low and did not appear to be of concern.

With respect to immunological adverse events, as the medicinal product contains an extract and not a single, defined active substance, there is a theoretical at least possibility that the product contains constituents that may induce hypersensitivity reactions. However, available data on this is limited and the issue will remain under review and is included in the RMP as an important identified risk.

Non-clinical and clinical data are only available up to 4 weeks use. Thus, safety data on long-term use are not available, however the proposed duration of use in the SmPC is up to 4 weeks.

Balance

Importance of favourable and unfavourable effects

A statistically significant efficacy for Episalvan gel compared to standard of care treatment was demonstrated for the primary endpoints, both in healing of split-thickness wounds and Grade 2a burn wounds. Even if the differences were in absolute terms small, they were considered of clinical significance. Wounds with difficulties to heal present with many challenges and there is an unmet medical need for products with wound healing properties.

The safety profile of Episalvan gel, due to its low absorption is limited to local reactions which are considered manageable with the routine risk minimisation measures included in the SmPC and the RMP.

Benefit-risk balance

The benefit-risk balance of Episalvan gel in the treatment of partial thickness wounds in adults is considered positive.

Discussion on the benefit-risk balance

Episalvan gel has demonstrated a statistical significant effect on shortening of time to wound healing of different wound origin. The shortened time to wound healing induced by Episalvan gel is considered clinically relevant in a condition with limited therapeutic alternatives.

Furthermore Episalvan gel has a mild safety profile with adverse events limited to local application reactions which can be managed adequately with the routine risk minimisation measures described in the product's SmPC and RMP.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Episalvan gel is not similar to Nexobrid of authorised orphan medicinal products within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Episalvan gel in the treatment of partial thickness wounds in adults is favourable and therefore recommends the granting of the marketing authorisation circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that Birch bark extract from *Betula pendula* Roth, *Betula pubescens* Ehrh as well as hybrids of both species with n-heptane as extraction solvent is qualified as a new active substance.