22 April 2022
EMA/260035/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Filsuvez

International non-proprietary name: birch bark extract

Procedure No. EMEA/H/C/005035/0000

Note

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

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List of abbreviations

AE	adverse event
ANCOVA	analysis of covariance
BDRM	blind data review meeting
BMI	Body mass index
BP Ag	bullous pemphigoid antigen
BSAP	body surface area percentage
$[Ca^{2+}]_{ex}$	extracellular calcium ion
CAS	Completer analysis set
CCC	confirmation of complete closure
CHW	Cui, Hung, Wang
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COX2	cyclooxygenase 2
CSR	clinical study report
CYP	Cytochrome P450
DBP	double-blind phase
DDEB	dominant dystrophic epidermolysis bullosa
DEB	dystrophic epidermolysis bullosa
DEJZ	dermo-epidermal junction zone
EB	epidermolysis bullosa
EBDASI	Epidermolysis Bullosa Disease Activity and Scarring Index
EBS	epidermolysis bullosa simplex
eCRF	electronic case report form
EDBP	end of the double-blind phase
EMA	European Medicines Agency
EoT	end of treatment
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FLACC	Face, Legs, Activity, Cry, Consolability
GMP	Good Manufacturing Practice
IDMC	Independent Data Monitoring Committee
IFN-γ	interferon-gamma
IL6	interleukin 6
IL8	interleukin 8
IND	Investigational New Drug
INV	involucrin
IP	interferon-gamma inducible protein
iscorEB	Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa
ISE	Integrated Summary of Efficacy
ITT	Intention-to-treat
IWRS	Interactive Web Response System
JEB	junctional epidermolysis bullosa
KS	Kindler syndrome
LALA	Locally applied, locally acting
LC-MS	liquid chromatography with mass spectrometric detection
LLOQ	Lower limit of quantification
LS	least squares
MAA	Marketing Authorization Application
MAPK	mitogen-activated protein kinase
MCID	minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MTWDC	mean time to wound dressing change
NA	not applicable
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
n.d.	not done
NDA	New Drug Application
NE	not estimable
NEBR	National Epidermolysis Bullosa Registry
OLP	open-label phase

OR	odds ratio
PK	pharmacokinetics
POSAS	Patient and Observer Scar Assessment Scale
PPS	Per protocol set
PRO	patient-reported outcome
PT	preferred term
QP	Qualified person
RANTES	regulated upon activation, normal T cell expressed and presumably secreted
RDEB	recessive dystrophic epidermolysis bullosa
RhoA	Ras homolog gene family, member A
SAE	serious adverse event
SAF	Safety analysis set
SAP	statistical analysis plan
SCC	squamous cell carcinoma
SD	standard deviation
SE	standard error
SmPC	Summary of Product Characteristics
STAT	signal transducer and activator of transcription 3
STSG	split-thickness skin graft
TBSA	total body surface area
TBWB	total body wound burden
TE	triterpene extract (birch bark extract, dry extract from birch bark, refined)
TEWL	transepidermal water loss
TNFα	tumor necrosis factor alpha
TPP	Treatment per protocol
TSQM	Treatment Satisfaction Questionnaire for Medication
UK	United Kingdom
US	United States
VAS	visual analog scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amryt Pharmaceuticals DAC submitted on 8 March 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Filsuvez, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 March 2018.

Filsuvez, was designated as an orphan medicinal product EU/3/10/845 on 23 February 2011 in the following condition: Treatment of epidermolysis bullosa.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Filsuvez as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/filsuvez.

The applicant applied for the following indication:

Treatment to achieve accelerated healing of wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients from birth onwards.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

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).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0425/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0425/2020 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the fact that the strength of the evidence generated with Filsuvez to support fulfilment of an unmet medical need in dystrophic and junctional EB was not deemed undoubtedly convincing. The efficacy was regarded as modest, no disease-modifying effect has been demonstrated, nor any effects on prevention of complications like infections, full-thickness ulceration and malignant transformation.

1.6. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
17 November 2011	EMEA/H/SA/2179/1/2011/PA/III	Dieter Deforce and Norbert Benda
23 February 2017	EMEA/H/SA/2179/1/FU/1/2016/PA/SME/III	Carin Bergquist and Karl-Heinz Huemer
20 September 2018	EMEA/H/SA/2179/1/FU/2/2018/PA/SME/II	Karl-Heinz Huemer and Carin Bergquist

The Protocol assistance pertained to the following *quality, non-clinical, and clinical* aspects:

- *Acceptability of the manufacturing process.*
- *Sufficiency of the overall nonclinical investigation package*
- *Acceptability of the study design of the 3-month local tolerance and toxicity study in minipigs*
- *Acceptability of not conducting juvenile animal studies*
- *Acceptability of not conducting an Environmental Risk Assessment*
- *Acceptability of the study design of the pivotal study BEB-13, in particular the primary and secondary endpoints, statistical plan, and the plan to conduct only one single pivotal study*
- *Sufficiency of the safety data generated*
- *Acceptability of the study design of the Healthy Volunteer Study.*

1.7. Steps taken for the assessment of the product

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

CHMP Rapporteur: Kristina Dunder CHMP Co-Rapporteur: Peter Kiely

The application was received by the EMA on	8 March 2021
The procedure started on	25 March 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 June 2021
The CHMP co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 June 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	28 June 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 July 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	09 September 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	18 October 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 October 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	04 November 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	11 November 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	10 December 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 January 2022
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	20 January 2022
The CHMP agreed on a second list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	27 January 2022
The applicant submitted the responses to the CHMP second List of Outstanding Issues on	22 February 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	09 March 2022
An AHEG was convened to address questions raised by the CHMP on The CHMP considered the views of the AHEG as presented in the	15 March 2022

minutes of this meeting	
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	17 March 2022
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	22 March 2022
The CHMP agreed on a third list of outstanding issues to be sent to the applicant on	24 March 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	06 April 2022
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	13 April 2022
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 Filsuvez on	22 April 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applied indication for Filsuvez is: *Treatment to achieve accelerated healing of wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients from birth onwards.* Thus, the indication targets two of the main sub-types of EB (see further description below).

2.1.2. Epidemiology

Epidermolysis bullosa (EB) is a rare ('orphan') heterogeneous group of genetic skin fragility disorders characterised by blistering and erosions of epithelial surfaces in response to minor trauma or friction.

Information on the epidemiology of EB is limited. Overall, data available from European countries are supported by data from the US NEBR and estimates of the prevalence of EB range from 4.4 (Romania) to 80 (United Kingdom; UK) per 1 million ([Dănescu 2015]; [Mellerio 2010]). Throughout the European Union (EU), it is estimated that EB affects less than 50 per 1 million (0.5 in 10,000 people) which is equivalent to fewer than 25,000 people in the EU.

2.1.3. Biologic features

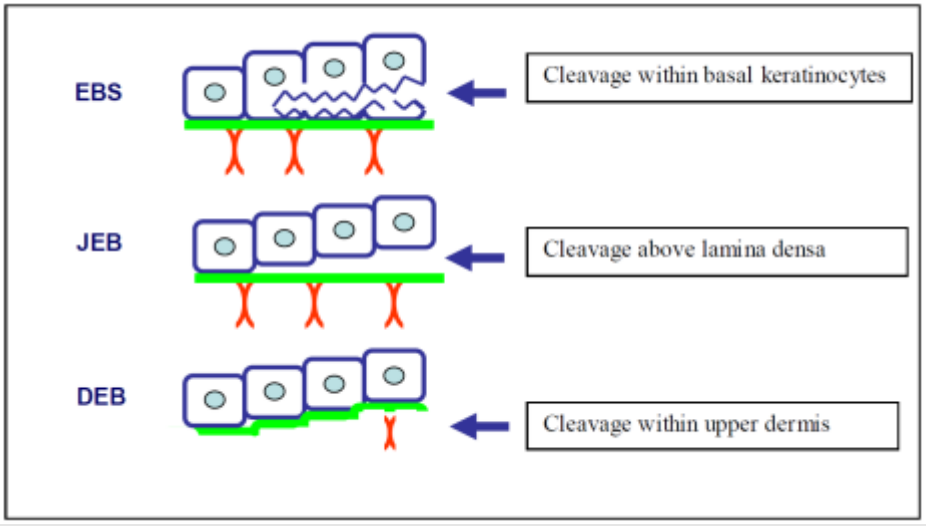
EB is caused by more than 1,000 known mutations in as many as 21 genes encoding anchoring proteins of the dermo-epidermal junction (Vahidnezhad 2019). Defects of these proteins lead to different levels of cleavage within the skin according to their location in the dermis and epidermis ([Fine 2010]).

In 2014, a revised EB consensus classification was published. It divides EB into 4 major subtypes, based on the level of skin cleavage [Fine 2014]:

1. Epidermolysis bullosa simplex (EBS, intraepidermal skin separation).
2. Junctional epidermolysis bullosa (JEB, skin separation within the lamina lucida or central basement membrane zone).
3. Dystrophic epidermolysis bullosa (DEB, sublamina densa or dermal separation). Based on the mode of inheritance, this is subdivided into dominant (DDEB) and recessive (RDEB) forms.
4. Kindler syndrome (variable level of separation in the skin within basal keratinocytes, at the level of the lamina lucida or below the lamina densa).

In 2020, an additional consensus report on the classification of EB and other skin fragility diseases was published [Has 2020]. Since the revised 2014 classification of EB, several new genes and clinical subtypes had been identified. This latest consensus report sought to reclassify disorders with skin fragility, with a focus on EB, based on new clinical and molecular data.

Figure 1: Different cleavage levels within the skin of EB patients



Abbreviations: DEB=dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; EBS=epidermolysis bullosa simplex; JEB=junctional epidermolysis bullosa

EBS is the most common subtype of EB and causes mild to moderate disease in the majority of cases. In the most frequent variant, localised EBS, blistering is usually limited to the hands and feet. There are also more severe variants of EBS, in particular generalised severe EBS [Coulombe 2009], but in general, EBS is almost always compatible with normal life span [Pillay 2008]. EBS wounds are generally episodic skin blistering in areas of the body prone to trauma or friction, smaller and more superficial than wounds in other subtypes of EB, and dynamic in nature with rapid onset and short healing cycles. As these wounds are smaller and more dynamic, subjects with EBS were not included in the pivotal Phase 3 study (BEB-13) to support the EB indication. With rare exceptions, EBS is inherited in an autosomal dominant fashion.

JEB is less frequent and has a broad spectrum of severity, from the most severe form in the JEB, generalised severe subtype which is usually fatal in the first year of life, to generalised intermediate JEB which is associated with sepsis, failure to thrive, pseudosyndactyly, and shortened life expectancy, to very mild forms of JEB often diagnosed later in life. JEB has an autosomal recessive inheritance.

DEB has 2 forms, dominant DEB (DDEB) and recessive DEB (RDEB), are defined by the mode of inheritance. Both forms cause moderate to severe skin fragility and scarring; DDEB is milder with more localised skin involvement often limited to the hands, feet, knees, and elbows, while patients with

RDEB have more extensive skin involvement especially in the generalised severe form. Hence, a high proportion of patients in EB specialist clinics have RDEB which enabled this severely affected group of patients to be enrolled into the BEB-13 study. Severely affected patients suffer from widespread blistering and painful wounds that cause multiple secondary medical complications (e.g., anaemia, malnutrition, oesophageal stenosis, susceptibility to infections) that often lead to physical impairment [Bruckner-Tuderman 2010]. In RDEB, particularly generalised severe RDEB, many patients survive only to their fourth decade as a result of aggressive metastatic squamous cell carcinoma (SCC) that arises within areas of repeated scarring [Soro 2015].

Kindler syndrome is the rarest form of EB. In this subtype, blistering occurs at various skin depths. It is characterised by generalised blistering at birth and the later development of characteristic poikilodermatous pigmentation and photosensitivity.

2.1.4. Clinical presentation, diagnosis and prognosis

See above, regarding the clinical presentation and prognosis for different EB subtypes.

2.1.5. Management

No approved therapy exists for EB in the EU. There are no medical treatments that have demonstrated efficacy in the treatment or prevention of the recognised clinical manifestations of this rare genetic disorder, which include debilitating symptoms and substantial morbidity; those with moderate to severe disease may have life-threatening manifestations and in a proportion of patients, the disease reduces life expectancy.

One of the most significant problems in EB is the lifelong presence of skin blistering and partial-thickness wounds that result in pruritus, pain, scarring, deformity, loss of function, and immobility as well as a high risk of complications such as infection. In addition, there is an increased incidence of aggressive cutaneous SCC at a younger age than in the general population. In patients with generalised severe RDEB, SCC occurs in approximately 80% of patients by their mid-40s and can occur as early as adolescence.

Since no medicinal product is approved for the treatment of EB, symptomatic and professional wound care is the mainstay of therapeutic intervention. Patients may have several wounds affecting large areas of the body surface. Wounds need to be cleaned and non-adhesive dressings applied frequently to protect the wounds and enable healing to occur. The removal of the dressings involves soaking in warm water or using damp compresses. After cleansing the wounds, the new dressings are applied. The changing of dressings may be painful and time consuming. Patients with extensive wounds may rotate the dressing changes such that not all wounds are dressed at the same time. A range of emollients, such as petrolatum, are used in association with wound dressing; however, there is a paucity of scientific data on the effectiveness of emollients. An international consensus document on "Best Practice Guidelines for Skin and Wound Care in Epidermolysis Bullosa" was published [Denyer 2017] in collaboration with the DEB Research Association, a global patient association focusing on EB.

Avoiding infection in EB wounds is difficult and they are frequently colonised with bacteria that impair healing. Topical antibiotics and antimicrobial dressings are used judiciously to prevent or minimise bacterial colonisation. Wound infections, characterised by increasing wound size, exudate, odor, pain, surrounding erythema, and edema require treatment with topical and frequently systemic antibiotics. Recurrent or chronic wound infections may become resistant to standard antibiotics and thus increasingly difficult to eradicate and can lead to sepsis. Multidrug-resistant EB wound infections are problematic. Infections impair the ability of the wound to heal and a vicious cycle that is difficult to break ensues.

Pain from partial-thickness wounds occurs as sensory nerve endings are present in the wound bed. This is especially distressing during dressing changes and is managed by the administration of

nonsteroidal anti-inflammatory analgesics or opioids. The psychological impact of the pain associated with dressing changes is substantial and includes anticipatory anxiety that can be debilitating and traumatic for patients (most of whom are children) and their parents or caregivers.

Skin pruritis is difficult to control and occurs in the majority of patients, particularly those with generalised severe RDEB ([De Palma 2019]; [Snauwaert 2014]). Intractable pruritus may result in difficulty falling asleep, disturbance of routines, change in behaviour, and loss of appetite [Jeffs 2020]. Antihistamines are widely used despite being generally ineffective in this setting. A variety of other oral medications with no scientific evidence demonstrating their effectiveness are also prescribed in an attempt to reduce the distress associated with chronic pruritus, e.g., corticosteroids, antiepileptics, tricyclic antidepressants, serotonin 5HT-3 receptor antagonists, and benzodiazepines. For the treatment of severe recalcitrant itching, agents such as thalidomide and cyclosporine are prescribed; however, there are limited data to support their use.

Patients with EB need a higher calorie intake to compensate for the increased energy expenditure required for wound healing. However, patients with severe disease, such as many with RDEB, frequently have involvement of the gastrointestinal mucosa with oropharyngeal (including dental) manifestations. Buccal blistering may progress to fusion of the tongue to the floor of the mouth. Erosions in the oesophagus, development of strictures and webbing may result in dysphagia [Fine 2008]. The oesophageal complications often require repeated endoscopic dilatation procedures or surgical intervention and may eventually lead to the need for percutaneous endoscopic gastrostomy or nasogastric tube feeding. Vitamin and mineral supplements are commonly required. These gastrointestinal conditions impact the patient's ability to achieve adequate calorie intake and may result in failure to thrive or develop, particularly in children [Shinkuma 2015], as well as reduced wound healing ability. Minerals deficiency, in particular zinc, also adversely affects wound healing as it is essential in this process [Reimer 2020].

In summary, the current treatment of EB wounds is symptomatic, including early judicious treatment of wounds to prevent or minimize infection and wound protection with non-adhesive dressings to enable wound healing. Patients with EB take care to minimise new wounds; however, this is particularly difficult for young children as minor trauma or friction results in partial-thickness wounds. The efficacy of topical agents aimed at improving wound healing may have direct implications on outcomes and quality of life for patients with EB. There is currently no topical medication approved in the EU to accelerate wound healing. With regular application of such a product, the total wound burden and associated symptoms and complications of unhealed wounds such as infections, itching, and pain would be expected to decrease. Most experts agree that "any acceleration" and "each day gained" in time to wound healing would be important and clinically significant for EB patients with partial-thickness wounds.

2.2. About the product

Filsuvez (also referred to as Oleogel-S10 in this report) is a non-aqueous gel containing (per gram) 100 mg of extract (as dry extract, refined) from *Betula pendula* Roth, *Betula pubescens* Ehrh. as well as hybrids of both species, cortex (equivalent to 0.5-1.0 g birch bark), including 84-95 mg triterpenes calculated as the sum of betulin, betulinic acid, erythrodiol, lupeol and oleanolic acid. Extraction solvent: n-Heptane.

Oleogel-S10 is formulated with sunflower oil (90%) and has thixotropic properties that facilitate application to the wound. Thus, Oleogel-S10 behaves as a viscous gel under normal conditions but becomes less viscous when applied.

The indication initially applied for was: Treatment to achieve accelerated healing of wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients from birth onwards. See section 2.6.6. for final indication granted by CHMP.

The proposed posology is as follows: The gel should be applied to the wound surface at a thickness of approximately 1 mm and covered by a sterile non-adhesive wound dressing or, applied to the dressing so that the gel is in direct contact with the wound. The gel should not be applied sparingly. It should not be rubbed in. The gel should be reapplied at each wound dressing change, until the wound is healed.

The product in the same concentration and formulation is already approved in the EU (date of authorisation 14 January 2016) as Episalvan gel, approved for the treatment of partial thickness wounds in adults. The active substance has shown to accelerate re-epithelialization in an *in vitro* wound scratch assay using human primary keratinocytes at the dosage of 1 µg/ml, and in a porcine *ex vivo* wound healing model at the dosage of 10 µg/ml.

The precise mechanism of action of the active substance in wound healing in humans is not known.

2.3. Type of Application and aspects on development

The primary clinical data in support of the EB indication for Filsuvez is a single phase 3 study (BEB-13), with some support also from a small phase 2 study in EB patients; BEB-10. In addition, the studies included in the submission for Episalvan in the indication "Treatment of split-thickness skin graft (STSG) donor site wounds" were included in the dossier as supportive data. Furthermore, Phase 2 healthy subject studies with the control gel (AHV-18-A and AHV-18-B) are referred to in support of the EB application.

There is no CHMP guidance available on the development of medicinal products in EB. The Applicant received Scientific Advice from the CHMP for the EB indication, see section 1.6. Protocol assistance.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as gel containing 100 mg of extract per 1 g of gel (as dry extract, refined) from *Betula pendula* Roth, *Betula pubescens* Ehrh. as well as hybrids of both species, cortex (equivalent to 0.5-1.0 g birch bark), including 84-95 mg triterpenes calculated as the sum of betulin, betulinic acid, erythrodiol, lupeol and oleanolic acid. The extraction solvent is n-heptane.

The only other ingredient is refined sunflower oil.

The product is available in white collapsible aluminium tube, interior lacquered with epoxy phenolic coating, and with a sealing compound in the fold. The tube is closed with a tamper evident aluminium membrane and fitted with a white polypropylene screw cap, as described in section 6.5 of the SmPC. It is available in two sizes, 9.4 g and 23.4 g tubes. The product is for single use only and should be used immediately after opening and then discarded.

2.4.2. Active Substance

2.4.2.1. General information

The dossier contains appropriate information on both the herbal substance (birch bark) as well as the herbal preparation/active substance (dry extract from birch bark).

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. Appropriate declarations were provided confirming the herbal substance is sourced according to the principles of the guideline on Good Agricultural and Collection Practice (GACP) for starting materials of herbal origin. The main constituents in the bark of birch are pentacyclic triterpenes. The outer bark of birch contains a large amount of betulin and related triterpenes lupeol, betulinic acid, erythrodiol, and oleanolic acid. One property of the outer bark is the resistance against microorganisms, said to be because of the suberin (cork substance) and the hydrophobic and antimicrobial effect of betulin.

The herbal preparation is the dry extract from birch bark; it appears as a white to almost white dry powder. The herbal preparation, which is the active substance of the finished product, is also referred to in the dossier as Triterpene Extract (TE). The extract is refined and is declared as a '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 five triterpene markers: betulin, lupeol, betulinic acid, erythrodiol and oleanolic acid. The DER value is 5-10:1. The extraction solvent is n-heptane.

The main constituents of the herbal preparation are pentacyclic triterpenes from the lupane (betulin, lupeol, betulinic acid) and oleanane (erythrodiol, oleanolic acid) groups. These are illustrated in Figure 2.

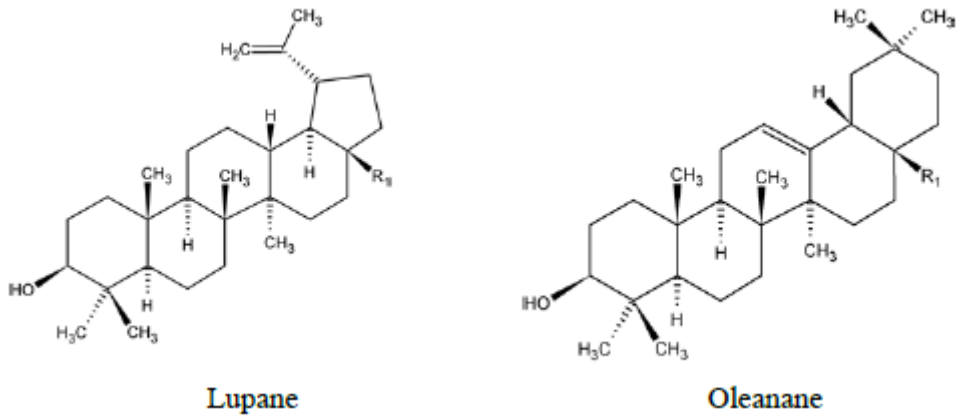


Figure 2: active substance structure

2.4.2.2. Manufacture, characterisation and process controls

Herbal substance (birch bark)

The birch species used for production are *Betula pendula* Roth (silver birch) and *Betula pubescens* Ehrh. (white birch) as well as hybrids of both species. Trees are collected in accordance with GACP requirements. The bark is stripped, dried and cut. The last cutting/sieving is under GMP standard (QP declarations have been provided).

Herbal preparation (dry extract from birch bark)

The dry extract is manufactured using extraction with n-heptane.

QP declarations have been provided confirming that the manufacturing complies with the principles and guidelines of good manufacturing practice.

The manufacturing process is validated and shown to be robust and result in batch-to-batch consistency.

2.4.2.3. Specification

Specifications and controls of the herbal substance are adequately drawn up and in line with Ph. Eur. and EMA guideline requirements. Control of impurities include heavy metals/elemental impurities, mycotoxins, pesticides, radioactivity and microbial load.

The active substance specification includes tests for: characters (visual), identification (GC-FID fingerprint, HPLC-DAD fingerprint), degradation products (GC-FID fingerprint, HPLC-DAD fingerprint), residual solvents (GC- FID), elemental impurities (ICP-OES), microbial limits (Ph. Eur.), assay (GC-FID), consistency of a test oleogel (texture analyser), segregation of oil of a test oleogel (centrifugation), and specific surface area (Ph. Eur. volumetric method).

Specific impurities controlled are elemental impurities as well as residues of the extraction solvent n-heptane.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay has been presented.

Batch data has been provided for a large number of batches. Data comply with the specification and batch-to-batch consistency has been investigated and presented.

2.4.2.4. Stability

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 48 months with no special storage precautions in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The medicinal product is a herbal medicinal product containing the herbal preparation dry extract from birch bark (5-10:1), extraction by n-heptane, as the active substance.

The finished product is presented as a semi-solid preparation called an oleogel, a lipophilic colourless to slightly yellowish opalescent gel for cutaneous application.

Triterpene Extract (TE) is not soluble in water but forms an oleogel on mixing with oil. A 10% w/w concentration in sunflower oil was determined as optimal for use as a topical gel. There are no other excipients.

Filsuvez, also referred to as Oleogel-S10, is a gel intended for topical use in the treatment of wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients from 6 months of age. Therefore, it is a sterile gel, for single use only. Once opened, the product should be used immediately and discarded after use. It is described as a viscous, thixotropic, water-free preparation with a consistency similar to petroleum jelly that will not soften at body temperature. The thixotropic properties facilitate the product to be expressed from the tube and applied to the wound where it will not move.

Pivotal clinical trials in epidermolysis bullosa, BEB-13, were conducted using Oleogel-S10 manufactured according to the process described in the dossier.

Investigations on the microbiological attributes demonstrate that the finished product shows microbiologically hostile conditions.

The finished product is filled and stored in white 10 ml or 25 ml collapsible aluminium tubes, closed by an aluminium membrane and a white PP screw cap. The container closure system is a standard packaging material for this type of dosage form. The materials in contact with the finished product are in compliance with the food legislation in accordance with EMA CPMP/QWP/4359/03 Guideline on Plastic Immediate Packaging Materials. The packaging is considered suitable for the proposed application.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process of the finished product is relatively simple where the active substance, *i.e.* the dry extract from birch bark, is mixed and homogenised with sunflower oil.

In process controls and critical steps are clearly described and justified. Holding times were validated and are acceptable. The applicant demonstrates good process understanding.

The sterilisation process is validated for both tube sizes and is considered to be acceptable.

Process validation data were provided for three consecutive full size batches of the 25 ml tube, and the data indicated that the process is capable of reproducibly producing a product of consistent quality. The bulk manufacturing process for the 10 ml tube is considered the same as that validated for the 25 ml tube. Process validation for the smaller tube size has also been submitted and is also considered to be acceptable.

2.4.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: description (visual), identification (GC-FID, HPLC-DAD), degradation products (GC-FID, HPLC-DAD), assay (GC-FID), assays of amount of triterpene extract (GC-FID), sterility (Ph. Eur.), container closure system integrity (dye ingress), acid value (titration), peroxide value (titration), fineness of grind (EN ISO1524:2013), viscosity (Ph. Eur.), segregation of oil (centrifugation), and consistency (texture analyser).

The proposed specification parameters and limits are acceptable. The potential presence of elemental impurities in the finished product has been assessed in line with the ICH Q3D Guideline for Elemental Impurities. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed as it was requested by CHMP as a Major Objection, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report-Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The applicant has during the procedure updated and subsequently submitted an acceptable risk evaluation regarding potential nitrosamine impurities in the finished product, thereby resolving the Major Objection. Based on the information provided, it is

accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay has been presented.

Batch analysis results were provided for numerous batches of different scale confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from commercial scale batches of 23.4 g in 25 ml tubes presentation finished product stored for up to 36 months under long term conditions (25°C / 60% RH and for three batches 30°C / 75% RH) and for three batches up to six months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. Additionally, a stability study has been initiated with one pilot scale batch of the 9.4 g in 10-ml tubes presentation at both long-term (25°C /60% RH, 48 months) and accelerated (40°C/75% RH, 6 months) conditions. Data is available for up to 12 months under long term conditions (25°C / 60% RH) and 6 months under accelerated conditions (40°C / 75% RH). The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The analytical procedures used are stability indicating. No out of specification results were observed and the results are comparable between batches.

The possible impact of the different tube lengths with regard to stability was evaluated. Importantly, in both pack sizes the tube is completely filled with the gel with only a very small volume of air (unavoidable for technical reasons) trapped inside at the fold of the tube. The different tube length alters the surface-to-volume ratio of the primary packaging material and the gel. Compared to the 23.4 g pack size, the surface-to-volume ratio is increased by 36% for the 9.4 g pack size. With the only difference between the 23.4-g and 9.4-g pack size being the length of the tube, the stability demonstrated for the 23.4-g presentation is considered to be representative also for the smaller (shorter) 9.4-g presentation. Accordingly, the same shelf-life claim is acceptable for both.

Considering the demonstrated stability of the 23.4 g pack size with no evidence of degradation, the fact that the aluminum tube is virtually impenetrable and the small difference in surface-to-volume ratio minimizing a potential (expected negligible) impact of small amounts of trapped air in the sealed tube, it is justified to extrapolate the stability results and the shelf-life claim of the original 23.4 g pack size to the 9.4 g pack size.

Based on available stability data, the proposed shelf-life of 4 years when stored below 30°C as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance and finished product are the same as for the authorised product Episalvan (formerly Oleogel-S10). Since the assessment of Episalvan, the dossier has been updated with additional development work, validation as well as batch and stability data.

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. The Major Objection raised on risk assessment on the presence of nitrosamine impurities was adequately resolved by providing an updated risk assessment during the procedure.

2.4.5. 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.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

The initial non-clinical package performed for Episalvan for treatment of partial thickness wounds allowed for a treatment duration of up to 4 weeks. Since then, the non-clinical package has been expanded to cover chronic wound treatment of EB patients.

In wound healing models, TE showed inflammation-modulating effects, stimulation of keratinocyte migration and differentiation, and accelerated re-epithelialisation.

No *in vivo* EB animal model is available that can recapitulate the fragility of the skin and the low solubility of the active constituents has caused limitations in regarding which administration routes can be used for *in vivo* studies. However, Oleogel-S10, gel, TE and its main constituents were investigated using a set of *in vitro*, *ex vivo,* and *in vivo* test systems evaluated by the applicant. In addition, supporting data was derived from published literature.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The wound healing properties of Oleogel-S10 and the triterpene dry extract from birch bark (TE) have been studied in a variety of in vitro and ex vivo studies. The applicant has presented results on accelerated re-epithelialisation in the in vitro wound scratch test using human primary keratinocytes. Further, the porcine ex vivo wound healing model, where punch biopsies are taken from the plicae of pig ears, has been shown to have similarity to the human wound healing process. In the porcine ex

vivo wound healing model, TE exhibited acceleration of dermis re-epithelialisation at the dosage of 10 µg/ml. Nevertheless, no proof of concept studies have been provided and the applicant has asserted that the previous studies using a porcine wound healing model are applicable to the EB population. However, in patients with dystrophic and junctional EB the integrity of the skin barrier is affected by mutations in genes responsible for the expression of structural proteins involved in influencing the integrity and adhesion of the skin. The applicant was therefore asked to discuss any potential consequences of these mutations to undermine the pharmacological action of Oleogel-S10. In the response, the applicant suggested that the components of the birch bark extract act on the general mechanism of wound healing and is not limited to a single pathway. Furthermore, the birch bark extract induces re-epithelialisation and keratinocyte migration which are not directly affected by these mutations. However, based on evidence in the literature, COL7A1 expression, whose gene is frequently mutated in DEB, was required for re-epithelialisation through organisation of laminin-332 at the dermal-epidermal junction and affected keratinocyte migration (Nyström et al., 2013). Therefore, it remains unclear how mutations in COL7A1, and or other genes mutated in EB, may negatively impact the pharmacological action of the birch bark extract. Furthermore, the applicant suggested that Filsuvez accelerates the re-epithelialisation of wounds in part by enhancement of keratinocyte proliferation. However, the birch bark extract or its components did not induce proliferation in the submitted in vitro and ex vivo pharmacology studies which seems to contradict this assertion.

It was suggested that no suitable pre-clinical EB model exists in which Filsuvez could be tested. This issue was not further pursued from a non-clinical perspective as ultimately, it is accepted that the clinical efficacy data from such patients which will determine whether Filsuvez is effective.

In addition, the applicant has performed studies on cellular mechanisms in human primary keratinocytes. However, human re-epithelialisation includes a combination of multiple factors and various *in vitro* models typically address a single factor. The results from *in vitro* studies on the active substance of Oleogel-S10 showed influence on different mediators of the re-epithelialisation process but cannot explain the mechanism of action in patients. Hence, the clinical relevance of these *in vitro* findings is not known.

2.5.2.2. Secondary pharmacodynamic studies

No studies addressing secondary pharmacodynamics have been performed. This is considered acceptable given the low systemic exposure from dermal application of Oleogel-S10 to EB patients.

2.5.2.3. Safety pharmacology programme

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

A hERG study was performed where betulin-induced inhibition of the hERG tail current amplitude was recorded in HEK293 cells. While a significant inhibition of the tail current was noted at 200 nM (maximum feasible concentration), the inhibition was less than 30% compared to control. No EC50-value could be estimated. However, there were concerns with this study which question its utility in drawing conclusions as to the effects of betulin on the hERG channel. These concerns included the lack of an expiry date for the test article, inhibition of the hERG channel at middle dose concentration of 12.61 nM which was very similar to that seen at the higher concentration of 190 nM (22 versus 23% inhibition) and significant differences in the nominal concentrations of betulin compared to the achieved values measured. In the response, the applicant suggested that a 1-year warranty from the date of receipt was provided by the supplier of the betulin and the assay was conducted within this

time period. However, no actual data or certification was however provided to support this claim. It was also noted that the expiry data of the test article was excluded from the GLP compliance statement for the study. Regarding the inhibition of the hERG-channel at the middle dose, the applicant explained that the reason for the non-linear inhibition of hERG activity is unknown but may be related to non-specific binding to either the cell surface or to plastics. The latter has been seen to particularly occur at low concentrations and likely explain the difference in nominal versus achieved concentration values. An IC50 could not be determined as higher concentrations than 200nM were not technically feasible.

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.

No exposure data were obtained in the safety pharmacology studies and no toxicokinetic data were available from intraduodenal administration in dogs or intraperitoneal administration in mice, therefore the relevance for the clinical situation from these studies is unclear. However, based on low systemic exposure following topical application in the clinical setting, these shortcomings are not of importance. Overall, it is considered that the risk for CV-related adverse effects following clinical use of Filsuvez is very low.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been performed. This is considered acceptable given the low systemic exposure from topical application of Oleogel-S10 to EB patients.

2.5.3. Pharmacokinetics

A number of non-clinical studies have been performed by the applicant to characterise the pharmacokinetics (PK) of Filsuvez. The studies involving human tissues and cells have mainly been assessed in the clinical PK section.

Methods of analysis

The methods used in the programme have been appropriately described, and the bioanalytical methods are considered adequate based on the provided validation reports.

Absorption

No dedicated studies to characterize the PK profiles of betulin in plasma have been performed. However, the exposure to betulin (mouse, minipig) and betulinic acid (minipig only) was evaluated in the dermal repeated-dose toxicity studies as detailed in the toxicokinetics section. Dermal exposure to Oleogel-S10 resulted in no to very low exposures to betulin and betulinic acid in the 4-week study in minipig. However, in the 9-month study, exposures up to 184 and 58 ng/ml for betulin and betulinic acid respectively were noted. Further, a possible slight accumulation of betulin with time was observed for male and female animals treated once daily with 50 mL Oleogel-S10/animal by dermal application.

Distribution

A protein binding study was performed where the *in vitro* protein binding of betulin was determined in human, rat, and minipig plasma. Collectively the study indicates that unbound fraction of betulin in plasma is below 0.1% and the fraction bound (fb,p) is > 99.9% in all species tested.

Metabolism

In vitro metabolism of betulin has been evaluated in mouse, rat, minipig and human. Four human main metabolites were identified, three of which were covered in at least one non-clinical species. The human metabolite M4 (19% abundance relative to parent) was not covered in any of the non-clinical species. However, considering that the metabolite is a phase 2 metabolite (sulfation metabolite of betulin) it is not considered likely that it is of toxicological concern given the limited toxicity of the parent. Accordingly, no further metabolite studies are considered needed.

2.5.4. Toxicology

Testing strategy

The toxicity profile of TE has been examined in male and female mice, rats, rabbits, dogs and minipigs. Animals were exposed to the test-item dermally (the intended route of administration in patients), but also via the oral gavage, intraperitoneal (i.p.) or subcutaneous (s.c.) route to observe different exposure levels following different routes of administration.

Acute dose toxicity studies with s.c. and i.p. application were performed in mice and rats. Non-pivotal repeat dose toxicity studies with TE or Oleogel-S10, gel were performed in mice (14-day dermal), rats (14-day i.p.), rabbits (7-day oral) and dogs (14-day i.p.). No Segment II studies in rabbits were performed because of lack of systemic exposure following oral administration in this species.

Pivotal studies include repeated-dose toxicity studies in mice (13-week dermal), rats (4-week oral and 6-month oral), dogs (4-week s.c.) and minipigs (4-week and 9-month dermal; intact and wounded skin). The 4-week dermal study in minipigs applied an occluded setting, where the administration site is covered by an occlusive dressing after treatment. In contrast, the 9 months dermal study on minipigs left the treatment sites open/non-occluded.

The genotoxicity profile of TE was evaluated in an Ames test, and an *in vitro* clastogenic activity study. No carcinogenicity studies have been performed with TE or Oleogel-S10, gel.

Reproductive and developmental toxicity studies with TE were performed following oral administration in rats and included evaluation of male and female fertility, embryo-fetal development and pre- and post-natal development. In addition, a toxicity study was performed in the juvenile rat with administration through oral gavage.

The sensitisation potential of TE was assessed in a standard assay in guinea pigs. The phototoxic potential of TE was evaluated in an *in vitro* 3T3-NRU assay and the photoallergic potential was assessed in an *in vivo* study in guinea pigs, respectively. The risk after inadvertent exposure of Oleogel-S10, gel to the eye was evaluated in a bovine corneal opacity assay.

The toxicity studies were performed with different formulations of TE. The pivotal dermal toxicity studies were performed with the final formulation of Oleogel-S10, gel (Filsuvez).

The applicant has ensured that all studies were conducted in compliance with GLP and in accordance with current European and ICH guidance.

2.5.4.1. Single dose toxicity

TE was administered to mice and rats as single i.p. or s.c. injections at doses up to 2000 mg/kg. The LD_{50} values for the male and female animals at 24 hours and 14 days after i.p. administration could not be calculated as no mortality was observed (>2000 mg/kg; highest tested dose). Published data were also provided to support low acute toxicity of the constituents of TE (Betulinic acid, Oleanolic acid and Lupeol).

Both mice and rats showed slightly reduced motility, ataxia, dyspnoea and reduced muscle tone after i.p injections of 500 mg/kg or more. In addition, white deposits/whitish layers on the

diaphragm/abdominal organs, adhesions of kidney, spleen, stomach, liver, intestines or all abdominal organs was obvious upon necropsy. The applicant did not mention these findings but claimed that TE was well tolerated by both species when administered as single i.p. or s.c. injections at doses up to 2000 mg/kg. It is assumed that the reduced motility, ataxia, dyspnoea and reduced muscle tone are a secondary effect of the deposits caused by the i.p. injections of the test item and its vehicle. In the single dose experiments, no control groups were included. It is hence not possible to deduce whether the effects are caused by the test item or the vehicle. Due to the solubility issues of the TE, the Applicant has explored several different animal models for the repeat dose studies and it appeared that the i.p. route is not suitable for higher doses of TE in the vehicles tested.

Based on the results from the dose repeat studies described below, further tests regarding single dose toxicity are not considered justified.

2.5.4.2. Repeat dose toxicity

The repeat dose toxicity studies submitted for the Episalvan MAA have been supplemented with a number of new studies. Due to the solubility issues of the TE, the Applicant has explored several different animal models and routes of administration, in order to obtain a satisfactory systemic distribution, as measured by plasma levels of betulin.

After s.c., i.p., administration, a small systemic distribution was observed, but as the applicant stated it; these repeat dose toxicity studies did not reveal any systemic toxicity of TE except for local, irritant and inflammatory effects related to the application of a substance nearly insoluble in aqueous systems.

Despite the shortcomings of several of the repeat dose tests, through solubility issues etc., a small but obvious systemic distribution was observed in all species, regardless of the route of administration.

After administration through oral gavage, a higher systemic exposure, with a dose related increase in plasma levels of betulin was seen. This administration route was also used in the tests on reproductive and developmental toxicity. After oral gavage, slight effects were observed regarding body weight and food intake, and similar to other administration routes, inflammatory effects were seen in some animals. It is agreed that the effects seen are related to solubility issues and the vehicles used in the respective studies.

As the product is intended for dermal use and a low systemic absorption was observed in humans after dermal administration, it was not considered justified to perform additional studies regarding the effects of systemic exposure. It should also be emphasised that a background exposure to betulin from food sources etc. is anticipated in patients. In the clinical assessments, a betulin background plasma level of up to 54.5 ng/ml was observed in untreated patients.

Dermal application studies have been performed in both mice and minipigs. In mice, the Oleogel-S10 gel was applied once daily for 13 weeks without occlusion. Whilst treatment was associated with a 16% increase in mean terminal body weight and a 58% increase in mean body weight gain in females compared with the control mean, it was noted that this treatment group was heavier at start of treatment and food consumption was higher. No other systemic effects were noted and the gel was well tolerated at the application site with no local tolerance issues. Dermal administration of the product to minipigs, produces a low but robust systemic distribution. The highest measured C_{max} was 339 ng/ml in male mice after 13 weeks treatment and 184 ng/ml in minipigs treated for 39 weeks. A slight accumulation of betulin with time was observed for both male and female minipigs after 4 weeks as well as 39 weeks of treatment. No signs of accumulation were however observed in mice after 13 weeks of dermal administration.

The frequency of administration in the dermal studies is either once daily (13 Week mouse study and 9 months, minipigs) or three times weekly (4 weeks sub-chronic minipig study). This should be compared to the suggested posology and method of administration in the SmPC.

As no comparison or discussion was included regarding frequency of administration or dose applied in the repeat dose studies, compared to what is suggested in the SmPC, the Applicant was requested to further evaluate this. In the day 120 response, the Applicant has provided sufficient clarifications. It was agreed that the frequency of administration and systemic exposures achieved in the non-clinical studies provide adequate justification for the proposed posology.

After dermal administration of either Oleogel-S10, gel or its vehicle, several reactions were observed at the site of administration in minipigs (but not in mice):

- Four weeks treatment of abraded or intact skin with Oleogel-S10, gel caused inflammatory effects, particularly lympho-histiocytic inflammatory cell infiltration and epithelial hyperplasia, to the application site in both abraded and intact skin.
- Nine months treatment of intact skin with either vehicle and Oleogel-S10, gel, caused epidermal hyperplasia, orthokeratotic hyperkeratosis, dermal lymphocytic and/or neutrophilic infiltration, and pustules in the stratum corneum.

Vehicle treated controls were included only in the 39-week study, while the 4 weeks study applied occlusive wound dressing without further treatment as controls. The combination of vehicle and occlusive dressing has not been tested.

In the primary assessment of the application, duration of treatment, state of the treated skin, characteristics of the triterpenes, repeated covering of wounds with an oily material, and the use of occlusive dressings, were all pointed out as factors of potential importance for the local inflammatory reactions seen in minipigs.

In order to evaluate the impact of each factor to the overall responses seen, the applicant was asked to compare the findings within the respective treatment groups of the different studies. The study designs however were too different to enable direct comparison between the treatment groups, and the results were inconclusive between the two studies.

The comparisons indicate that the presence of the insoluble triterpenes in an open (or partially healed) wound, as well as the repeated administration of the oily product may contribute to the inflammatory reactions seen in these two dermal repeat use studies.

The applicant additionally emphasised that the use of occlusive dressings is standard of care in EB, and observations from the clinical experience did not raise any safety concerns referring to the use of occlusive dressings and their effect on the inflammatory reactions to the product.

The applicant emphasised that activation of the immune system with infiltration of immune cells and production of inflammatory substances such as interleukins and cytokines are natural parts of the healing process.

It was indeed noted in the primary assessment that the reactions seen in healthy animals in the repeat dose studies, were very similar to the desired effects, tested and discussed within the sections on pharmacology. The applicant was hence requested to discuss the similarities and differences between the desired effects in wound healing (*i.e.,* inflammation-modulating effects, stimulation of keratinocyte migration and differentiation, and accelerated re-epithelialisation) as compared to the same effects potentially causing adverse events such as the commonly reported complications in wound healing.

The Applicant emphasised that, as no dedicated endpoints for evaluation of the wound healing process in animals with wounded skin have been included, no conclusion in terms of wound healing can be

drawn from the obtained data. However, based on a macroscopic analysis as well as histopathology results, study 26742 did not point to any complications associated with wound healing (i.e., impairment, significant inhibition of wound healing, or re-opening of wounds) following treatment with Filsuvez.

As regards the adverse events classified as 'wound complication' in the clinical studies, no histological assessments are performed. It is acknowledged that a generalised 'wound complication' cannot be differentiated from local reactions to the product, or from the natural course of the disease, without detailed information from histological examinations of the wound tissue.

It should however be emphasised that the inflammatory reactions were also observed in the dermal repeat use studies on healthy animals with intact skin, which cannot be attributed solely to the natural wound healing process. The concern that the inflammatory reactions would potentially induce local tumorigenesis remains a cause for concern. It is well known that a chronic immune response may lead to tumorigenesis.

2.5.4.3. Genotoxicity

The genotoxic potential of TE was studied in *in vitro* mutagenicity assays (Ames test and chromosome aberrations test in human lymphocytes) and an *in vivo* micronucleus test in mice.

Neither of the *in vitro* tests showed any mutagenic or genotoxic potential, nor did the *in vivo* micronucleus test. The relevance of the *in vivo* test was however questioned as it was performed through i.p. administration, and betulin plasma levels were not determined during the test.

Given the results of the repeat dose toxicity studies, i.p. is considered to be an inappropriate administration route for observation of systemic effects of TE. The oral gavage, for example produced a higher systemic absorption. A satisfactory systemic exposure was therefore not obtained in the *in vivo* chromosomal aberrations test.

The non-clinical package on genotoxicity is hence considered incomplete. As the product is intended for local use with low systemic absorption in humans, it is not considered justified to perform additional *in vivo*, systemic studies on genotoxicity. The issue is not further pursued.

2.5.4.4. Carcinogenicity

The applicant requested a waiver for systemic carcinogenicity studies and proposed a dermal carcinogenicity study to be performed post-approval. As previously stated, the direct effect of Oleogel-S10 on cell differentiation and/or proliferation, *i.e.,* an underlying potential local carcinogenic action, was considered a risk. It was however acknowledged, that additional systemic tests would not be relevant for this application. Bearing in mind that the product is intended for dermal use with low systemic absorption in humans, it was considered justified to exclude further systemic testing of the genotoxicity or the potential carcinogenicity.

Within the scientific advice (SA) requested in 2018 (EMEA/H/SA/2179/1/FU/2/2018/PA/SME/II), the CHMP advised the applicant to use *in vitro* approaches in diseased cells aimed specifically at EB. Such studies have not been submitted within the application or reflected upon by the Applicant. More generalised wound healing models have been used.

Within the same SA, the applicant was advised to include proliferation biomarkers (e.g. Ki67) in a 3 or 6 months study to confirm the absence of a potential risk. Also, histopathological findings during the recovery period (e.g. increased proliferation) were considered of importance.

In addition to the information in this section, several aspects from the dermal repeat dose studies were considered. The 4- and 39-weeks study on minipigs that receive dermal treatment with Oleogel-S10 or its vehicle, sunflower oil, are hence considered pivotal.

The applicant repeatedly stated that no preneoplastic or neoplastic findings were observed in the dermal repeat dose studies. There were however a number of findings from the dermal repeat dose studies, i.e., epidermal hyperplasia, etc. that needed further elucidation. The applicant clarified that the treatment sites were assessed by experienced dermato-pathologists and were subsequently peer reviewed. In the dermal repeat dose studies, no benign or malignant neoplasms were observed at the sites of application of Filsuvez. Epidermal hyperplasia was noted at the treatment sites following the administration of Filsuvez for 13 or 39 weeks. This finding was characterised by an increased number of cells in the lower epidermis, however there was no evidence of any unusual features such as cellular atypia and the epidermis showed normal cellular stratification. The applicant was of the view that this appearance was not consistent with pre-neoplasia and was typically observed as part of a normal regenerative process. Significant regression of the hyperplasia was observed by the end of the 4-week recovery period.

The results of *in vitro* and *ex vivo* pharmacology studies indicated that TE or its components did not induce proliferation. In *in vivo* studies in actinic keratosis patients with TE, a decrease / normalisation of Ki67 expression was seen. An increase in Ki67-positive cells was observed in the intact skin of minipigs, treated with Oleogel-S10, gel for 39 weeks, while a reduction in Ki67-positive cells was seen after 4 weeks treatment (abraded skin, not seen in intact skin).

In the analysis of Ki67-stained skin samples in the 39 weeks study, an increased epidermal thickness was also observed at the administration sites in both sexes compared to untreated controls. An increase in Ki67 positive cells as well as epidermal thickness, albeit not statistically significant, was observed also for vehicle treated animals. The applicant stated that the observed (small) increase in epidermal cell proliferation and epidermal thickness was considered in part to be associated with normal skin regeneration and in part to be due to the physical effects of the long-term application of test material to normal skin rather than the primary pharmacological effects of birch bark extract.

There is a general lack of understanding of the pharmacological target of the components of the triterpene extract. As indicated in the applicant's proof of concept studies, a key mechanism of action of the Oleogel-S10 may be the upregulation of IL-6 and subsequent activation of Stat3 signalling. As there was evidence of increased IL-6 signalling in EB, this action added to the concerns regarding the potential risk for local site carcinogenicity. IL-6 has been demonstrated to be a key player in the growth of epithelial tumours including head and neck SCC and oesophageal SCC (Choudhary et al., 2016; Wu et al., 2017; Qiao et al., 2018). It has been hypothesised that hyper-activation of the IL-6 signalling cascade could explain the increased risk of RDEB patients to develop SCC (Condorelli et al., 2019). The applicant was therefore requested to provide a robust discussion on the specific risk for local site carcinogenicity with the topical use of Filsuvez, taking into account the proposed mechanism of action, the underlying risk in the EB patient population, and the histopathological findings from the 39-week study in minipigs.

The applicant argued that the induction of IL-6 by the TE was transient in nature primarily based on observations in the porcine WHM and primary keratinocytes as published in Ebeling *et al*, 2014. However, since the studies performed by Ebeling *et al.* used a single administration of the TE, their relevance to chronic use is limited. Therefore, there is no information on the potential levels of IL-6 induction and STAT3 activation after repeated administration with the TE.

The absence of a mutagenic/genotoxic risk associated with the TE is acknowledged and there is no concern for carcinogenic potential via a genotoxic mechanism. The histopathology results from the

chronic repeat dose toxicity studies in minipigs provide some assurance, however, these were in the context of healthy animals who did not have an underlying predisposition to developing skin malignancies.

A potential theoretical risk of carcinogenicity remained in the EB patient population based on the reputed pharmacology of the TE. Based on the presented data however, the risk that Filsuvez would cause malignancies directly or through chronic inflammations, was considered small.

A number of precautions and follow up measures were enforced and/or are planned, such as a warning in section 4.4 of the SmPC, a follow-up Questionnaire for Skin Malignancies and a registry-based study as routine and additional pharmacovigilance activities, respectively, to monitor the risk of SCC (including other skin malignancies), listing of SCC and other malignancies as an important potential risk in the RMP. Therefore, the issue was not pursued further from a non-clinical perspective (see sections 2.6 and 2.7 of this report).

The applicant proposed to perform a dermal carcinogenicity study in the mouse post-authorisation. ICH S1A does allow for carcinogenicity studies to be performed post-approval for life threatening or severely debilitating diseases. However, it needs to be considered that although the unmet medical need in these patients is appreciated, the therapy is symptom modifying rather than disease modifying. Cases of SCC have already been identified in clinical trials. It is arguable that a negative dermal carcinogenicity study, performed in healthy animals with no underlying genetic mutation that may predispose them to developing SCC, may fully provide assurance as to no increased risk for carcinogenesis in the proposed patient population.

In addition, the mouse was not considered a suitable species for the intended study, since the local reactions seen after dermal administration to minipigs were absent in mice, when treated dermally for 13 weeks.

The absence of a suitable model resembling the EB patient population for carcinogenicity testing is acknowledged and the fact that rodents are historically used as the species for testing. However, the limitations of the study for the intended patient population remain. The theoretical risk of repeated IL-6 induction and STAT3 signalling activation, which may be exacerbated in this patient population, cannot be excluded by evidence provided by the applicant. In addition, there are significant differences in the skin of mice compared to humans and potential for differences in systemic exposure.

Taken together the relevance of negative findings in a 2-year carcinogenicity study in mice was thus questioned. Based on the above, and in line with the principles of "three Rs", the applicant's proposal to submit a 2-year carcinogenicity study in mice as a post-approval commitment was not supported by the CHMP.

2.5.4.5. Reproductive and developmental toxicity

In a fertility and early embryonic development study performed in rats at doses up to 100 mg/kg/day via oral gavage no effects were seen on fertility and mating indices in either males or females.

Similarly, in the EFD study in rats the test article was well tolerated with no evidence of maternal toxicity at doses up to 100 mg/kg. No treatment-related effects were seen on the mean number of corpora lutea, pre- and post-implantation loss, resorptions (early and late resorptions), or dead foetuses. However, a statistically significant reduction in the mean number of implantations was seen across all test article groups. This correlated with a similar decrease in the mean number of live foetuses and litter weight. As dosing did not commence until after implantation, the statistically significant reduction in the mean number of implantations cannot be attributed to Filsuvez.

External malformations were seen in each of the test-article treated groups, however, none were seen in the vehicle treated group. The applicant has suggested that these were not test-item related and has justified the statement with historical control data for similar findings for the test site.

In addition, it was noted that in the DRF study both C_{max} and AUC increased with dose which contrasted significantly with the definitive study where exposure at the 30 mg/kg and 100 mg/kg dose levels were very similar. The applicant clarified that the apparent increase in exposure for the 100 mg/kg dose group in the DRF study was likely the result of significantly higher exposures measured in a single female. The exposure of the other females in this dose group were comparable to that of the definitive study.

Only an EFD in a single species has been performed. The applicant concluded that based on a tolerability study in rabbits (Study ZDA0007) there was negligible exposure to Betulin in rabbits. Whilst the provided study report did suggest that Betulin levels were below the LLOQ (50 ng/ml) there were measured levels of up 225 ng/ml. The study was non-GLP and no formulation or homogenicity analysis has been performed. Considering these limitations, the low number of animals used, limited sample collection as well as issue with the viscosity of the formulation, the applicant was requested to justify the assumption of no exposure in rabbits following oral administration.

The applicant emphasised that only 3 out of 48 samples from the two groups exposed to the birch bark extract gave concentrations of betulin above the lower limit of quantification (<50 ng/mL). Appropriate measures appeared to have been taken to insure homogeneity. Other routes of administration are unlikely to provide systemic exposure in rabbits. Taken in the context of the low systemic exposure levels measured clinically, the lack of an EFD in a second species was acceptable by the CHMP.

A PPND study did not identify any effects on either the F0 or F1 generation at any dose level up to 100 mg/kg/day. The analysis of the F1 generation included a full assessment of reproductive function which did not find any differences amongst treatment groups. No toxicokinetics were performed and therefore no information is available as to the transfer of TE into the breast milk and the subsequent exposure of pups in the post-natal period.

Juvenile animals

A definitive juvenile animal study was performed in rats in which pups were dosed orally from Day 10 up to Day 63 via oral gavage. The age of the pups at the start of dosing was generally supportive of a patient population from birth. In general, the TE was well tolerated. Relevant endpoints for a paediatric population included long bone growth, developmental milestones and neuro-functional behaviour assessment, all of which did not detect any test article related adverse events. Furthermore, the mating and pregnancy sub-group analysis did not detect any differences. The NOAEL was the top dose of 300 mg/kg/day.

Exposure to Betulin on Day 10 was higher than on Day 63. The reason for this is unclear, however, the rat GI tract is known to be immature for the first 2 weeks of life and after this period undergoes significant development especially around weaning (Downes, 2017). Given the variability seen in the measured samples, it is likely that the higher exposure seen on Day 10 is related to higher levels of absorption from the GI tract in rats at this age. Considering the clinical route of application is dermal it is possible that the absorption via this route may differ in paediatrics. However, the skin barrier function is generally mature at birth in term of neonates. Furthermore, even in the instance that absorption was higher in neonates, the lack of toxicity noted in the oral juvenile animal study did provide some assurance.

2.5.4.6. Local Tolerance

TE showed no sensitising properties in the maximisation test in guinea pigs. In addition, Oleogel-S10 was not irritant or corrosive to bovine eyes. In the 39-week minipig repeat-dose toxicity study, several local findings were observed at the application site following dermal administration, including alterations in the epidermis, dermis and subcutis. However, the incidence and/or severity of these findings were comparable to the vehicle control.

2.5.4.7. Other toxicity studies

Phototoxicity

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 edema formation were evaluated. In this study, TE revealed no photosensitising properties.

2.5.5. Ecotoxicity/environmental risk assessment

Filsuvez contains triterpenes as dry extract, refined, derived from Betulae cortex (birch bark) and sunflower oil, refined. These components are considered unlikely to result in a significant risk to the environment. In accordance with the document "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00 corr 2), ERA studies were not submitted.

2.5.6. Discussion and conclusion on non-clinical aspects

The pharmacology programme provided was very similar to the one that was used to support the Episalvan MAA. While the precise mechanism of action is unknown, the programme was considered sufficient to support the present application.

The toxicology programme has revealed that Oleogel-S10 has the ability to cause local reactions, at the site of administration. Despite a measurable systemic distribution, the reactions seen after dermal administration to minipigs were confined to the direct surrounding of the administration site.

The possibility that Oleogel-S10 exerts a direct effect on cell differentiation and/or proliferation, i.e., has an underlying potential local carcinogenic action, remains a concern. Nevertheless, based on the presented data, the risk that Filsuvez would cause malignancies is considered small. A number of precautions and follow up measures are enforced and/or planned from the clinical point of view. These include a warning in section 4.4 of the SmPC, a follow-up Questionnaire for Skin Malignancies and a registry-based study as routine and additional pharmacovigilance activities, respectively, to monitor the risk of SCC (including other skin malignancies). Therefore, the issue was not pursued further from a non-clinical perspective.

Animal studies did not indicate direct or indirect harmful effects with respect to reproductive toxicity. No effects during pregnancy are anticipated, since systemic exposure to Filsuvez is negligible. Filsuvez can therefore be used during pregnancy. Further, no effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breastfeeding woman to Filsuvez is negligible. Filsuvez can therefore be used during breast feeding, unless the chest area is subject to treatment. No adverse effects on fertility were observed in male and female rats administered birch bark extract. No effects on human fertility are anticipated, since the systemic exposure is negligible (SmPC sections 4.6 and 5.3).

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, it is not expected to pose a risk to the environment.

In conclusion, the application for Filsuvez in the treatment of patients with EB is considered approvable from the non-clinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Overviewof Completed or Ongoing Clinical Studies of Oleogel-S10 and Control Gel

Study Number & Phase **Country** **Study Status**	**Study Population/ Indication**	**Study Design**	**Endpoints**	**Study Treatment(s) and Duration of Treatment** **Duration of Follow-Up**	**Number of Study Subjects** **Demographics**
Treatment of epidermolysis bullosa (EB) skin wounds					
BEB-13 **(EASE Study)** Phase 3 Argentina, Australia, Austria, Brazil, Chile, Colombia, Czech Republic, Denmark, France, Georgia, Germany, Greece, Hong Kong, Hungary, Ireland, Israel, Italy, Romania, Russia, Serbia, Singapore, Spain, Switzerland, Ukraine, United Kingdom, United States (26 countries) Double-blind phase (DBP) completed Open-label phase (OLP) ongoing	Subjects ≥21 days of age with **inherited EB** (subtypes JEB, DEB, or Kindler syndrome)[a] with EB partial-thickness wound of 10 cm^2 to 50 cm^2 in size, aged ≥ 21 days and <9 months	Double-blind, randomized, control gel-controlled, efficacy and safety study with 24-month open-label follow-up of Oleogel-S10 with pharmacokinetic sampling to determine systemic concentration of Betulin	Primary: Proportion of subjects with first complete closure of the EB target wound within 45±7 days of treatment with Oleogel-S10 compared to control gel Key Secondary: Time to first complete closure of the EB target wound (Day 90±7); Proportion of subjects with first complete closure of the EB target wound at Day 90±7; The incidence of wound infection between baseline (DBP Day 0) and Day 90±7; The maximum severity of wound infection between baseline (DBP Day 0) and Day 90±7); Change from baseline (DBP Day 0) in total body wound burden as evidenced by clinical assessment using Section I) of the '*EB Disease Activity and Scarring Index*' (EBDASI) at Day 90±7; Change from baseline (DBP Day 0) in itching using the '*Itch Man Scale'* in subjects ≥ 4 years and up to 13 years of age and the '*Leuven Itch Scale'* in subjects ≥ 14 years of age before wound dressing changes at Day 90±7	Oleogel-S10 plus non-adhesive wound dressing vs. control gel plus non-adhesive wound dressing applied directly to the wound or wound dressing every 1 to 4 days during dressing changes for **90 days** (DBP). Target wounds and all other EB partial-thickness wounds were treated during the DBP. If a wound was confirmed as closed, it was not necessary to continue to apply study medication to that wound. Oleogel-S10 was applied in the same manner to all EB partial-thickness wounds for up to **24 months** during OLP. Subjects were followed during the 24-month OLP (Follow-up period).	223 subjects enrolled: 109 Oleogel-S10 114 Control gel (At the time of database lock on 26 Aug 2020, 134 subjects remained in the OLP). 60% Male Median age 12 years (range 6 months to 81 years) Race: 83% White 5% Not reported 5% Asian 1% Black Fitzpatrick skin type: 6% Type I, 49% Type II, 34% Type III, 9% Type IV, 2% Type V, <1% Type VI

Study Number & Phase Country Study Status	Study Population/ Indication	Study Design	Endpoints	Study Treatment(s) and Duration of Treatment Duration of Follow-Up	Number of Study Subjects Demographics
			Adverse event (AE)/serious adverse event (SAE) reporting; assessment of tolerance; Betulin exposure levels		
BEB-10 Phase 2 Germany Completed	Subjects 1 to 95 years of age with **inherited EB** at least 1 skin wound between 10 and 200 cm^2 or 2 similar wounds of at least 5 cm^2 each	Open-label, blindly evaluated, prospective, intra-individually controlled study	Primary: Intra-individual Difference in Re-epithelialization of Wound (Halves) at Day 14 in 'Recent Wounds' or Day 28 in 'Chronic Wounds' [Time Frame: 14 days for 'recent wounds', 28 days for 'chronic wounds'] Secondary: Percentage of Wound Epithelialization at Day 7±1; Percentage of Wound Epithelialization at Day 14±1, AE/SAE reporting; assessment of tolerance	Oleogel-S10 plus non-adhesive wound dressing vs. non-adhesive wound dressing alone. The eligible wound (half) was topically treated with Oleogel-S10 and covered with wound dressing (Mepilex) on Day 0. Wound dressings were changed about every 24 to 48 hours until discharge from hospital or until the end of treatment at **Day 14** in 'recent wounds' or **Day 28** in 'chronic wounds.' No follow-up beyond Day 14 or 28.	10 subjects enrolled and treated (12 wound pairs, as 2 subjects received 2 cycles of treatment) 70% male Median age 20 years (Range: 6 to 48 years) Race: not collected Fitzpatrick skin type: 60% Type I, 20% Type II, 20% Type III
Treatment of split-thickness skin graft donor site wounds					
BSH-12 Phase 3 Austria, Bulgaria, Czech Republic, Finland, Germany, Poland	Subjects ≥18 years of age with a **split-thickness skin graft donor site wounds** of a minimum size of 15 cm^2 and a minimum width of 3 cm	Open-label, blindly evaluated, prospective, intra-individually controlled, randomized, multicenter study with pharmacokinetic	Primary: Intra-individual difference, time to wound closure between halves (mean result, 3 blinded evaluators) Secondary: Intra-individual difference, time to closure between halves (individual	Oleogel-S10 plus non-adhesive wound dressing vs. non-adhesive wound dressing alone at each dressing change (every 3 to 4 days) until full wound	111 subjects enrolled 107 subjects treated 64% male Median age 56 years (range: 18 to 86 years)

Study Number & Phase Country Study Status	Study Population/ Indication	Study Design	Endpoints	Study Treatment(s) and Duration of Treatment Duration of Follow-Up	Number of Study Subjects Demographics
Completed		sampling to determine systemic concentration of Betulin	evaluators); Time from surgery to closure; Percent subjects w/ earlier wound healing with Oleogel-S10 vs. standard of care; Percent subjects w/ wound closure at each time point; Percent epithelialization at each time point; Global assessment of efficacy; AE/ SAE reporting; Global assessment of tolerance	closure or up to **28 days**. Treatment allocation to the halves of the wound was randomly assigned. Subjects attended follow-up visits at 3 and 12 months post treatment.	100% Caucasian Fitzpatrick skin type: 3% Type I, 77% Type II, 18% Type III, 3% Type IV
BSG-12 Phase 3 France, Greece, Latvia, Spain Completed	Subjects ≥18 years of age with a **split-thickness skin graft donor site wounds** of a minimum size of 15 cm^2 and a minimum width of 3 cm	Open-label, blindly evaluated, prospective, intra-individually controlled, randomized, multicenter study with pharmacokinetic sampling to determine systemic concentration of Betulin	Primary: Intra-individual difference in time to wound closure between halves (mean result, 3 blinded evaluators) Secondary: Intra-individual difference in time to wound closure between halves (individual evaluators); Time from surgery to closure; Percent of subjects with earlier wound healing Oleogel-S10 vs. Standard of care; Percent subjects w/ wound closure at each time point; Percent epithelialization at each time point; Global assessment of efficacy; AE/SAE reporting; Global assessment of tolerance	Oleogel-S10 plus non-adhesive wound dressing vs. non-adhesive wound dressing alone until full wound closure or up to 28 days. Treatment allocation to the halves of the wound was randomly assigned. Subjects attended follow-up visits at 3 and 12 months post treatment.	113 subjects enrolled 112 subjects treated 66% male Median age 49 years (range: 19 to 90 years) Race: 88% Caucasian 10% Not reported 2% Other 1% Black Fitzpatrick skin type: 1% Type I, 29% Type II, 36% Type III, 17% Type IV, 18% Type V
Treatment of Grade 2a thermal burn wounds					
Study **BBW-11** Phase 3 Germany, Sweden, Switzerland, United Kingdom	Subjects ≥18 years of age with **Grade 2a burn wounds** between 80 cm^2 and <25% of total body surface area	Open, blindly evaluated, prospective, intra-individually controlled,	Primary: Percent of subjects w/earlier wound healing Oleogel-S10 vs. Octenilin(mean, 3 blinded evaluators)	Oleogel-S10 plus fatty gauze dressing vs. Octenilin plus fatty gauze dressing applied every other	66 subjects enrolled 61 subjects treated 69% male

Study Number & Phase **Country** **Study Status**	**Study Population/ Indication**	**Study Design**	**Endpoints**	**Study Treatment(s) and Duration of Treatment** **Duration of Follow-Up**	**Number of Study Subjects** **Demographics**
Completed	(TBSA) or 2 comparable wounds with size >40 cm^2 each and <12.5% of TBSA each	randomized, multicenter study with pharmacokinetic sampling to determine systemic concentration of Betulin	Secondary: Percent of subjects w/ earlier wound healing Oleogel-S10 vs. Octenilin (each evaluator); Intra-individual difference in time to closure; Time to closure; Percent w/ wound closure by time point; Percent epithelialization by time point; Assessment of efficacy; Microbial colonization; AEs/SAEs; Global assessment of tolerance	day until full wound closure or for up to **21 days**. Treatment allocation to the 2 halves of the wound (or 2 comparable wounds) was randomly assigned. Subjects attended follow-up visits at 3 and 12 months post treatment.	Median age 41 years (range: 18 to 79 years) Race: 84% Caucasian 8% Asian 7% Black 2% Other Fitzpatrick skin type: 12% Type I, 49% Type II, 21% Type III, 8% Type IV, 3% Type V, 7% Type VI
Healthy Subject Studies with Control Gel					
AHV-18-A Phase 2 Germany Completed	Healthy adult subjects 18 to 45 years of age with Fitzpatrick skin type II to III who receive mechanically induced partial-thickness wounds	Exploratory randomized, intra-individual controlled study	Primary: Days until complete healing according to clinical score and days until complete healing according to planimetry. Secondary: mean clinical score per day, mean wound surface area in mm^2, and mean transepidermal water loss (TEWL) per wound in $g/h/m^2$; local tolerance AEs/SAEs and all AEs/SAEs	Three mechanically induced wounds of approximately 8 mm diameter were treated: 1 wound with control gel, 1 wound with petrolatum, and 1 wound was not treated. The treatments were applied once daily for **21 consecutive days** at the study center. During the first 10 days, all wounds were covered with non-adhesive wound dressings. Subjects returned for a follow-up	12 subjects were enrolled and treated 50% Male Mean Age: 26 years (range: 20 to 41 years) Race: not collected

Study Number & Phase Country Study Status	Study Population/ Indication	Study Design	Endpoints	Study Treatment(s) and Duration of Treatment Duration of Follow-Up	Number of Study Subjects Demographics
				assessment 1 week after the last treatment.	
AHV-18-B Phase 2 Germany Completed	Healthy adult subjects 18 to 45 years of age with Fitzpatrick skin type II to III who receive mechanically induced partial-thickness wounds	Confirmatory, randomized, intra-individual controlled study	Primary: Days until complete healing according to clinical score and days until complete healing according to planimetry. Secondary: mean clinical score per day, mean wound surface area in mm^2, and mean TEWL per wound in $g/h/m^2$; local tolerance AEs/SAEs and all AEs/SAEs	Two mechanically induced wounds of approximately 8 mm diameter will be treated: 1 wound with control gel, and 1 wound with petrolatum. The treatments will be applied once daily for **16 consecutive days** at the study center. During the first 10 days, both wounds will be covered with non-adhesive wound dressings. Subjects will return for a follow-up assessment 1 week after the last treatment.	16 subjects were enrolled and treated 50% Male Mean Age: 31 years (range: 19 to 45 years) Race: not collected

Abbreviations: AE=adverse event; DBP=double-blind phase; DEB=dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; EBDASI=Epidermolysis Bullosa Disease Activity and Scarring Index; JEB=junctional epidermolysis bullosa; OLP=open-label phase; SAE=serious adverse event; TEWL=transepidermal water loss

[a] Subjects with the EBS subtype were originally enrolled in the study but removed from eligibility criteria in Protocol Version 4.0 (2 EBS subjects enrolled).

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Introduction

Oleogel-S10 is a sterile and stable gel for topical use.

The indication initially sought was treatment to achieve accelerated healing of wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients from birth onwards. See section 2.6.6. Discussion on clinical efficacy for final indication granted by the CHMP.

The gel should be applied to the wound surface at a thickness of approximately 1 mm and covered by a sterile non-adhesive wound dressing or applied to the dressing so that the gel is in direct contact with the wound. The gel should not be applied sparingly. It should not be rubbed in. The gel should be reapplied at each wound dressing change. The maximum total wound area treated in the pivotal EB clinical study was 5,300 cm^2 with a median total wound area of 735 cm^2.

The following *in vitro* studies for betulin, which is the main component of the extract, were included in this submission:

- Protein Binding (Study No. G A VIT-20-051)
- Caco-2 Transporter Study (Study No. G-A-VIT-20-032)
- *In vitro* Metabolic Profile of Betulin in Hepatocytes (Study No. G-A-VIT-19-050)
- Cytochrome P450 Reaction Phenotyping Using Recombinant Human CYP Enzymes (Study No. G-A-VIT-19-059)
- Cytochrome P450 Phenotyping by Chemical Enzyme Inhibition in Cryopreserved Human Hepatocytes (Study No. G-A-VIT-19-060)
- Betulin as Direct, Time-Dependent, and Metabolism-Dependent Inhibitor of Cytochrome P450 Isoenzymes in Human Liver Microsomes (Study No. G-A-VIT-19-057)
- Betulin as an Inducer of CYP1A2, 2B6, 3A4, and 3A5 Isoenzymes in Cultured Human Hepatocytes (Study No. G-A-VIT-19-058).

PK samples were taken in the phase 3 BEB-13 study in patients with EB (dried blood spots and venous blood), which was conducted using the final Oleogel-S10 formulation (see Table 2). The Phase 2 clinical study BEB-10 (in EB) and studies in healthy subjects with control gel AHV-18-A and AHV-18-B did not contain PK data.

Oleogel-S10 was approved under the trade name Episalvan on 14 January 2016 in the European Union (EU/1/15/1069) for the "treatment of partial-thickness wounds in adults" after having demonstrated efficacy and safety in split-thickness skin graft (STSG) donor site wounds and in Grade 2a burn wounds. The Episalvan submission was supported by PK data from clinical studies BSH-12, BSG-12, and BBW-11 and the corresponding bioanalysis. No *in vitro* PK was included in the Episalvan submission.

Methods

Plasma or whole blood concentrations of betulin were determined with two validated LC/MS/MS methods. No cross validation was performed, as the matrices differ.

Method N-A-BIO-12-047 (plasma) was used for samples from clinical studies BSH-12, BSG-12, and BBW-11 in subjects with Split-Thickness Skin Graft Donor Sites and Burn Wounds.

Due to the fragile skin of the EB population, as well as the difficulty in taking venous blood draws from children and infants, a less invasive, dried blood spot analytical technique using capillary blood samples (finger or heel prick) was developed to measure Betulin whole blood concentrations. The bioanalysis method with dried blood spots (DBS) (N-A-BIO-16-100_E01) was used for samples from the phase 3 study in EB patients (BEB-13), both for capillary and venous blood samples.

PK parameters were not calculated in this application.

Absorption

High permeability of betulin was demonstrated in a pilot Caco-2 study.

In three clinical studies in subjects with Split-Thickness Skin Graft Donor Sites and Burn Wounds, plasma sampling was performed before treatment and at certain timepoints during treatment, to measure the systemic concentration of betulin. 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. Of the 929 plasma samples, 37 (4%) had quantifiable betulin concentrations, 14 of these were pre-dose samples and 23 during the treatment period. The betulin concentrations ranged from 1.1 to 43.9 ng/ml (predose) and from 1.1 to 68.6 ng/ml (treatment).

Betulin occurs naturally and is present in olives and some fruits. Therefore, dietary uptake of Betulin cannot be excluded and it is likely that the low concentrations observed in the pre-dose samples (and possibly in later samples) stemmed from food containing Betulin consumed by the subjects.

Distribution

The unbound fractions of betulin in plasma ($f_{u,p}$) could not be determined as betulin concentrations in buffer compartments were below LLOQ. This indicates that the $f_{u,p}$ of betulin is below 0.1% and fraction bound ($f_{b,p}$) is >99.9% in human, rat and minipig plasma.

No *in vivo* distribution studies have been conducted.

Elimination

No *in vivo* elimination studies have been conducted.

In total, structures of six metabolites (M1-M6) were identified from incubation with hepatocytes (Figure 3). In humans, only four were observed: M2-M5. M2, formed by oxygenation, methylation, and sulfation, was the most abundant (26.9%), followed by M4 (sulfation, 19.0% abundance), M5 (glucuronidation, 12.0% abundance), and M3 (sulfation, 10.2% abundance). Metabolism was virtually complete after 5h.

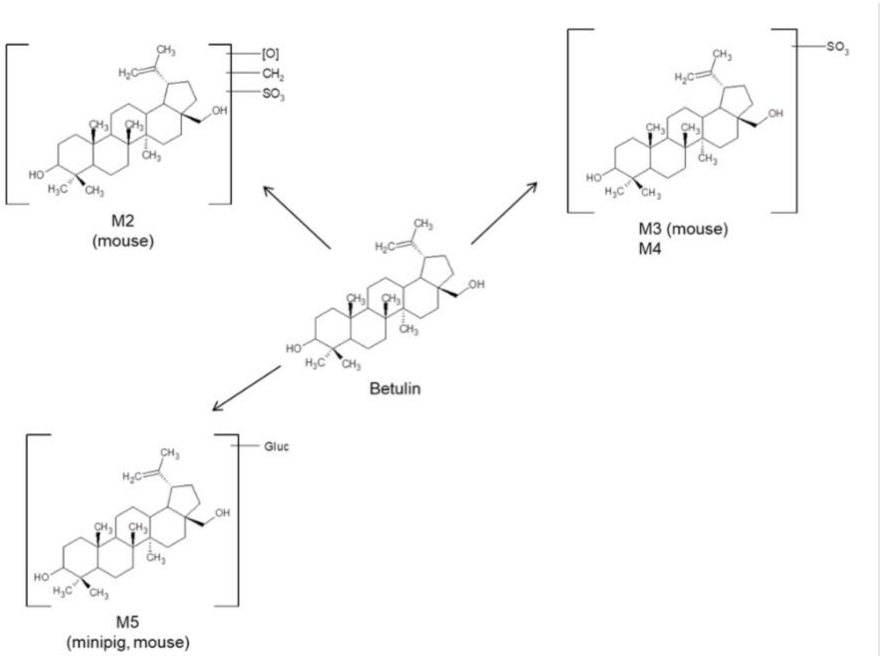


Figure 3. Proposed In Vitro Metabolic Pathways of Betulin in Human Hepatocytes and Indication of their occurrence in Non-clinical Species

Based on the CL_{int} values determined for the individual CYP isoforms using recombinant enzymes and considering their abundance in the human (Caucasian) liver, the relative contribution of rhCYP3A5, 3A4, 2C8, and 2C19 to the overall CYP-mediated metabolism of betulin was calculated to be roughly 60%, 40%, 0.3%, and 0.07%, respectively.

The CYP contribution was confirmed *in vitro* using specific inhibitors. CYP3A contributed most of the CYP-mediated pathway, while contributions of CYP2C8 and CYP2C19 to the metabolism of Betulin were negligible. However, non-CYP enzymes were found to play the predominant role in the hepatic metabolism of Betulin, most likely phase II conjugation enzymes.

Dose proportionality and time dependencies

PK in target population

In the Phase 3 BEB-13 study, Oleogel-S10 or the control gel were applied topically at approximately 1 mm thickness to the EB target wound and to all areas on the subject's body that were affected by EB partial-thickness wounds. Wound areas were then covered with a standard of care non-adhesive wound dressing. This procedure was repeated during all dressing changes (at least every 4 days).

Periodic blood samples were obtained to assess the potential systemic exposure of Betulin following topical administration of Oleogel-S10. The majority of patients were not fasting at the timepoint of PK sampling. Betulin systemic exposure results for the capillary DBS samples obtained by finger or heel stick, if consent was obtained, were obtained for Day 0, 7, 14, 30, 45, 60, 90 and CCC (confirmation of complete closure of target wound) visit.

Due to lack of subject consent to capillary blood sampling sticks, the protocol was amended in Version 4.0 to allow venous DBS sampling and Betulin assays on Days 0 and 90 and Month 24 using the safety laboratory venous samples. These microsamples were directly obtained from EDTA-whole blood samples, avoiding the need for additional finger pricks. Aliquots from these samples were subsequently applied to the collection cards and submitted for analysis.

Baseline samples were in the range 0-122 ng/ml which could be due to the intake of food or natural substances containing Betulin. A similar range is seen in samples from control gel-treated patients in both capillary and venous samples.

Of the post-dose capillary blood samples, 2/43 (5%) were <LLOQ in the Oleogel-S10 arm and 61/63 (97%) in the control gel arm. For post-dose venous blood samples 57/69 (82%) were <LLOQ in the Oleogel-S10 arm, and 106/111 (95%) in the control gel arm. Data per sampling type and treatment is summarised in Table 2.

Several capillary samples resulted in unexplained high concentrations of Betulin, with capillary samples at several time points with values above 1000 ng/ml and 4 subjects had systemic exposure values above 2000 ng/ml. The reason for these elevated capillary Betulin blood values is ultimately unknown, although the applicant considered it was likely that sample contamination from Oleogel-S10 at the site of the finger stick process may have contributed to these high concentrations.

Table 2: Betulin concentration [ng/mL] in capillary vs venous blood samples from Oleogel-S10 or control gel-treated patients

Visit	Statistics	Oleogel-S10 Capillary	Control gel Capillary	Oleogel-S10 Venous	Control gel Venous
Day 0	N	13	8	55	57
	Mean (SD)	9.4 (34)	0 (0)	1.5 (6.1)	0.8 (4.1)
	Median	0.0	0.0	0.0	0.0
	Min-Max	0-122	0-0	0-27	0-27
Day 7	N	9	10	2	10
	Mean (SD)	490 (533)	0 (0)	0 (0)	0 (0)
	Median	202	0.0	0.0	0.0
	Min-Max	0-1290	0-0	0-0	0-0
Day 14	N	8	12	4	12
	Mean (SD)	1963 (3151)	0 (0)	0 (0)	1.2 (4.2)
	Median	207	0.0	0.0	0.0
	Min-Max	17-8890	0-0	0-0	0-15
Day 30	N	6	10	5	11
	Mean (SD)	691 (721)	0 (0)	2.9 (6.5)	0 (0)
	Median	562	0.0	0.0	0.0
	Min-Max	0-1890	0-0	0-15	0-0
Day 45	N	3	9	3	12
	Mean (SD)	174 (168)	0 (0)	0 (0)	0 (0)
	Median	80	0.0	0.0	0.0
	Min-Max	74-368	0-0	0-0	0-0

Visit	Statistics	Oleogel-S10 Capillary	Control gel Capillary	Oleogel-S10 Venous	Control gel Venous
Day 60	N	8	11	2	11
	Mean (SD)	638 (694)	0 (0)	0 (0)	0 (0)
	Median	351	0.0	0.0	0.0
	Min-Max	92-2020	0-0	0-0	0-0
Day 90	N	5	8	53	53
	Mean (SD)	149 (225)	0.0	8.9 (32)	1.5 (7.9)
	Median	13	0.0	0.0	0.0
	Min-Max	0-516	0-0	0-207	0-55
CCC Visit	N	4	3	0	2
	Mean (SD)	1081 (1305)	43 (75)		0 (0)
	Median	827	0		0
	Min-Max	0-2670	0-130		0-0

CCC=confirmation of complete closure (of target wound); Max=maximum; Min=minimum; SD=standard deviation.

Figure 4 illustrates betulin concentration per sample type and total wound area.

As a basis for comparison and interpretation, several subjects had both capillary and venous sample values on Betulin treatment. One subject had elevated capillary results at Day 7 (1190 ng/ml), Day 14 (298 ng/ml), and Day 60 (458 ng/ml), but his open-label phase Month 24 venous blood DBS sample value was 16 ng/ml, reflecting long-term, steady-state treatment and low systemic Betulin exposure with Oleogel-S10. Another subject had elevated capillary results at Day 14 (8890 ng/ml) and Day 45 (368 ng/ml), but at Day 90, his venous Betulin concentration was 36 ng/ml. Finally, a subject had elevated capillary results at Day 14 (4030 ng/ml), Day 30 (1110 ng/ml), and at the time of his wound closure (2670 ng/ml), but the Day 90 venous concentration was below the LLOQ. These data suggest that the higher capillary Betulin concentrations may be falsely elevated due to contamination of the sampling process from topical Betulin and that the venous concentrations may be a more accurate representation of the Betulin systemic exposure. The highest venous blood concentration of betulin was 207 ng/mL.

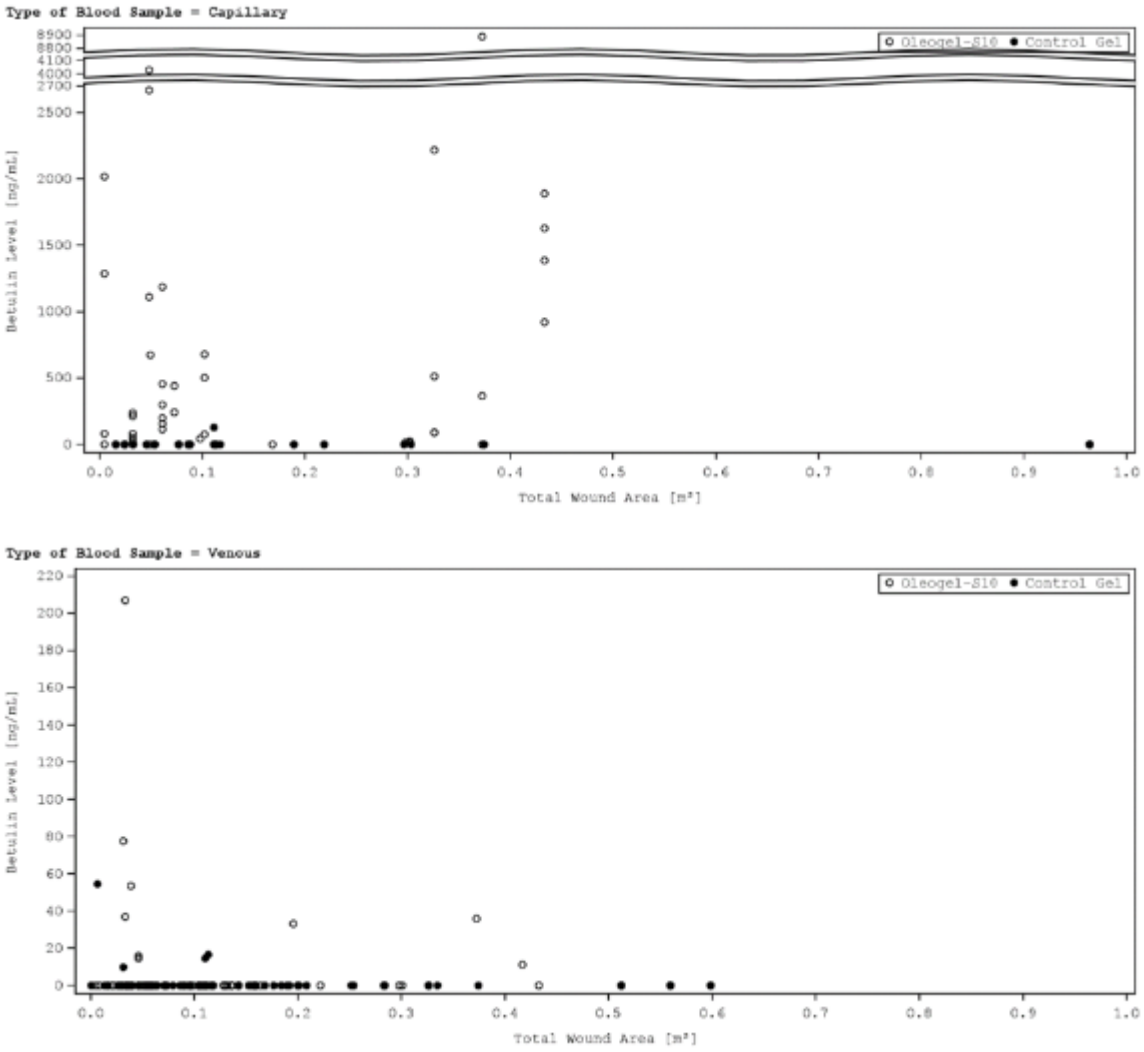


Figure 4: Scatter plot of betulin concentration vs total wound area at screening (study BEB-13). Capillary blood sample (top) and venous blood sample (bottom)

Special populations

No studies have been conducted with Oleogel-S10 in patients with renal or hepatic impairment.

Betulin concentration did not correlate with BMI or age. The elderly subjects for trials with betulin PK sampling i.e., BEB-13, BBW-11, BSG-12 and BSH-12 are summarised in the table below.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	37/508	27/508	8/508

Pharmacokinetic interaction studies

The potential of betulin to inhibit the cytochrome P450 (CYP) isoenzymes 1A, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A was investigated using human liver microsomes (hLM) at betulin concentrations up to 80 µM, as summarised in Table 3.

Table 3 Summary of Direct, Time-Dependent, and Metabolism-Dependent Inhibition of CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A by Betulin.

Enzyme	Reaction	without pre-incubation	30 min pre-incubation without NADPH	30 min pre-incubation with NADPH
CYP1A	Phenacetin O-Dealkylation IC_{50} (µM)	>80	>80	>80
CYP2B6	Efavirenz 8`-Hydroxylation IC_{50} (µM)	>80	>80	>80
CYP2C8	Amodiaquine N-Deethylation IC_{50} (µM)	0.60	0.41	0.35
CYP2C9	Diclofenac 4`-Hydroxylation IC_{50} (µM)	>80	>80	>80
CYP2C19	S-Mephenytoin 4`-Hydroxylation IC_{50} (µM)	>80	>80	>80
CYP2D6	Dextromethorphan O-Demethylation IC_{50} (µM)	>80	>80	>80
CYP3A	Midazolam Hydroxylation IC_{50} (µM)	0.17	0.24	0.36
	Testosterone 6β-Hydroxylation IC_{50} (µM)	0.62	0.55	1.2

Betulin did not induce the mRNA expression of CYP3A4, CYP2B6 and CYP1A2 at physiologically relevant levels.

The effect of betulin on drug transporters was not studied.

Exposure relevant for safety evaluation

The highest systemic concentration measured in EB patients was 207 ng/mL.

2.6.2.2. Pharmacodynamics

Mechanism of action

The application for Filsuvez contained no dedicated studies to support the proposed mechanism of action to achieve accelerated wound healing in patients with EB. Published references supporting beneficial effects of triterpenes on wound healing in general have been submitted and are briefly summarised below.

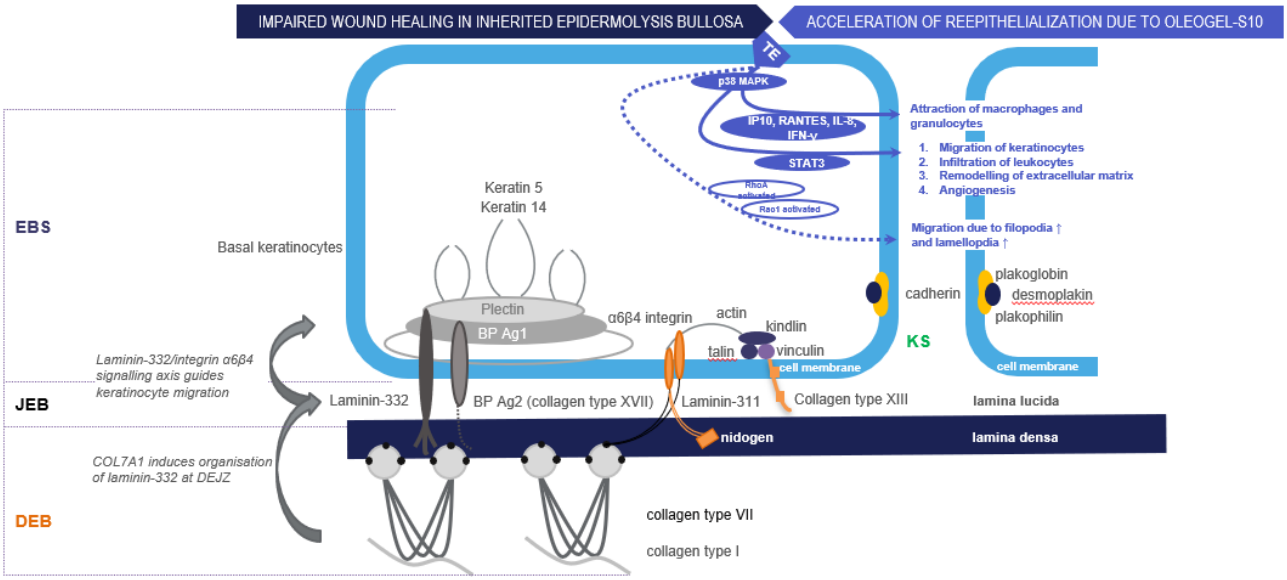
Oleogel-S10 contains triterpenes from birch bark, namely Betulin, Betulinic acid, and Oleanolic acid, which have been shown to have antibacterial, antiviral, antimycotic, and anti-inflammatory effects ([Alakurtti 2006], [Lee 2006], [Suksamrarn 2006]). Oleogel-S10 has been developed to meet the need for an effective treatment for wounds associated with EB by accelerating wound healing.

In EB, the structural integrity of the skin is compromised. Depending on the EB subtype and variant, different proteins are defective or missing. However, the various gene mutations that cause EB are not thought to impede the molecular pathways to skin re-epithelialisation and keratinocyte migration,

which are stimulated by birch bark extract, the active component of Oleogel-S10 ([Ebeling 2014]). As all subtypes of EB are associated with partial-thickness wounds which heal by the same process of re-epithelialisation (driven by keratinocyte migration, differentiation, etc.), the applicant considered that they share the same wound healing pathway. Further, the applicant was of the view that Oleogel-S10 accelerates wound closure by exerting effects on different wound healing phases. *In vitro* tests with human primary keratinocytes and fibroblasts and e*x vivo* studies with porcine skin showed that birch bark extract modulate immune inflammatory mediators including cyclooxygenase 2 (COX 2), interleukin 6 (IL-6), interleukin 8 (IL-8), tumor necrosis factor alpha (TNFα), and RANTES (regulated upon activation, normal T cell expressed and presumably secreted), all key players in the inflammation phase in wound healing ([Ebeling 2014]; [Wardecki 2016]) and associated with activation of intracellular pathways known to be involved in keratinocyte differentiation [Wölfle 2010] and migration [Ebeling 2014].

Formation of a new skin barrier involves cellular proliferation, migration, adhesion, deposition of matrix, and keratinocyte differentiation. Birch bark extract support the differentiation of keratinocytes by upregulating the expression of differentiation markers keratin, type I cytoskeletal 10 (KRT 10) and involucrin (INV), and the adhesion protein transglutaminase in human keratinocytes. KRT 10 expression induced by birch bark extract depends on an up-regulation and an indirect activation of TRPC6 by high $[Ca^{2+}]_{ex}$ (see [Wölfle 2010]). Furthermore, birch bark extract influence the cytoskeleton, in particular via induction of filopodia and lamellipodia mediated by an activation of the Rho GTPase RhoA (Ras homolog gene family, member A) (see [Ebeling 2014] and [Wardecki 2016]).

Figure 5. Skin Impairments in EB and Promotion of Wound Healing by Oleogel-S10



Abbreviations: BP Ag=bullous pemphigoid antigen; DEB=dystrophic epidermolysis bullosa; DEJZ=dermo-epidermal junction zone; EB=epidermolysis bullosa; EBS: epidermolysis bullosa simplex; IFN-γ=interferon-gamma; IL-8=interleukin-8; IP-10=interferon-gamma inducible protein 10; JEB=junctional epidermolysis bullosa; KS=Kindler syndrome; MAPK=mitogen-activated protein kinase; Rac1=Ras-related C3 botulinum toxin substrate; RANTES=regulated on activation, Normal T Cell Expressed and Secreted (chemokine); RhoA=Ras homolog gene family, member A; STAT3=signal transducer and activator of transcription 3 (transcription factor); TE=Dry extract from birch bark, refined

Primary and Secondary pharmacology

Since no specific pharmacodynamic studies (*ex vivo* or *in vivo*) in EB patients have been performed, the postulated beneficial effects rely on the assumption that wound healing processes are similar in skin of healthy, non-EB subjects and EB patients according to the applicant. The mechanism of action

is thus more of a general support to achieve a faster wound healing rather than a specific mechanism of action targeting specific EB sub-types.

There were no secondary pharmacology studies submitted in this application, for instance a thorough QT study (see Safety section).

No interaction studies have been performed.

With respect to pharmacodynamic interactions, the product is locally applied and locally acting. Hence, systemic drug-drug interactions are not expected. The proposed SmPC states that interactions with topical products have not been investigated in clinical trials and that other topical products should not be concomitantly used together with Filsuvez but rather sequentially or alternatively depending on the clinical need.

No dedicated studies have been performed to evaluate genetic differences in PD response. The potential differences between different EB sub-types (e.g. DDEB, RDED, JEB) in clinical response is discussed in the efficacy sections below.

No analyses on the relationship between plasma concentration and effect have been presented. The effect is local; hence, exposure-response and PK/PD have low relevance for this application, unless potentially for evaluation of exposure-safety relationships. However, no AEs suggestive of systemic actions of betulin (or related components) were observed in the clinical safety data. Betulin levels above 70 ng/mL in the DBP of BEB-13 were reviewed to determine if there was any suggestion of an associated safety signal within 4 weeks of the elevated venous or capillary betulin value. No robust relation between systemic exposure of betulin and AE could be established.

2.6.3. Discussion on clinical pharmacology

As this is a known active substance 8(3)/12(3) application, full documentation is required. In consequence, the data from the Episalvan submission (clinical studies BSH-12, BSG-12, and BBW-11 and the corresponding bioanalysis) has also been submitted. The assessment of this data is in line with the original assessment (EMEA/H/C/3938) and is reflected in the respective sections.

In Episalvan, as only low and sporadic levels of betulin were found in plasma, it was concluded that the systemic absorption was minimal, and thus it was accepted that no further study on the elimination, special populations or drug-drug interactions was performed.

The *in vitro* PK data is new to this submission, as well as the bioanalytical assay using dried blood spots, which was used to analyse samples from the phase 3 study BEB-13 in the EB population. Further differences between the submissions are linked to the indication, with Filsuvez seeking an indication in EB patients from 6 months of age (Episalvan is approved in adults only). Inherent to the type of wound, larger wounds and chronic administration are expected in EB patients.

Only betulin, the main component of the betulae cortex dry extract, was studied, which is in line with the received advice (Q7, EMA/CHMP/SAWP/865922/2011).

Methods

In general, method N-A-BIO-12-047 (plasma) was satisfactorily validated, and within-run performance appeared acceptable.

Method N-A-BIO-16-100_E01 (DBS) was satisfactorily validated, and within-run performance appeared acceptable. Incurred sample reanalysis (ISR) was however not performed. Samples from venous blood in study BEB-13 had similar levels as in plasma samples from study BSH-12, BSG-12 and BBW-11 (up

to 68.6 ng/mL). Considering the small number of quantifiable results; the lack of ISR is considered acceptable by the CHMP.

As the value of capillary blood samples was strongly diminished by contamination issues (see below), the CHMP considered that there was no need for ISR for those samples.

Absorption

No formal PK study was conducted. Occasional samples with measurable concentrations of betulin were found both pre- and post-dose, and all reported positive samples and had betulin levels in the range 1-70 ng/ml. The applicant pointed out that some common nutrients such as lingonberries, olives and apples contain betulin, and speculated that they could be a source of measurable betulin plasma levels. The LLOQ 1 ng/ml is believed to be high enough to identify biologically active drug levels. The applicant´s conclusion that the betulin plasma levels resulting from topical treatment of Oleogel-S10 were not higher than natural background levels originating from e.g. nutritional sources, is overall endorsed. No conclusion can be drawn on variability as this is confounded by the intake of betulin containing food.

Apart from betulin, Oleogel-S10 contains also other minor components such as betulinic acid, lupeol, oleanolic acid, and erythrodiol. Betulin is however the main component, all other components are present in substantially lower concentrations, and bioanalysis of betulin only is thus accepted by the CHMP.

As only low and sporadic betulin plasma levels were found, it can be concluded that the systemic absorption of betulin was minimal (SmPC section 5.2).

Distribution

The unbound fractions of Betulin in plasma (fu,p) could not be determined in any species as Betulin concentrations in buffer compartments were below the LLOQ of 1 nM. The conclusions that the fu,p of Betulin is below 0.1% and the fraction bound is >99.9% in plasma for all three species tested is agreed and in line with SmPC section 5.2.

Elimination

The lack of *in vivo* studies is acceptable for a LALA product. This is adequately reflected in the SmPC section 5.2.

Metabolism

The extent of Betulin metabolism was practically complete in all species (after 5 h incubation with hepatocytes) where 4 metabolites were identified in human. No human specific metabolites were identified.

PK in target population

In Q5 of the scientific advice received (EMA/CHMP/SAWP/97017/2017), concern was expressed regarding the treatment of larger body surface areas in EB and the length of use, and the importance of identifying the extent of betulin absorption. The sampling strategy, including a new sampling method with dried blood spots was supported to increase the consent to PK sampling. These aspects were adequately addressed by the applicant.

A different picture of systemic betulin exposure upon treatment with Oleogel-S10 was provided depending on the sampling type. The majority (82%) of the on-treatment venous samples were less than the lower limit of quantification (i.e., 10 ng/ml). The systemic exposure (up to 207 ng/mL post-dose, 27 ng/mL pre-dose) was generally relatively similar to what was seen in other indications where

up to 68.6 ng/mL was measured. This is also in the range that can be expected upon consumption of betulin containing food. This has been adequately reflected in SmPC section 5.2.

When considering capillary blood samples however, significantly higher betulin concentrations were measured. Should this finding be true, then a correlation with the total wound area, as a surrogate for the administered dose, would be expected, both for venous and capillary blood samples. This was not the case. The applicant considered the elevated levels in capillary samples likely to be due to contaminations at the site of sampling. No detailed information was given in the study protocol on how to take the capillary sample, which may have been helpful to avoid such contaminations. The explanation for high concentrations as the result of contaminations is nevertheless accepted. This is further supported by a few subjects with both venous and capillary blood sampling, where the elevated levels are only present in capillary samples. Thus, it is acceptable to base the overall assessment of PK and the SmPC information on data from venous samples. As only low and sporadic betulin plasma levels were found, it can be concluded that the systemic absorption of betulin was minimal. No further *in vivo* studies on the elimination of betulin or special populations were performed. This is acceptable to the CHMP.

Overall, the results indicate low Betulin systemic exposure following topical administration of Oleogel-S10 to partial thickness wounds in the majority of patients with EB. The findings are reasonably consistent with 3 previous studies of Oleogel-S10 in non-EB partial-thickness wounds (BSH-12, BSG-12 and BBW-11). However, overall, the systemic absorption of Betulin appeared to be slightly higher in patients with EB compared to patients with non-EB wounds. The applicant considered that these differences may be due to difference in skin permeability in the patient populations, more widespread areas for drug treatment, and therefore a larger surface area as compared to the body size of the EB patients, who are generally younger. Any differences in systemic absorption in the various patient populations were modest and were not suggestive of systemic adverse events. The explanation was acknowledged by the CHMP.

Special populations

The absence of study in special populations is acceptable, given the low systemic exposure. This is adequately reflected in the SmPC, with no dose adjustment being required for patients with renal or hepatic impairment.

Analyses of betulin exposure per body mass index and age did not indicate the need for dose adjustment, in line with the expected low exposure for a LALA medicinal product. Gender and race were not addressed by the applicant, but similarly low exposures are expected across genders and races. No dose adjustments are required.

The CHMP SAWP considered the skin to be a relatively mature organ at birth and that it can be assumed that percutaneous translocation of compound in the blood will be similar in neonates, children and adults.

Interactions

DDI cut-offs are only relevant for systemic betulin concentration since this drug product is locally applied to the skin. In the present application, no Cmax can be defined, as most samples were taken before changing wound dressing and thus may be considered as Ctrough. In most cases, systemic concentrations of Betulin were <LOQ, which was similar to what was previously observed in subjects with Split-Thickness Skin Graft Donor Sites and Burn Wounds, and where the lack of drug interaction studies was accepted. Further, no correlation was observed between exposure and total wound area, BMI or age, which supports the extrapolation of PK from already authorised indications.

In vitro studies did not indicate clinically relevant signals for inhibition or induction of CYP enzymes. Interactions (both as victim or perpetrator) with drug transporters were not studied, which the applicant considered justified by the minimal systemic exposure of betulin. This view is agreed, and this is adequately reflected in the SmPC.

Pharmacodynamics

No specific pharmacodynamic studies (*ex vivo* or *in vivo*) in EB patients have been performed to support a positive effect of Oleogel-S10 in the acceleration of wound healing in EB skin. The postulated beneficial effects rely on the assumption that wound healing processes are similar in skin of healthy, non-EB subjects and EB patients. The mechanism of action is thus more of a general support to achieve a faster wound healing rather than a specific mechanism of action targeting specific EB sub-types. The effect is local; hence, exposure-response and PK/PD have low relevance for this application, unless potentially for evaluation of exposure-safety relationships. The exposure/safety analysis was performed regardless of blood sample type and may thus be biased by contaminations for the measurements from capillary blood samples. It is however agreed that no correlation between betulin levels and AE was apparent. No AEs suggestive of systemic actions of betulin (or related components) were observed in the clinical safety data.

2.6.4. Conclusions on clinical pharmacology

Limited PK data on the marker substance betulin is available, indicating low systemic exposure. Since Oleogel-S10 is a locally applied, locally acting medicinal product, the extent of data is considered to be acceptable by the CHMP.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

No dose response studies are included in the application. Since the effect is local, PK/PD modelling is not applicable. One small Phase 2 study has been performed (Study BEB-10) but no dose finding was included in this study. It is described below (Supportive studies).

2.6.5.2. Main study

This application contains one pivotal phase 3 study; BEB-13.

Study BEB-13 (EASE study)

Study BEB-13 is a randomised, controlled, 90-day double-blind phase 3 study, with a 24-month open-label follow-up of Oleogel-S10 in subjects with inherited EB. Each subject was to participate for 90 days in the randomised double-blind phase (DBP). At the end of the DBP (Day 90), subjects in both treatment arms were invited to enter the single-arm open-label phase (OLP) with Oleogel-S10 treatment of all wounds for 24 months. The total duration of study participation (DBP and OLP) was planned to be approximately 27 months.

The final results for the DBP of the study were submitted as well as the preliminary safety data for subjects who entered the OLP and had data at the time of an OLP data cut-off (11 June 2020). Further efficacy and safety data from the OLP will be submitted once available (i.e., by Q1 2023).

Methods

- **Study Participants**

Inclusion criteria

- Male and female subjects aged ≥4 years with the following subtypes of inherited EB: DEB, JEB, and Kindler syndrome (the EBS subtype was removed from the eligibility criteria in Protocol Version 4.0)
  Note: Children ≥21 days old and <4 years could be included, but only after confirmation by the Independent Data Monitoring Committee (IDMC) upon review of the safety and bioanalytical (betulin) data at the interim safety review

- Subjects with an EB target wound (*i.e.*, EB partial-thickness wound of 10 cm^2 to 50 cm^2 in size, aged ≥21 days and <9 months) outside of the anogenital region (specification of outside the anogenital region clarified in Protocol Version 6.0)

- Subject and/or his/her legal representative was informed, read, and understood the subject information/ICF, and gave written informed consent

- Subject and/or his/her legal representative had to be able and willing to follow study procedures and instructions.

Exclusion criteria

- Subject had EB subtype EBS (added in Protocol Version 4.0)

- EB target wound that was ≥9 months old (added in Protocol Version 4.0) or had clinical signs of local infection

- Use of systemic antibiotics for wound-related infections within 7 days prior to enrolment

- Administration of systemic or topical steroids (except for inhaled, ophthalmic, or topical applications, such as budesonide suspension for esophageal strictures [e.g., Pulmicort Respules 0.25 mg/2 ml or 0.5 mg/2 ml]) within 30 days before enrolment

- Immunosuppressive therapy or cytotoxic chemotherapy within 60 days prior to enrolment

- Subject had undergone stem cell transplant or gene therapy for the treatment of inherited EB

- Current and/or former malignancy including basal cell carcinomas and squamous cell carcinomas (SCCs)

- Enrollment in any interventional study or treated with any investigational drug for any disease within 4 weeks prior to study entry

- Factors present in the subject and/or his/her legal representative that could have interfered with study compliance such as inability to attend scheduled study visits or compliance with home dressing changes

- Pregnant or nursing women

- Women of childbearing potential, including post-menarchal female adolescents, and men (reference to men added in Protocol Version 4.0) who were not willing to use an effective form of birth control with failure rates <1% per year (e.g., implant, injectable, combined oral contraceptive, intra-uterine contraceptive device, sexual abstinence, vasectomy or vasectomized

partner) during participation in the study (and at least 3 months thereafter)

- Subject was a member of the investigational team or his/her immediate family
- Subject lived in the same household as a study participant.

The inclusion and exclusion criteria are broadly found acceptable, with some comments.

Following a protocol amendment, patients with the EB subtype EBS (EB Simplex) were not to be included. The reason for this change was that EBS wounds are generally smaller, more superficial, and dynamic in nature. Inclusion of such wounds would likely have increased the rate of healing in the control group as determined by the primary endpoint and reduced the statistical power of the primary efficacy endpoint comparison. This is acknowledged and the proposed indication wording does not include EBS.

It was not stated in the inclusion criteria how the EB diagnosis should have been confirmed, e.g. if genetic testing was needed or if immunofluorescence mapping or electron microscopy or a clinical EB diagnosis only would suffice. The applicant was asked to explain and justify the reason for a genetic confirmation of EB diagnosis only being optional. This is discussed further below.

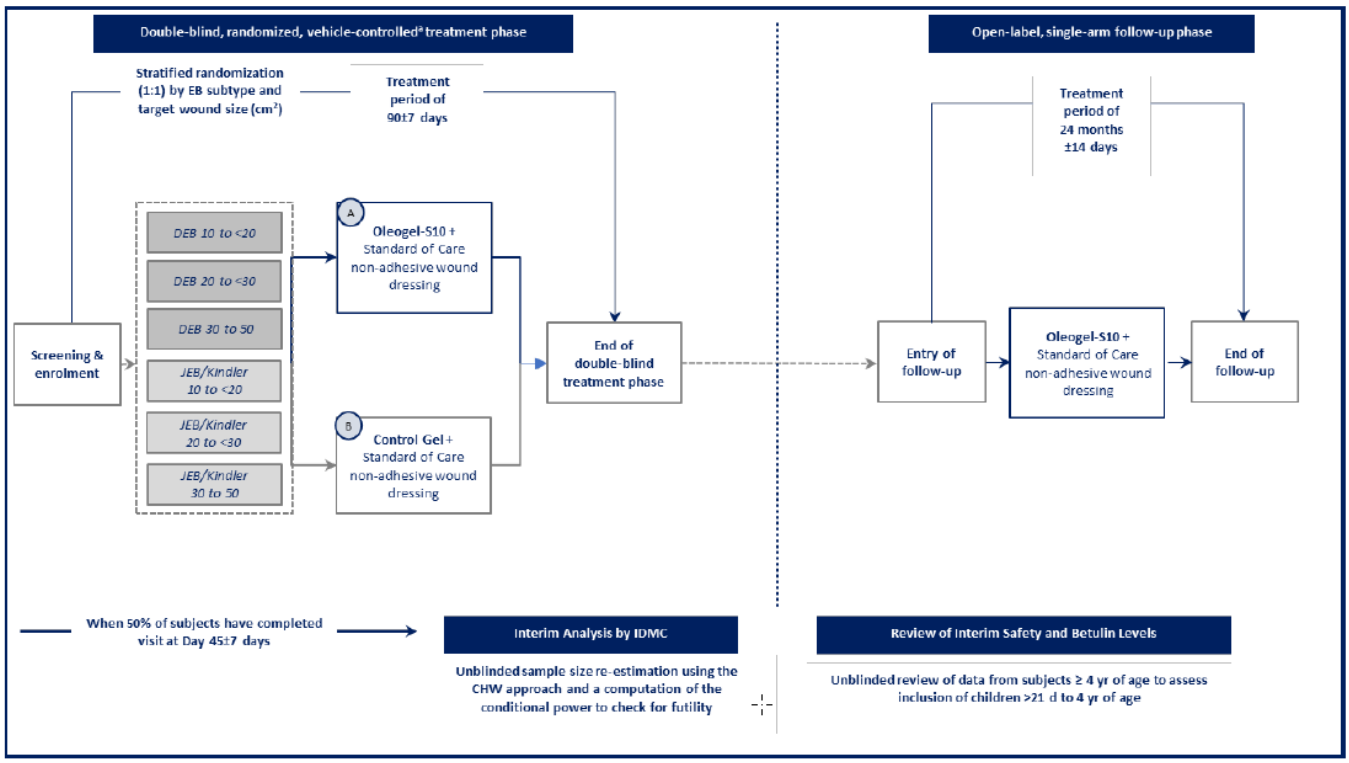
A target wound was defined as having a size 10 cm^2 to 50 cm^2, aged ≥21 days but less than 9 months, and should be present outside of the anogenital region. This is endorsed. Following discussions in the Protocol assistance in 2017 (EMEA/H/SA/2179/1/FU/1/2016/PA/SME/III), an upper size limit of 50 cm^2 was set. The target wound should not have clinical signs of local infection. An upper age limit of 9 months for the target wound was included following an amendment.

The study had broad age inclusion criteria; subjects from the age of 21 days could be included. The inclusion of children below 4 years of age was only made after confirmation by the IDMC upon review of the safety and bioanalytical (betulin) data at the interim safety review. This approach is reasonable, and the inclusion of children and infants is relevant due to the unmet need also in this group of EB patients.

- **Treatments**

An overview of the study design is shown below.

Figure 6. Study Design



Abbreviations: CHW=Cui, Hung, Wang; DEB=dystrophic EB; EB=epidermolysis bullosa; IDMC=Independent Data Monitoring Committee; JEB=junctional EB.
[a] Vehicle=control gel.

Double-Blind Phase

The randomised DBP consisted of 3 periods:

1. Screening (up to 28 days prior to baseline)

Study sites invited subjects from site-specific databases for screening. Subjects who failed screening could be rescreened if they later became eligible, as deemed appropriate by the investigator.

2. Baseline, enrolment, and stratified randomisation (Day 0)

The investigator confirmed eligibility for the subject on Day 0 and, providing the subject was eligible, enrolled the subject into the study. There was a baseline assessment of demography and medical history, and the EB target wound was selected based on the Investigator's Worksheet. According to this worksheet, the wound with the largest size, maximum depth and longest duration should be chosen as the target wound. Subjects were stratified according to their EB subtype and target wound size (cm^2) into the following groups: DEB 10 to <20; DEB 20 to <30; DEB 30 to 50; JEB/Kindler 10 to <20; JEB/Kindler 20 to <30; and JEB/Kindler 30 to 50. Subjects were randomized 1:1 to receive either Oleogel-S10 or control gel.

3. Intervention (90 days)

The EB partial-thickness target wound and all areas on a subject's body that were affected by EB partial-thickness wounds were treated with Oleogel-S10 and standard of care non-adhesive wound dressing or with control gel and standard of care non-adhesive wound dressing. The randomised treatment was to be applied during all dressing changes (at least every 4 days) until the end of DBP (EDBP). Each subject participated for 90 days in the DBP of the study.

Oleogel-S10 or the control gel were applied topically at approximately 1 mm (0.04 inch) thickness to the EB target wound and to all areas on the subject's body that were affected by EB partial thickness wounds. The subject (or caregiver) could apply study medication directly to the wound or on to the wound dressing used to cover the wound, based on personal preference. The subject was permitted to keep their usual schedule of wound dressing changes as long as dressing changes and study medication application took place at least every 4 days. The subject was asked to maintain a regular schedule of wound dressing changes (*i.e.*, not to change intervals) and to report this schedule to the investigator at each clinic visit.

The study medication was not to be rubbed into the wounds or mixed with other skin products at the time of application. If a wound was closed, it was not necessary to continue to apply study medication. The subject could use wound dressing on the closed wound to protect the area, if desired. Areas on the subject's body that were not affected by EB partial-thickness wounds were not to be treated with study medication. The study medication was not intended for use on full-thickness wounds.

During the 90-day DBP, there was a Site Visit or Home Visit at Day 7 (±2 days; could also have been a phone call instead of a site or home visit) and Site visits at Day 14 (±5 days), Day 30 (±7 days), Day 45 (±7 days), Day 60 (±7 days) and Day 90 (±7 days). At the Day 14 and Day 45 visits, the investigator could visit the subject at home.

After first clinical assessment of complete closure of the EB target wound (based on clinical assessment by an investigator at a scheduled visit), a site study team member (e.g., study nurse) visited the patient at home 7 days (+2 days) for confirmation of complete closure (CCC) of the EB target wound. Alternatively, the patient visited the site 7 days (+2 days) after first clinical assessment of complete closure of the EB target wound for CCC. The target wound was photo-documented with the ARANZ Silhouette system. Photographs were reviewed by the investigator. Wound dressings were to be changed, and the study medication continued to be applied to any remaining EB wounds matching target wound criteria. It was not necessary to continue to apply study medication to the closed wound.

Oleogel-S10

Oleogel-S10 contains birch bark extract in a white to almost white powder consisting of approximately 80% (w/w) betulin and other closely related triterpene compounds. The powder forms a gel when mixed with oil in the optimum combination ratio. Oleogel-S10 is a sterile, colourless to slightly yellowish, opalescent, non-aqueous gel packed in white collapsible aluminum tubes containing 23.4 g of gel each.

Control Gel

The sterile control gel matched Oleogel-S10 in texture and visual appearance. The control gel consisted of sunflower oil, Cera flava/yellow wax and Carnauba wax.

Standard of Care Non-adhesive Wound Dressings

Standard of care non-adhesive wound dressings were defined as modern non-adhesive wound dressings or equivalents. The eligibility criteria in this study did not exclude the use of specific wound dressings. Subjects were permitted to continue using their standard of care non-adhesive wound dressings, with the exception of silver dressings, which were not allowed on EB target wounds or additional wounds meeting target wound criteria until complete closure and confirmed epithelialisation. This was applicable in both phases of the study. To reduce the diversity of wound dressings, the protocol recommended that they be limited to a small number of products such as Mepitel (Mölnlycke Health Care AB, Sweden) or PolyMem (Ferris Mfg. Corp., US). For further products, the 'International Consensus Best Practice Guidelines for Skin and Wound Care in Epidermolysis Bullosa' was referenced.

During the course of the study, it was discovered that some subjects were using Vaseline gauze or other dressings containing topical emollients, even though topical emollients were not permitted per the protocol (Versions 3.0 through 6.0). The protocol was amended (Version 6.0) to clarify that dressings containing topical emollients (e.g., Vaseline gauze) were not allowed.

The rationale for the requirement to avoid the use of dressings containing topical emollients was conservative in nature. As topical emollients may potentially aid wound healing, these were prohibited in the original protocol. Although dressings containing emollients are quite different from an actual topical application, there is a small amount of emollient that permeates these dressings.

The investigators were instructed to not change dressings in enrolled subjects, but to avoid using "nonpermitted dressings containing topical emollients" in future subjects. In addition, the investigators were instructed to report all dressings containing emollients (both prior to implementation of the amendment and thereafter) as protocol deviations to allow a subgroup analysis of these subjects. Efficacy was evaluated in terms of modern non-adhesive (permitted) versus other (nonpermitted) dressings (Prohibited Wound Dressing/Contact Layers).

Open-Label Phase

Once the EDBP visit was completed, the subject could enter the single-arm, 24-month OLP.

Topical Oleogel-S10 was to be administered to all areas on the subject's body that were affected by EB partial-thickness wounds on Day 0 of the OLP. Wound areas were to be covered with standard of care non-adhesive wound dressings. This procedure was to be repeated during all dressing changes (at least every 4 days) until the end of treatment at Month 24. Subjects participating in the OLP were to receive Oleogel-S10 treatment for 24 months.

The treatments compared in this study are Oleogel-S10 on top of standard of care (non-adhesive wound dressing) vs. control gel and standard of care non-adhesive wound dressing. The control gel used in this study was not merely the gel vehicle without the active substance (the extract) as would be common practise in a controlled study with a topical treatment. Due to the galenical properties, with the betulin extract and sunflower oil forming an 'oleogel', it was not possible to simply use the gel vehicle in this case, i.e. pure sunflower oil (with different viscosity etc. vs the active product). Therefore, a dedicated 'control gel' was developed and used in the study. This approach was extensively discussed in the scientific advice procedures (EMEA/H/SA/2179/1/FU/1/2016/PA/SME/III and EMEA/H/SA/2179/1/FU/2/2018/PA/SME/II). There was a concern that in case a beneficial effect of the active treatment (Oleogel-S10) was observed, sufficient reassurance would be needed to establish that this was not merely due to a detrimental effect on wound healing caused by the 'control gel'. To overcome this concern, the applicant conducted studies AHV-18-A and AHV-18-B (See below, supportive studies).

Oleogel-S10 or the control gel were to be applied on the EB target wound and also to all areas on the subject's body that were affected by EB partial-thickness wounds. It did not appear as if a maximum body surface area to be covered was specified in the protocol.

The attempts to standardise the type of wound dressings to be used, to the extent possible in a global study, is acknowledged. However, some subjects still used Vaseline gauze or other dressings containing topical emollients, although these were not permitted per the protocol (Versions 3.0 through 6.0). A subgroup analysis of these subjects was performed and is discussed below.

- **Objectives**

The primary objective of the DBP was to compare the efficacy of Oleogel-S10 with vehicle (referred to as control gel) in the promotion of healing of EB partial-thickness wounds.

Secondary objectives of the DBP were to compare the efficacy of Oleogel-S10 with control gel based on several different evaluations (please refer to secondary endpoints described below), to compare the safety of Oleogel-S10 with control gel (based on the incidence, severity and relatedness of AEs, and laboratory assessments), to compare the tolerability of Oleogel-S10 with control gel and to assess betulin exposure.

Two objectives of the 24-month OLP were addressed in the evaluation of the interim OLP data; to evaluate the safety of Oleogel-S10 based on the incidence, severity and relatedness of AEs, and laboratory assessments and to evaluate local tolerability of Oleogel-S10.

The study objectives are considered adequate.

- **Outcomes/endpoints**

Primary efficacy endpoint

The primary efficacy endpoint of the DBP was the proportion of subjects with first complete closure of the EB target wound (defined as EB partial-thickness wound of 10 cm^2 to 50 cm^2 in size and ≥21 days to <9 months in age) in subjects with inherited EB (subtypes DEB, JEB, or Kindler syndrome) within 45 days of treatment with Oleogel-S10 compared with control gel based on clinical assessment by the investigator (the wound was to be rated as "closed" at first appearance of complete re-epithelialisation without drainage).

The choice of this endpoint was discussed and agreed in the CHMP protocol assistance in 2017 (EMEA/H/SA/2179/1/FU/1/2016/PA/SME/III). Assessing the proportion of patients achieving wound closure within a period of 45 days, rather than time to first wound closure within 90 days was found acceptable. Also, the time point 45 days was preferred to the initially proposed 60 days.

The target EB wound was defined as an EB partial-thickness wound of 10 cm^2 to 50 cm^2 in size and ≥21 days to <9 months in age. This definition provides reassurance that the wound has not healed for a period of 3 weeks, while still not being a chronic wound aged more than 9 months. A wound size of 10-50 cm^2 is deemed relevant. The definition is considered adequate and in agreement with what was discussed in the CHMP PA in 2017.

First complete closure of the EB target wound was based on clinical assessment by the investigator and the wound was rated as "closed" at first appearance of complete re-epithelialisation without drainage. This is endorsed. A *re-opening* of a closed target wound is however also of great interest since EB skin is very fragile and a benefit of a healed wound would be larger if the healing is sustained. This was discussed in the PA procedure 2017 and it was considered that the incidence of re-injury of the target wound should be reported. In the study protocol, it was clarified that confirmation of complete closure was assessed by a site study team member (e.g., study nurse) at home 7 days (+2 days) after first clinical assessment of complete closure of the EB target wound or the patient could visit the site 7 days (+2 days) after first clinical assessment of complete closure of the EB target wound. A requirement for sustained healing was not part of the primary endpoint but was assessed in a supportive analysis.

Secondary Endpoints

The key secondary efficacy endpoints were:

- Time to first complete closure of the EB target wound based on clinical assessment until EDBP (Day 90)
- Proportion of subjects with first complete closure of the EB target wound at Day 90 based on clinical assessment by the investigator

- The incidence of wound infection between baseline (DBP Day 0) and Day 90 as evidenced by AEs and/or use of topical and/or systemic antibiotics (related to wound infection)
- The maximum severity of wound infection between baseline (DBP Day 0) and Day 90 as evidenced by AEs and/or use of topical and/or systemic antibiotics (related to wound infection)
- Change from baseline (DBP Day 0) in total body wound burden (TBWB) as evidenced by clinical assessment using Section I (assessment of the skin except for the anogenital region) of the EB Disease Activity and Scarring Index (EBDASI) [Loh 2014] at Day 90
- Change from baseline (DBP Day 0) in itching using the Itch Man Scale [Morris 2012] in subjects ≥4 years and up to 13 years of age and the Leuven Itch Scale [Haest 2011] in subjects ≥14 years of age, before wound dressing changes at Day 90

Other secondary efficacy endpoints of the DBP were:

- Change from baseline (DBP Day 0) in "procedural" pain using the FLACC scale [Merkel 1997] in subjects <4 years of age and the Wong-Baker FACES® Pain Rating Scale [Wong 2015] in subjects ≥4 years of age after wound dressing changes at Days 7, 14, 30, 45, 60, and 90
- Change from baseline (DBP Day 0) in "background" pain using the Face, Legs, Activity, Cry, Consolability (FLACC) pain rating scale [Merkel 1997] in subjects <4 years of age and the Wong-Baker FACES Pain Rating Scale [Wong 2015] in subjects ≥4 years of age before wound dressing changes at Days 7, 14, 30, 45, 60, and 90
- Proportion of subjects with first complete closure of the EB target wound at Days 14, 30, and 60 based on clinical assessment by the investigator
- Proportion of subjects with first complete closure of the EB target wound at Days 7, 14, 30, 45, 60, and 90 based on subject assessment
- Proportion of subjects with first complete closure of the EB target wound at Days 7, 14, 30, 45, 60, and 90 based on blinded evaluation of photographs
- Percentage change from baseline (DBP Day 0) in EB target wound size as evidenced by blinded evaluation of photographs taken at Days 7, 14, 30, 45, 60, and 90
- Change from baseline (DBP Day 0) in TBWB as evidenced by clinical assessment using Section I (assessment of the skin except for the anogenital region) of the EBDASI [Loh 2014] at Days 30 and 60
- Change from baseline (DBP Day 0) in body surface area percentage (BSAP) of TBSA affected by EB partial-thickness wounds as evidenced by clinical assessment based on the Lund and Browder chart [Miminas 2007] at Days 30, 60, and 90
- Change from baseline (DBP Day 0) in itching using the Itch Man Scale [Morris 2012] in subjects ≥4 years and up to 13 years of age and the Leuven Itch Scale [Haest 2011] in subjects ≥14 years of age before wound dressing changes at Days 7, 30, and 60
- Change from baseline (DBP Day 0) in impact of wounds on sleep (in subjects ≥14 years of age) as measured by differences in 11-point Likert scales [Blome 2014] at Days 7, 30, 60, and 90
- The number of days missed from school or from work due to EB as reported by subjects at Day 0 for the last 14 days and cumulatively for all visits until Day 90
- Evaluation of the treatment response (in subjects ≥14 years of age) using the TSQM [Bharmal 2009], Version 9, before wound dressing changes at Days 7, 30, 60, and 90

Safety endpoints of the DBP were:

- Incidence, severity, and relatedness of AEs
- Local tolerability as judged by the investigator
- Laboratory assessments
- Vital signs
- Electrocardiograms (ECGs)

Exposure to betulin was also assessed.

Safety endpoints for the 24-month OLP, listed above for the DBP, were evaluated using interim OLP data.

As outlined above, a large number of secondary endpoints have been evaluated, six of them being classified as key secondary efficacy endpoints and included in the multiple testing procedure. These endpoints reflect other aspects of wound healing, e.g., time to first closure and proportion of subjects with first complete closure up to Day 90, the incidence and severity of wound infections between baseline and Day 90, change from baseline in total body wound burden (TBWB) based on EBDASI at Day 90 and change from baseline in itching. In addition to the key secondary endpoints a range of other secondary endpoints were also evaluated, e.g., addressing "procedural" pain and "background" pain, evaluating target wound closure at other time points, TBWB, change from baseline in body surface area percentage affected by EB partial-thickness wounds and itch. These are relevant efficacy endpoints in an EB study. Safety endpoints are also acceptable.

- **Sample size**

The assumed true control rate for the primary endpoint of first complete closure of the EB target wound was 27%. Based on the use of a 2-sided chi-square test of equality of binomial proportions at the alpha=0.05 level of significance, a total sample size of 182 subjects (91 subjects per arm) provides 80% power to detect an improvement of 20 percentage points (i.e., a true Oleogel-S10 rate of 47%). A total of 192 subjects were planned to be enrolled into the study and treated to account for a dropout rate of 5%, as dropout rates in studies with EB subjects are reported to be small.

An unblinded interim analysis for sample size re-estimation was conducted by the IDMC on 21 December 2018 when approximately 50% of subjects had completed Day 45. This analysis involved an unblinded sample size re-estimation using the CHW approach and a computation of the conditional power to check for futility [Cui 1999].

Based on the results of the sample size re-estimation, the IDMC recommended that the sample size be increased by 48 subjects (24 per arm) for a total of 230 evaluable subjects.

In the months preceding 06 March 2020, the rate of enrolment into the study had slowed, which reflected the low number of subjects with this rare disease. As of 06 March 2020, 223 subjects had been randomized to the study. After consultation with an independent expert, the Sponsor concluded that the statistical impact of further subject recruitment would most likely be negligible and decided to cease enrolment and proceed to database lock of the DBP.

- **Randomisation and Blinding (masking)**

A 1:1 randomisation to Oleogel-S10 or control gel was used, stratified for EB subtype and size of target wound (cm^2) in six different strata: DEB 10 to <20; DEB 20 to <30; DEB 30 to 50; JEB/Kindler 10 to <20; JEB/Kindler 20 to <30; and JEB/Kindler 30 to 50. Once a randomization number was assigned,

that number could not be used again for any other subject (e.g., if a subject was withdrawn from the study, that subject's randomization number was not reused for any other subject).

The stratification factors are considered adequate. Other stratification factors discussed during the PA procedure were anaemia or nutrition status, as these variables could have a substantial impact on wound healing. The applicant argued that adding further strata would not be feasible due to the limited patient numbers of each subtype and that the proposed stratification factors were considered most relevant prognostic factors. This was understood and agreed, however, sensitivity analyses of further possible confounding factors such as wound size, co-morbidities or study centre/regional effects were recommended. The CHMP also recommended considering seasonal change (see below).

Concerning the blinding, during the double-blind period, investigators and subjects were blinded to the treatment allocation. An independent unblinded biostatistics team maintained the randomisation scheme key in a separate location and was only to distribute this to approved personnel. All randomisation materials, including the key, were placed in an unblinded folder with restricted access, which remained restricted until after DBP completion and subsequent locking of the study database for the DBP. For emergency unblinding, a specific procedure was to be used.

There was an unblinded interim analysis performed by the unblinded biostatistician and evaluated by the IDMC for the purpose of a sample size re-estimation. This information was not shared with the Sponsor, the investigators, or any other parties. Details of the unblinded sample size re-estimation were described in the SAP. The sample size re-estimation was performed when approximately 50% of subjects had completed Day 45.

There was also an unblinded IDMC review of interim safety and betulin exposure data to confirm if the study could be expanded to allow inclusion of children to all ages (*i.e.*, ≥21 days and <4 years).

The final unblinding of the study did not take place until all subjects completed the DBP of the study, all queries were resolved, and the DBP database was locked.

The control gel used in this study matched Oleogel-S10 in terms of texture and visual appearance to allow for double blinding. The packaging for Oleogel-S10 gel and the control gel were identical.

Adequate procedures and measures seem to have been taken to ensure blinding, to the extent possible. As described above, using the pure vehicle (sunflower oil) was not considered possible due to different galenic properties, e.g., viscosity, that would have led to unblinding. Nevertheless, the use of a different 'control gel' can have implications for the interpretation of a difference observed between treatment arms. This is discussed further in relation to assessment of the supportive studies AHV-18-A and AHV-18-B and in the section *Discussion on clinical efficacy*.

In the OLP, all subjects were to be treated with Oleogel-S10 and there was no blinding applied during that period. Both the investigator and the subject were aware of the treatment to be received.

- **Statistical methods**

The study included interim safety reviews (blinded and unblinded), an interim analysis (IA) with sample size re-estimation for the Independent Data Monitoring Committee (IDMC), a final primary analysis of the double-blind treatment period and a follow-up analysis of the open-label treatment period. The follow-up analysis of the open-label treatment period was not included in the initial application.

Analysis populations

The Full Analysis Set (FAS) included all randomised subjects treated at least once with study medication. Subjects were analysed according to the randomised treatment regimen. The FAS was used as the primary analysis set for all efficacy analyses.

The Per-Protocol Set (PPS) included all subjects who met the eligibility criteria, received the planned study medication, and had reasonably adhered to all relevant protocol conditions. Subjects were analysed according to randomised treatment regimen. Supportive analyses of the primary efficacy endpoint and key secondary endpoints were conducted using the PPS.

The Completer Analysis Set (CAS) included all subjects from the FAS who did not discontinue the DBP of the study early, irrespective of the reason for discontinuation. Subjects were analysed according to the randomised treatment regimen. Supportive analyses of the primary efficacy endpoint and key secondary endpoints were conducted using the CAS.

Primary Efficacy Analyses

The primary efficacy endpoint was the proportion of subjects with first complete closure of the EB target wound within 45 days of treatment. The analysis of the primary efficacy endpoint was performed on the FAS.

The proportion of subjects with first complete closure of the EB target wound within 45 days based on clinical assessment by the investigator was initially compared using the Cochran-Mantel-Haenszel (CMH) test, stratified by EB subtype and target wound size class. The hypothesis was defined in terms of the common odds ratio (OR). H0: OR=1 versus H1: OR $\neq$ 1.

The analysis of the primary efficacy endpoint considered missing data with regard to wound closures as failures.

The final statistical analysis of the primary efficacy endpoint was performed based on the Cui, Hung, Wang (CHW) approach to adjust the estimates provided by the CMH test for the sample size re-estimation.

The statistical hypotheses were appropriate. The statistical analyses methods using the CMH were also appropriate for the type of endpoint. However, there were concerns raised related to the method of analysis using the Cui, Hung approach for controlling the type I error as a result of sample size reassessment, as outlined below.

The authors of the cited article report in Table A1 of this article presented simulations that describe the impact on the type I error. An approach using simulation is not acceptable to demonstrate type I error control as it cannot be guaranteed that the simulation parameters provided in the paper meet exactly the conditions of the trial. Table A1 was the 'old' method for which type I error was inflated. The 'new' method did appear to control the type I error. However, simulations are used for Table A2, but it was unclear whether the type I error was fixed and then the (conditional) power was computed for varying sample sizes (which seems to be the case). The paper stated, "Monte Carlo Simulation was conducted to estimate the size and gain in power for the new test". Table A2 showed the type I error to be exactly 0.025 (this could mean ≤0.025), but that was unclear. It is odd that the type I error is the same at all information fractions (the chance of a false positive would intuitively seem to be higher with a smaller information fraction). The method based on conditional power assumed a linear projection of the test statistic at the interim to the final. There was no evidence provided this projection was linear – that is, the slope of the projection, if nonlinear, could result in a smaller test statistic, and therefore a possible impact on the type I error (Prochan, Lan & Wittes: Statistical Monitoring of clinical trials, Springer 1980).

Therefore, further verification and justification that the type I error was adequately controlled was requested. Moreover, given the multiple amendments to the SAP and protocol and lack of guarantee that statistical hypotheses were conducted repeatedly, and a data driven approach could have been undertaken, the potential for a biased estimate with an increase in the type I error cannot be easily dismissed. Consequently, the applicant had not convincingly proven that the type I error control is

below 2.5%. The applicant was requested to analytically prove that the type I error was controlled based on the method used and the estimate of the treatment effect is unbiased. In any case, in a single pivotal trial, a type I error control should be proven to be well below 2.5%.

Subgroup analyses were performed on the randomisation stratification subgroups and other relevant subgroups specified in the SAP.

In addition to the primary analysis described above, sensitivity and supportive analyses for the primary efficacy endpoint were performed.

Examples of sensitivity and supportive analyses for the primary endpoint were:

- The primary efficacy endpoint analysis was repeated similarly using the CAS and the PPS. For these analyses the adjustment of the CMH estimates with CHW was not used.
- An additional analysis was performed using the CMH test on the FAS with the first complete wound closure evaluation based on the clinical assessment by the investigator and confirmed by a second observation after 7 days [+2 days] at the confirmation of complete closure (CCC) visit. For this analysis, the first wound closure will only be considered a success if both the clinical assessment and the second observation assess the wound as closed.
- If the analysis of the primary efficacy endpoint significantly favours the Oleogel-S10 group, a sensitivity analysis based on multiple imputation (MI) was conducted using the tipping point approach to assess the departures from missing at random (MAR) to missing not at random (MNAR) assumptions only for the FAS. The distribution of missing responses in the Oleogel-S10 group was assumed worse than for the control group, i.e., non-closure of the EB target wound. Variations in the assumptions for the MI were examined to adjust the imputed values until the statistical significance was lost (i.e., the p-value is greater than 0.05).

Several sensitivity analyses were performed. The sensitivity analyses use different analyses populations, different definitions of the endpoint and different approaches to the statistical analysis. Of particular interest for assessing the robustness of the results is the tipping point analysis, challenging the MAR assumption. The worst-case imputation is not expected to give significant results since this is an overly conservative analysis.

Secondary Efficacy Analyses

If the primary analysis of the primary efficacy endpoint demonstrated superiority at the 5% significance level, hierarchical confirmatory testing of the 6 key secondary endpoints was planned on the FAS and presented in this application. If the primary efficacy endpoint did not show superiority at the 5% significance level, the analysis of the 6 key secondary endpoints was planned as non-confirmatory and descriptive.

Missing data

With respect to the endpoint of proportion of first wound closure at a specific visit x (including the primary endpoint), early withdrawals and patients discontinued due to target wound infection that were not available at visit x were considered as failures (wound not closed) if the EB target wound was not assessed as closed at a prior visit. If the wound was closed at a prior visit, the patient was considered a responder for visit x, although he/she was withdrawn or discontinued before visit x.

Missing data was imputed as failures in the primary analysis. Since more subjects discontinued the double-blind phase in the control treatment group than in the Oleogel-S10 treatment group this might not be a conservative approach for the treatment comparison. Hence, the sensitivity analyses are of importance.

Interim Analysis

An unblinded interim analysis (IA) for sample size re-estimation took place when approximately 50% of subjects completed Day 45. The interim analysis included an unblinded sample size re-estimation using the CHW approach and a computation of the conditional power to check for futility [Cui 1999].

In addition to the analysis of the primary efficacy endpoint, the interim analysis also included results of some selected secondary efficacy endpoints (descriptive summaries only) to allow the IDMC the flexibility to recommend study continuation in the event that the conditional power was <80% with the maximum sample size allowed. Depending on the results of the sample size re-estimation, the IDMC could have recommended to continue with the initial sample size, increase the sample size, or stop the study for futility. The IDMC recommended to increase the sample size.

The CHW weighted test-statistics for consideration of sample size re-estimation did not require an adjustment of the significance level for the sample size increase after the IA.

However, as outlined above, the concerns related to adequate type I error control with the CHW method, as well as the multiple amendments to both the protocol and statistical analysis plan (SAP) and an absence of statistically compelling evidence from a single pivotal trial put the robustness of the efficacy results at question.

In the response, the applicant provided a clear list of the important protocol changes, and no issues arise. The increase in sample size as a consequence of the sample size re-estimation has been pre-specified in the original protocol. The Primary endpoint was updated in version 5 of the Protocol. The requirement for target wound to be confirmed as closed within 7 days after first closure was removed from the primary endpoint and included as a sensitivity analysis. This sensitivity analysis was consistent with the analysis of the new primary endpoint. Hence, this change is not considered to have altered any conclusions from the trial. The Cui-Hung-Wang method is agreed to adequately control the type-I error. Also see section 2.6.6 'Discussion on clinical efficacy'.

Results

- **Participant flow**

Double-Blind Phase
Overall, 199 (89.2%) subjects completed the DBP of the study (91.7%, Oleogel-S10 vs. 86.8%, control gel), and 24 (10.8%) subjects discontinued (8.3%, Oleogel-S10 vs. 13.2%, control gel). Thus, the rate of completion in the double-blind part of the study was high.

The most common reasons for discontinuation from the DBP were reasons classified as Other and withdrawal of consent.

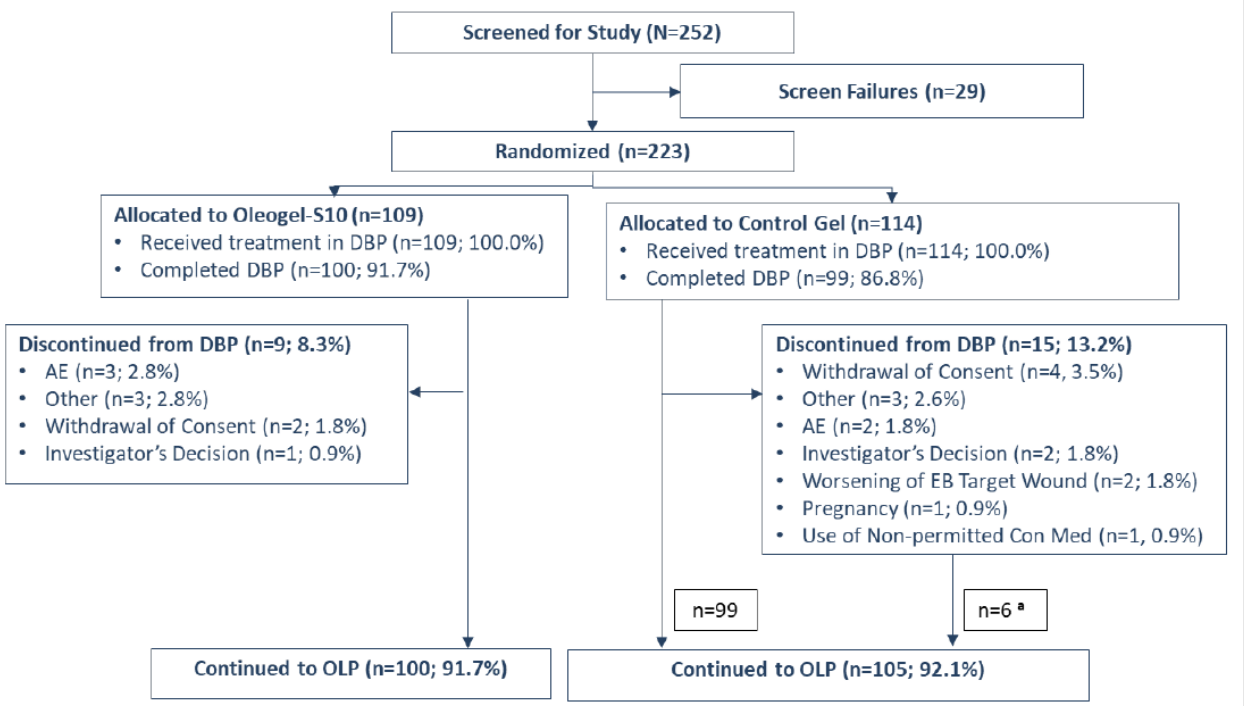
Six (2.7%) subjects, 3 (2.8%) in the Oleogel-S10 group and 3 (2.6%) in the control gel group, discontinued the DBP for reasons classified as Other. These included eligibility criteria not being met / randomisation error (n=3); anticipated use of non-permitted concomitant medication (n=1); relocation (n=1); and reasons related to the COVID-19 pandemic (n=1).

Another 6 (2.7%) subjects, 2 (1.8%) in the Oleogel-S10 group and 4 (3.5%) in the control gel group, discontinued the DBP due to withdrawn consent. Additional information was available for 3 of these 6 subjects; reasons for withdrawal included parental decision (n=1 per group) and dissatisfaction with treatment and difficulty reaching the clinic (n=1).

Five (2.2%) subjects, 3 (2.8%) in the Oleogel-S10 group and 2 (1.8%) in the control gel group, discontinued the DBP due to an AE.

Three (1.3%) subjects, 1 (0.9%) in the Oleogel-S10 group and 2 (1.8%) in the control gel group, discontinued the DBP at the investigator's discretion.

Figure 7. Flow Diagram of Subject Disposition: Double-Blind Phase (All Subjects)



Abbreviations: AE=adverse event; DBP=double-blind phase; EB=epidermolysis bullosa; n=number of subjects; OLP=open-label phase.

[a] Six subjects, all in the control gel group, discontinued the DBP prematurely due to worsening of the EB target wound status or due to EB target wound infection and continued into the OLP prematurely (at the investigator's discretion).

Open-Label Phase

Overall, the most common reason for discontinuation from the OLP was withdrawal of consent (12.1%). For 10 of these 12 subjects, withdrawal of consent was due to lack of efficacy (n=2, former Oleogel-S10 vs. n=3, former control gel), non-compliance (n=2, former Oleogel-S10), worsening of lesion (n=1, former Oleogel-S10), an AE (product adhesion issue; n=1, former control gel), and parental decision to withdraw due to itch (n=1, former control gel). Additional details were not provided for the other 17 subjects who withdrew consent.

Thirteen (5.8%) subjects, 6 (5.5%) in the former Oleogel-S10 group and 7 (6.1%) in the former control gel group, discontinued the OLP due to an AE. Ten (4.5%) subjects discontinued the OLP for reason classified as Other; e.g. ineffective treatment (n=3, all of whom had received control gel in the DBP). One case of fatal acute kidney injury was reported as an SAE (Subject former Oleogel-S10); however, the investigator reported the reason for discontinuation from the OLP as Other.

Table 4. Subject Disposition: Open-Label Phase (All Randomised Subjects)

	Former Oleogel-S10 (N=109) n (%)	Former Control Gel (N=114) n (%)	All Subjects (N=223) n (%)
Subjects who entered the OLP and received Oleogel-S10[a]	100 (91.7)	105 (92.1)	205 (91.9)
Subjects ongoing in the OLP	66 (60.6)	68 (59.6)	134 (60.1)
Subjects who completed the OLP	9 (8.3)	10 (8.8)	19 (8.5)
Subjects who discontinued from the OLP	25 (22.9)	27 (23.7)	52 (23.3)
Reason for discontinuation			
Withdrawal of consent	14 (12.8)	13 (11.4)	27 (12.1)
AE	6 (5.5)	7 (6.1)	13 (5.8)
Other	5 (4.6)	5 (4.4)	10 (4.5)
Noncompliance	0	1 (0.9)	1 (0.4)
Progression of medical condition	0	1 (0.9)	1 (0.4)

Abbreviations: AE=adverse event; DBP=double-blind phase; EB=epidermolysis bullosa; N=number of subjects in specific group; n=number of subjects; OLP=open-label phase.
[a] If a subject discontinued the DBP prematurely due to worsening of the EB target wound status or due to EB target wound infection, the subject could have continued into the OLP at the investigator's discretion.
Note: Calculation of percentages based on N of randomized subjects.

In data submitted with the Day 120 response, the applicant provided an update on the study. A total of 84 (41.0%) of 205 subjects have completed the OLP (including the 1 subject without an EOLP visit), and 62 subjects (30.2%) have discontinued the OLP; 60 subjects are currently continuing in the OLP and all of these have reached the Month 12 visit. Overall improvements seen with Oleogel-S10 treatment during the DBP were generally maintained during the OLP (mostly assessed at Month 3). Further data will be provided when available (i.e., by Q1 2023).

- **Recruitment**

Double-blind phase

A total of 252 subjects were screened (Figure 7); of these, 223 subjects were randomised to Oleogel-S10 (N=109) or control gel (N=114). Randomised subjects were enrolled across 49 sites in 26 countries and several geographic regions, including the US, Europe, South America, and Rest of World (Australia, Georgia, Hong Kong, Israel, Russia, Singapore, and Ukraine).

Open-label phase

A total of 205 (91.9%) subjects continued into the OLP and received treatment with Oleogel-S10. This included 199 subjects who completed the DBP and 6 subjects (all in the control gel group) who discontinued the DBP prematurely due to worsening of the EB target wound status or due to EB target wound infection and continued into the OLP prematurely (at the investigator's discretion). Results for the OLP are presented by former treatment group in the DBP (the denominator used was the total number of subjects enrolled in the DBP (N=223), rather than the number of subjects who entered the OLP (N=205)).

At the time of data cut-off for the initial report, 134 (60.1%) subjects were ongoing in the OLP (60.6%, former Oleogel-S10 vs. 59.6%, former control gel); 19 (8.5%) subjects had completed the

OLP (8.3%, former Oleogel-S10 vs. 8.8%, former control gel); and 52 (23.3%) subjects had discontinued the OLP (22.9%, former Oleogel-S10 vs. 23.7%, former control gel).

- **Conduct of the study**

Protocol deviations

Overall, 78 (35.0%) subjects, 35 (32.1%) in the Oleogel-S10 group and 43 (37.7%) in the control gel group, had a major protocol deviation related to the investigational product. The most common deviations of this nature were non-compliance with investigational product administration regimen (i.e., study medication not applied to all wounds, study medication applied on top of dressings, or frequency of dressing change >4 days) (17.4%, Oleogel-S10 vs. 21.9%, control gel) and incorrect (i.e., incomplete or missing) return of the investigational product kit / tubes (13.8%, Oleogel-S10 vs. 15.8%, control gel).

A total of 68 (30.5%) subjects, 31 (28.4%) in the Oleogel-S10 group and 37 (32.5%) in the control gel group, had a major protocol deviation related to use of prohibited concomitant treatment / prohibited dressings. This primarily involved use of prohibited wound dressings (26 [23.9%] subjects, Oleogel-S10 vs. 30 [26.3%] subjects, control gel).

Thirty-nine (17.5%) subjects, 21 (19.3%) in the Oleogel-S10 group and 18 (15.8%) in the control gel group, had a major protocol deviation due to a missed visit / visit outside window up to and including Day 45±7 days. These were primarily due to visits outside window (15.6%, Oleogel-S10 vs. 10.5%, control gel).

Twenty-seven (12.1%) subjects, 12 (11.0%) in the Oleogel-S10 group and 15 (13.2%) in the control gel group, had a major protocol deviation involving the ICF. Informed consent was obtained from all subjects in the study.

Six (2.7%) subjects, 4 (3.7%) in the Oleogel-S10 group and 2 (1.8%) in the control gel group, had a major protocol deviation classified as Other. These deviations involved disclosure of subject data / confidentiality breach, primarily related to inclusion of the subject's name on betulin samples sent for analysis.

- **Baseline data**

The baseline demographic characteristics of the treatment groups are displayed below.

Table 5. Demographics (Safety Analysis Set)

	Oleogel-S10 N=109	Control Gel N=114	All Subjects N=223
Age (years)			
Mean (SD)	16.8 (13.89)	16.5 (14.57)	16.7 (14.21)
Median	13.0	12.0	12.0
Min, max	1, 71	0[a], 81	0[a], 81
Age groups: n (%)			
0 to <4 years	7 (6.4)	10 (8.8)	17 (7.6)
4 to <12 years	42 (38.5)	43 (37.7)	85 (38.1)
12 to <18 years	25 (22.9)	29 (25.4)	54 (24.2)
≥18 years	35 (32.1)	32 (28.1)	67 (30.0)
Sex: n (%)			
Male	68 (62.4)	66 (57.9)	134 (60.1)
Female	41 (37.6)	48 (42.1)	89 (39.9)
Race: n (%)			
White	95 (87.2)	91 (79.8)	186 (83.4)
Black or African American	1 (0.9)	2 (1.8)	3 (1.3)
Asian	4 (3.7)	7 (6.1)	11 (4.9)
American Indian or Alaska Native	0	1 (0.9)	1 (0.4)
Unknown	1 (0.9)	1 (0.9)	2 (0.9)
NA[b]	4 (3.7)	8 (7.0)	12 (5.4)
Other[c]	4 (3.7)	4 (3.5)	8 (3.6)
Ethnicity: n (%)			
Hispanic or Latino	38 (34.9)	39 (34.2)	77 (34.5)
Not Hispanic or Latino	71 (65.1)	75 (65.8)	146 (65.5)
Geographic region: n (%)[d]			
Europe	48 (44.0)	55 (48.2)	103 (46.2)
South America	33 (30.3)	35 (30.7)	68 (30.5)
Rest of World	21 (19.3)	17 (14.9)	38 (17.0)
United States	7 (6.4)	7 (6.1)	14 (6.3)
BMI (kg/m^2)			
Mean (SD)	16.05 (4.979)	16.31 (5.037)	16.18 (4.999)
Median	14.60	14.60	14.60
Min, max	10.2, 43.0	9.3, 33.0	9.3, 43.0
BMI group: n (%)[e]			
Underweight	56 (51.4)	59 (51.8)	115 (51.6)
Normal weight	45 (41.3)	41 (36.0)	86 (38.6)
Overweight	5 (4.6)	6 (5.3)	11 (4.9)
Obese	3 (2.8)	8 (7.0)	11 (4.9)

Abbreviations: BMI=body mass index; Max=maximum; Min=minimum; N=number of subjects in specific group; n=number of subjects; NA=not applicable; SD=standard deviation.

[a] 6 months.

[b] Not applicable (NA) applies in countries where the collection of race was prohibited.

[c] Other applies if none of the races listed were appropriate or if the subject was of mixed race.

[d] Based on study site locations.

[e] *Adults*: underweight (<18.5 kg/m^2); normal (18.5 to 24.9 kg/m^2); overweight (25 to 29.9 kg/m^2); obese (≥30 kg/m^2). *Pediatrics*: underweight: <5th percentile; normal weight: ≥5th percentile to <85th percentile; overweight: ≥85th to ≤94th percentiles; obese: ≥95th percentile.

In the Safety Analysis Set, 60% of subjects were male and 40% were female. The median age was 12 years (range 6 months to 81 years). Divided by age categories, 8% of subjects were 0 to <4 years of age, 38% were 4 to <12 years, 24% were 12 to <18 years, and 30% were ⩾18 years of age. Of the 67 subjects who were ⩾18 years of age, 3 subjects were 65 years of age or older. Thus, the majority of subjects were in the age range 4-12 years and very few subjects were elderly (only three aged above 65 years). This reflects a population with severe EB, *i.e.,* that the condition is present from birth and that many EB patients with severe forms like DEB or JEB have a limited life span.

The majority (>80%) of subjects were White. Geographic regions in which subjects were enrolled (based on study site locations) included Europe (46%), South America (30.5%), Rest of World (17%), and the US (6%).

The mean BMI of subjects was 16.2 kg/m^2. Approximately half (51.6%) of subjects were underweight; 38.6% had normal weight; 5% were overweight; and 5% were obese. This also reflects a severely affected EB population, where many patients have nutritional problems.

One-third of subjects had a low albumin at baseline. Nearly two-thirds of the study population was anemic at baseline (defined differentially based on age and/or gender). The majority of subjects in the study population had normal renal function at baseline.

Overall, the demographics were well balanced between the two treatment groups.

The reported comorbidities (e.g., gastrointestinal disorders, blood and lymphatic system disorders, skin disorders other than EB, metabolism and nutrition disorders, infections) are generally anticipated in subjects with EB and are related to the disease and its complications. Medical and surgical histories were generally well balanced between the treatment groups, with some imbalances in pruritus and pain.

Prior and concomitant medication use were overall well balanced between treatment groups, although the proportions of subjects who used a dermatological medication both prior to and during the study were lower in the Oleogel-S10 group than in the control gel group.

The baseline clinical/disease characteristics of the treatment groups are displayed below.

Table 6. Epidermolysis Bullosa Subtype and Method of Diagnosis (Safety Analysis Set)

Parameter	Category	Oleogel-S10 N=109 n (%)	Control Gel N=114 n (%)	All Subjects N=223 n (%)
EB subtype				
RDEB	Total	91 (83.5)	84 (73.7)	175 (78.5)
	RDEB, generalized severe	62 (56.9)	62 (54.4)	124 (55.6)
	RDEB, generalized intermediate	23 (21.1)	16 (14.0)	39 (17.5)
	RDEB, localized	3 (2.8)	4 (3.5)	7 (3.1)
	RDEB, other	3 (2.8)	2 (1.8)	5 (2.2)
DDEB	DDEB	6 (5.5)	14 (12.3)	20 (9.0)
JEB	Total	11 (10.1)	15 (13.2)	26 (11.7)
	JEB, generalized severe	0	2 (1.8)	2 (0.9)
	JEB, generalized intermediate	8 (7.3)	9 (7.9)	17 (7.6)
	JEB, localized	1 (0.9)	0	1 (0.4)
	JEB, other	2 (1.8)	4 (3.5)	6 (2.7)
EBS	EBS, localized	1 (0.9)	1 (0.9)	2 (0.9)
Kindler	Kindler	0	0	0
Method of diagnosis	Genetic mutation identified	67 (61.5)	62 (54.4)	129 (57.8)
	Clinical diagnosis only	25 (22.9)	24 (21.1)	49 (22.0)
	Immunofluorescence mapping or electron microscopy	16 (14.7)	25 (21.9)	41 (18.4)
	Other	1 (0.9)	3 (2.6)	4 (1.8)

Abbreviations: DDEB=dominant dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; EBS=epidermolysis bullosa simplex; JEB=junctional epidermolysis bullosa; N=number of subjects in specific group; n=number of subjects; RDEB=recessive dystrophic epidermolysis bullosa.

In the Safety Analysis Set, 87% subjects had the DEB subtype of EB; of these, 175 (78.5%) subjects had RDEB and 20 (9%) subjects had DDEB. Twenty-six (11.7%) subjects had JEB. Two (0.9%) subjects had EBS, since implementation of Version 4.0 of the protocol, subjects with EBS were excluded from study participation. None of the subjects had Kindler syndrome.

Most of the 175 subjects with RDEB had generalized RDEB classified as severe or intermediate. Of the 26 subjects with JEB, most had generalized JEB classified as severe or intermediate.

EB subtype identification was based on genetic testing in 129 (57.8%) subjects, clinical diagnosis only in 49 (22.0%) subjects, immunofluorescence mapping or electron microscopy in 41 (18.4%) subjects, and method classified as Other in 4 (1.8%) subjects.

Justifications for clinical diagnosis only was requested. In the response, the applicant clarified that since genetic confirmation of the EB subtype could only be offered to subjects participating in BEB-13 at a later stage of the study due to operational reasons, an additional 4 subjects now have genetic confirmation of diagnosis, which reduced the proportion with clinical diagnosis only to 20.2%. In addition, since the OLP Month 12 Efficacy DBL genetic testing results have been received from the central laboratory for a further 11 subjects. Approximately 8 additional subjects are planned to undergo genetic testing prior to final database lock. Thus, it is anticipated that for the final CSR the proportion of subjects with clinical diagnosis only will be reduced to approximately 12%. This is acknowledged.

According to the applicant, a clinical diagnosis was in some cases seemingly only based on the presence of one clinical feature, e.g., anaemia or of dystrophic nails. This may seem very limited to

establish an EB diagnosis, however, for inclusion in the study, criteria based on a target wound of specific size and duration was also required.

It is also noted that according to the EB Consensus (Fine et al., 2014), which was accepted as the global standard at the time the study protocol was written, genetic confirmation was not required in order to make the diagnosis of EB. Even the current revised consensus classification of inherited EB is still primarily clinically oriented, as the EB classification is complex (Has, 2020).

It is acknowledged that a specific diagnosis of EB subtype can be challenging, and it is agreed that the chance of misdiagnosis or misclassification is low. The applicant used the available guideline and methods at the time when the pivotal study BEB-13 was planned.

The DEB and JEB disease subtypes and methods of diagnosis were generally well balanced between the 2 treatment groups. However, within the DEB subtype, the Oleogel-S10 group had a higher proportion of subjects with RDEB compared to the control gel (83.5%, Oleogel-S10 vs. 73.7%, control gel) and a lower proportion of subjects with DDEB (5.5%, Oleogel-S10 vs. 12.3%, control gel).

Target Wound characteristics

Table 7. Summary of Target Wounds (Safety Analysis Set)

Parameter	Category	Oleogel-S10 N=109	Control Gel N=114	All Subjects N=223
Partial-thickness wound: n (%)	Yes	109 (100)	113 (99.1)	222 (99.6)
	No	0	1 (0.9)	1 (0.4)
Wound size group: n (%)	10 to <20 cm^2	69 (63.3)	75 (65.8)	144 (64.6)
	20 to <30 cm^2	23 (21.1)	24 (21.1)	47 (21.1)
	30 to 50 cm^2	17 (15.6)	15 (13.2)	32 (14.3)
Wound size (cm^2)	n	109	114	223
	Mean (SD)	18.99 (8.640)	19.41 (10.104)	19.20 (9.398)
	Median	16.00	15.45	15.60
	Min, max	10.0, 45.6	10.0, 49.5	10.0, 49.5
Age of the wound (days)	n	109	113	222
	Mean (SD)	124.3 (327.44)	126.4 (459.99)	125.4 (399.54)
	Median	39.0	32.0	35.5
	Min, max	21, 2920	21, 4745	21, 4745
Age of the wound subset (days) [a]	n	101	107	208
	Mean (SD)	59.4 (50.47)	60.6 (57.25)	60.0 (53.94)
	Median	36.0	30.0	32.0
	Min, max	21, 230	21, 250	21, 250

Abbreviations: Max=maximum; Min=minimum; N=number of subjects in specific group; n=number of subjects in the analysis; SD=standard deviation.

[a] Subset of target wounds defined as wounds with an age limit of 9 months (approximately 270 days).

Overall, the mean (SD) size of the target wound in the Safety Analysis Set was 19.20 (9.4) cm^2 (range 10 cm^2 to 49.5 cm^2). The majority (64.6%) of subjects had a target wound between 10 to <20 cm^2; 21.1% between 20 to <30 cm^2, and 14.3% between 30 to 50 cm^2.

Mean (SD) age of the target wound was 125.4 (399.5) days (range 21 days to 4745 days); median wound age was 35.5 days. Fourteen subjects (n=8, Oleogel-S10 vs. n=6, control gel) with wounds

over 9 months of age (range: 11.5 to 156 months) were enrolled prior to the implementation of Version 4.0 of the protocol, which capped eligibility for the target wound at a maximum of 9 months for wound age. Hence, the overall median wound age is more meaningful than the mean wound age. In the subset of subjects with a target wound age of no more than 9 months (N=208), median wound age was 32.0 days.

The most common locations of target wounds were the lower leg (20.2%), knee (13.5%), and thigh (13.5%). Target wound size was well balanced between the two treatment groups; however, the median wound age was slightly greater in the Oleogel-S10 group (39 days, vs. 32 days for control gel). It was not fully clear how large body surface area in total that was treated. This was clarified in a safety question.

In the Safety Analysis Set, the 1 subject reported as not having a partial-thickness wound was 1 of 3 subjects who did not meet eligibility criteria for a partial-thickness target wound. These 3 subjects were randomized in error and subsequently withdrawn shortly after randomization; they were excluded from the PPS.

In the Safety Analysis Set, most (78.0%) of the subjects used a permitted contact layer / dressing on the target wound up to 45 and 90 days on study. Results were well balanced between treatment groups. The use of nonpermitted wound dressings is described below.

The majority of subjects changed their dressings daily (44.4%) or every 2 days (37.7%). Most subjects (91%) used the same type of dressing for all of their wounds (*i.e.*, target, additional, and other). Results were similar between the two treatment groups.

Characteristics of additional wounds matching Target wound criteria

On Day 0, the investigator selected the EB target wound and up to 4 additional wounds that met target wound criteria. A total of 63 subjects had at least 1 additional wound other than the EB target wound that met target wound criteria. Most of these subjects had no more than 2 additional wounds that met the criteria. A higher proportion of subjects had 2 or more additional wounds in the control gel group (13/30, 43.3%) compared to the Oleogel-S10 group (8/33, 24.2%). The median age of additional wounds was also greater in the control gel group (56 days vs. 41 days, Oleogel-S10).

Stratification Based on Disease Subtype and Size of Target Wound

In the Safety Analysis Set, the 2 largest stratification groups (based on actual data) were DEB 10 to <20 cm^2 (128 [57.4%] subjects) and DEB 20 to <30 cm^2 (43 [19.3%] subjects) (Table 8). Stratification was well balanced between the 2 treatment groups.

Table 8. Stratification Based on Disease Subtype and Size of Target Wound (Safety Analysis Set)

	Oleogel-S10 N=109 n (%)	Control Gel N=114 n (%)	All Subjects N=223 n (%)
Stratification factor (based on actual data)[a]			
DEB 10 to <20 cm^2	62 (56.9)	66 (57.9)	128 (57.4)
DEB 20 to <30 cm^2	22 (20.2)	21 (18.4)	43 (19.3)
DEB 30 to 50 cm^2	14 (12.8)	12 (10.5)	26 (11.7)
JEB/Kindler[b] 10 to <20 cm^2	7 (6.4)	9 (7.9)	16 (7.2)
JEB/Kindler[b] 20 to <30 cm^2	1 (0.9)	3 (2.6)	4 (1.8)
JEB/Kindler[b] 30 to 50 cm^2	3 (2.8)	3 (2.6)	6 (2.7)

Abbreviations: DEB=dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; EBS=epidermolysis bullosa simplex; JEB=junctional epidermolysis bullosa; N=number of subjects in specific group; n=number of subjects.
[a] All stratified analyses were based on actual stratification data (i.e., not on randomized strata); EBS subjects were included in the strata defined by the DEB subtype.
[b] There were no subjects with the Kindler EB subtype. Kindler is reported here because it was part of the randomization strata.

Other Baseline Wound Characteristics

Using the full EBDASI, total wound burden is rated as mild (EBDASI total score 0-42), moderate (EBDASI total score 43-106) or severe (EBDASI total score >106). However, since only Section I of the EBDASI assessing Skin Activity (blistering/erosions/crusting) was used in this study, it was not possible for subjects to be classified as having a severe total wound burden. The maximum possible score of the partial EBDASI based on Skin Activity only was 100, which falls below the score needed to be classified as severe (>106).

In the Full Analysis Set, the mean EBDASI skin activity score was 19.6 (SD: 11.91) at baseline.

The majority (57.8%) of subjects had a total BSAP <10% at baseline. More than half of the subjects had a total wound area <0.1 m^2 (55.2%); 34.5% had a total wound area between 0.1 m^2 and 0.3 m^2. Baseline characteristics displayed in

Table 9 were generally well balanced between treatment groups.

Table 9. Other Baseline Wound Characteristics (Safety Analysis Set)

	Oleogel-S10 N=109 n (%)	Control Gel N=114 n (%)	All Subjects N=223 n (%)
Total wound burden (EBDASI)[a,b]			
Mild	101 (92.7)	109 (95.6)	210 (94.2)
Moderate	7 (6.4)	4 (3.5)	11 (4.9)
Severe	0	0	0
Missing	1 (0.9)	1 (0.9)	2 (0.9)
Total wound burden (EBDASI)[c]			
≤1st tertile	34 (31.2)	43 (37.7)	77 (34.5)
1st – 2nd tertile	38 (34.9)	34 (29.8)	72 (32.3)
>3rd tertile	36 (33.0)	36 (31.6)	72 (32.3)
Missing	1 (0.9)	1 (0.9)	2 (0.9)
Total BSAP			
<10%	58 (53.2)	71 (62.3)	129 (57.8)
10-25%	38 (34.9)	27 (23.7)	65 (29.1)
>25%	13 (11.9)	15 (13.2)	28 (12.6)
Missing	0	1 (0.9)	1 (0.4)
Total wound area (m^2)			
<0.1	58 (53.2)	65 (57.0)	123 (55.2)
0.1 – 0.3	40 (36.7)	37 (32.5)	77 (34.5)
>0.3	11 (10.1)	11 (9.6)	22 (9.9)
Missing	0	1 (0.9)	1 (0.4)

Abbreviations: BSAP=body surface area percentage; EBDASI=Epidermolysis Bullosa Disease Activity and Scarring Index; N=number of subjects in specific group; n=number of subjects.

[a] The evaluation of total wound burden was based on clinical assessment using the EBDASI skin activity score (Section I: blistering/erosions/crusting). This was scored from 0 to 10 for each of 10 anatomical locations.

[b] Total wound burden: mild (EBDASI total score 0-42), moderate (EBDASI total score 43-106) or severe (EBDASI total score >106). Since only the Section I Skin Activity part of the EBDASI was used in the assessment of total wound burden (per footnote a), it was not possible for subjects to be classified as having a severe total wound burden. The maximum possible score in the partial EBDASI assessment was 100, which falls below the score needed to be classified as severe (>106).

[c] Tertiles are based on the distribution of baseline EBDASI total activity scores.

- **Numbers analysed**

All of the randomised subjects (N=223) were included in the Safety Analysis Set and the FAS. One hundred eighty-five (83.0%) subjects were included in the PPS, and 199 (89.2%) subjects were included in the CAS.

Table 10. Analysis Sets (All Randomized Subjects)

	Oleogel-S10 N=109 n (%)	Control Gel N=114 n (%)	All Subjects N=223 n (%)
Safety Analysis Set	109 (100.0)	114 (100.0)	223 (100.0)
FAS	109 (100.0)	114 (100.0)	223 (100.0)
PPS	92 (84.4)	93 (81.6)	185 (83.0)
CAS	100 (91.7)	99 (86.8)	199 (89.2)

Abbreviations: CAS=Completer Analysis Set; FAS=Full Analysis Set; N=number of subjects in specific group; n=number of subjects; PPS=Per-Protocol Set.

Subjects were excluded from the PPS based upon review of protocol deviations and case-by-case decisions made during the blind data review meeting held prior to database lock and unblinding of the DBP. Subjects may have been excluded from the PPS for more than one reason.

A total of 38 (17.0%) subjects, 17 (15.6%) in the Oleogel-S10 group and 21 (18.4%) in the control gel group, were excluded from the PPS. The most common reasons for exclusion from the PPS were missed visit(s) up to and including Day 45 and missed closure of wound clinical assessment up to and including Day 45.

Ten (4.5%) subjects, 7 (6.4%) in the Oleogel-S10 group and 3 (2.6%) in the control gel group, were excluded from the PPS for "other major protocol deviations which were regarded as clinically relevant." These involved treatment non-compliance, incorrect administration of investigational product, incorrect return of investigational product, and tube of investigational product used more than once.

The CAS includes all subjects from the FAS who did not discontinue the DBP of the study early, irrespective of the reason for discontinuation.

- **Outcomes and estimation**

Primary endpoint

Table 11. Primary Efficacy Analysis: Proportion of Subjects with First Complete Closure of Target Wound within 45 Days Based on Clinical Assessment (Full Analysis Set)

	Oleogel-S10 N=109	Control Gel N=114
Closure status: n (%)		
Closure	45 (41.3)	33 (28.9)
Nonclosure	64 (58.7)	81 (71.1)
Relative risk [95% CI][a]	1.44 [1.01, 2.05]	
Odds ratio [95% CI]	1.84 [1.02, 3.30]	
CMH test statistic		
p-value[b]	0.041	
CHW adjustment		
p-value[c]	0.013	

Abbreviations: CI=confidence interval; CHW=Cui, Hung, Wang; CMH=Cochran-Mantel-Haenszel; EB=epidermolysis bullosa; N=number of subjects in specific group, n=number of subjects in the analysis.

[a] Relative risk is the ratio of probabilities for first complete closure of target wound per treatments.

[b] Parameter and model estimates were based on a CMH test stratified by EB subtype and target wound size class. An odds ratio >1 represents a favorable outcome for Oleogel-S10 treatment

[c] p-value adjusted with the CHW method using the CMH test statistics. The CMH test statistics based on a test stratified by EB subtype and target wound size class were estimated separately for subjects assessed before (Stage 1) and after (Stage 2) the interim analysis for sample size re-estimation. The stagewise normal z-statistics were approximated using the square root of the chi-squared CMH statistics with 1 degree of freedom and pooled to derive the CHW statistic for calculating the adjusted p-value.

The primary efficacy endpoint was met as the proportion of subjects with first complete closure of the EB target wound within 45 days of initiating treatment was higher in the Oleogel-S10 group (41.3%) compared to the control gel group (28.9%). This finding was statistically significant in favour of Oleogel-S10 based on the CHW method using the CMH test statistics (p=0.013) and based on the unadjusted CMH test (p=0.041).

Even if study BEB-13 met its primary endpoint the difference between treatments is however small (12.4 % units) and the results are not of high statistical significance. Results for the PPS population did not reach statistical significance (p=0.151) even if the magnitude of the difference was almost similar to the FAS (Oleogel-S10 42.4% vs. control gel 33.3%, respectively).

Since the primary analysis used a non-responder imputation for missing data and the amount of missing data was larger in the control treatment group than in the Oleogel-S10 treatment group, this was not considered a sufficiently conservative analysis. The tipping point analysis described in the SAP using multiple imputation (MI) is considered of particular interest. The MI analysis without tipping gave borderline significant results and switching the result for only one control patient resulted in a non-significant p-value. Hence, the robustness of the results was questioned, and the applicant was asked to discuss this.

In the D120 response, the applicant provided further information on amount of missing data at the day 45 visit arguing that the amount and reasons of missing data was similar in the two treatment groups. This is agreed. However, this is no guarantee that data are Missing at Random (MAR). There could still

be mechanisms deviating from the MAR assumption that would create bias in the comparison. Hence, the tipping point analysis evaluating robustness to any such bias is still considered important.
In the pre-planned tipping point analysis, the MI analysis on original data gave borderline significant results and switching the result for only one control patient resulted in a non-significant p-value.
The applicant argued that the CMH (Cochran-Mantel-Haenszel) test did not work well with small strata and has provided post hoc analyses combining or removing the three JEB/Kindler strata. In those analyses the p-value was slightly smaller and switching one subject did not yield non-significant results (however switching two subjects did). The applicant hence considered that the primary analysis was robust and driven by the largest cohort, namely the dystrophic EB subtype. This was not agreed by the CHMP. Those analyses were performed post-hoc and were not prespecified in the SAP.

In conclusion, the primary analysis was borderline significant. The amount and reason of missing data at day 45 was similar between the two treatment groups, however the analysis still depends on the assumption of MAR. This assumption cannot be verified, and the results are not very robust when those assumptions are challenged with the tipping point analysis.

Although the primary endpoint was statistically significant at the nominal (2 sided) 5% level, this was not statistically compelling in the context of a single pivotal trial. This compounded with several amendments to the SAP and protocol as well as concerns about type I error control with the CHW method, raised questions around the integrity of the data. Both p-values of 0.041 and 0.013 as reported above are questionable. In the D120 response, justification for adequate type I error control with the CHW method was provided. Hence, even if concerns related to the type I error control have been alleviated, it was still questioned whether the results are sufficiently robust and compelling, thus a major objection was raised.

The non-responder imputation was questioned for one particular control patient who had the Day 45 investigator assessment of closure performed outside of the visit window but the patient reported that the target wound had closed within the visit window. At the oral explanation and upon request from the CHMP, the applicant presented results of the primary efficacy analysis switching this one single patient from non-responder to responder using the CHW methodology. This analysis demonstrated that the p-value remained statistically significant (i.e., p-value=0.021) with only small changes to point estimate and confidence interval.

The results presented by stratification factor are presented in Table 12.

Table 12. Proportion of Subjects with First Complete Closure of Target Wound within Day 45 by Stratification Factor (Full Analysis Set)

	Oleogel-S10			Control Gel		
	N	Closure n (%)	Nonclosure n (%)	N	Closure n (%)	Nonclosure n (%)
Overall closure status	109	45 (41.3)	64 (58.7)	114	33 (28.9)	81 (71.1)
DEB 10 to <20 cm^2	62	34 (54.8)	28 (45.2)	66	26 (39.4)	40 (60.6)
DEB 20 to <30 cm^2	22	6 (27.3)	16 (72.7)	21	2 (9.5)	19 (90.5)
DEB 30 to 50 cm^2	14	3 (21.4)	11 (78.6)	12	1 (8.3)	11 (91.7)
JEB/Kindler 10 to <20 cm^2	7	1 (14.3)	6 (85.7)	9	4 (44.4)	5 (55.6)
JEB/Kindler 20 to <30 cm^2	1	0	1 (100)	3	0	3 (100)
JEB/Kindler 30 to <50 cm^2	3	1 (33.3)	2 (66.7)	3	0	3 (100)

Abbreviations: DEB=dystrophic epidermolysis bullosa; JEB=junctional epidermolysis bullosa; N=number of subjects in specific group, n=number of subjects in the analysis.
Note: Subjects with the epidermolysis bullosa simplex subtype (n=2) were included in the strata defined by the DEB subtype (the largest subtype).

For the above presentation based on stratification factors, the DEB strata showed higher rates of wound closure for Oleogel-S10 vs. control gel across wound size. For the JEB/Kindler sub-types, however, the patient numbers were much smaller (n=26 in total) and conclusions are difficult to make.

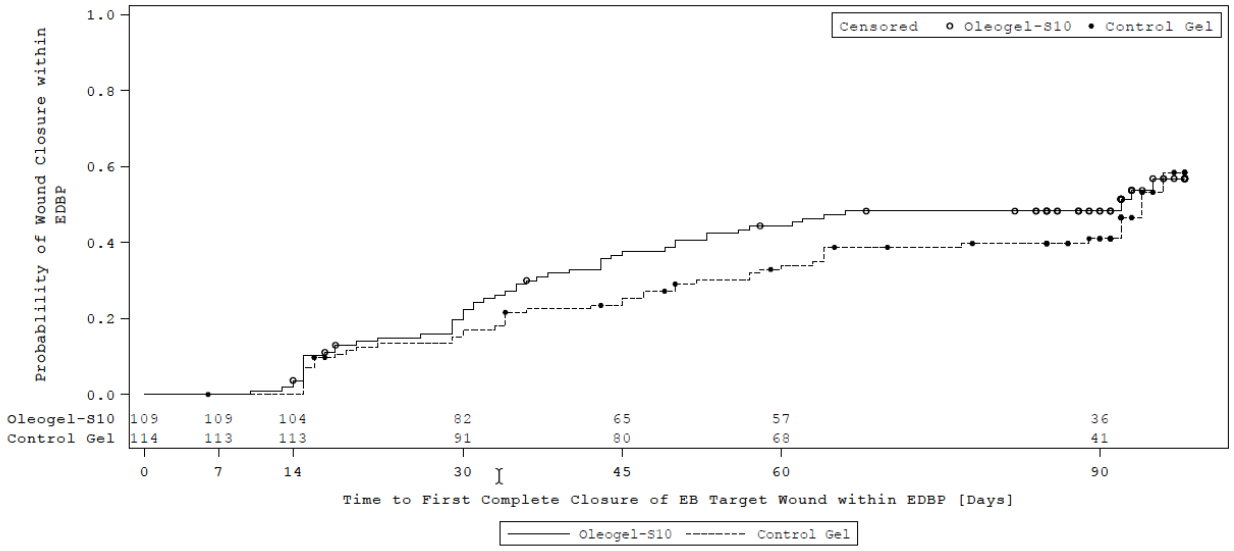
Secondary endpoints

The applicant had defined six 'key' secondary endpoints of the total 18 secondary endpoints in the protocol. The results for the first key secondary endpoint were not statistically significant, hence, the results for the key secondary endpoints are not confirmatory. The p-values reported for other analyses of the key secondary endpoints are not adjusted for multiplicity. The method of multiplicity adjustment was hierarchical: if the first secondary endpoint was not statistically significant, statistical testing on the remaining would not be possible. Consequently, all other secondary endpoints for the purpose of statistical inference were not considered.

Time to First Complete Closure of the EB Target Wound as by Clinical Assessment until EDBP (Day 90)

For the first key secondary endpoint (time to first complete closure of the EB target wound as evidenced by clinical assessment within 90 days) the difference between the 2 treatment groups was not statistically significant (p=0.302). The median time to closure within 90 days was similar between treatment groups (92 days Oleogel-S10 and 94 days control gel). This was the case also for the CAS and PPS populations.

Figure 8. Time to First Complete Closure of the Target Wound within 90 Days (Full Analysis Set)



Abbreviations: DBP=double-blind phase; EB=epidermolysis bullosa; EDBP=end of double-blind phase.
Notes: If wound closure did not occur prior to EDBP, time to first complete closure was censored at the EDBP visit date or at last assessment date of the EDBP in case of early discontinuation from DBP.
Numbers at the bottom of the figure represent the number of subjects without a first complete closure of EB target wound and not discontinued from the DBP at the specific time point.
The Day 7 efficacy assessments were not performed if the visit was conducted by phone. A large proportion of Day 7 visits were conducted by phone; therefore, Day 7 results are not presented in this figure.

Proportion of Subjects with First Complete Closure of the Target Wound Within 90 Days

The second key secondary endpoint was the proportion of subjects with first complete closure of the EB target wound within 90 days of treatment based on clinical assessment by the investigator. Within 90 days, 50.5% of subjects in the Oleogel-S10 group achieved first EB target wound closure vs. 43.9% of subjects in the control gel group. The difference in proportions was not statistically significant based on the CMH test stratified by EB subtype and target wound size class (p=0.296).

In both treatment groups, the percentages of subjects with first complete closure within 90 days were somewhat higher than those observed for first complete closure within 45 days, representing additional target wound closure in 27 total subjects (10 subjects, Oleogel-S10; 17 subjects, control gel) between Day 45 and Day 90.

Incidence of Target Wound Infection Between Baseline and Day 90

Overall, as evidenced by wound infection AEs and/or use of topical and/or systemic antibiotics (related to wound infection), 7 subjects (3.1%) had a target wound infection between baseline and Day 90. Of these, two subjects treated with Oleogel-S10 (1.8%) experienced a target wound infection between baseline and Day 90 compared with five subjects treated with control gel (4.4%) (p=0.326).

After database lock it was noted that an AE of wound infection in one subject was incorrectly reported in a target wound; this wound was in fact an infection in a nontarget, 'other' wound (which was bacteriologically confirmed and mild in severity). Therefore, only 1 Oleogel-S10 subject (0.9%) had a target wound infection between baseline and Day 90. A post hoc analysis to reflect the correct categorisation of the location of the wound infection (1 [0.9%] Oleogel-S10 subject vs. 5 [4.4%] control gel subjects; p=0.142) was presented.

One (0.9%) target wound infection in subjects treated with Oleogel-S10 was bacteriologically confirmed and 2 of 5 (1.8%) target wound infections in subjects treated with control gel were bacteriologically confirmed. Both target wound infections in Oleogel-S10 subjects and 3 of the 5 target wound infections in control gel subjects were treated with concomitant medications.

Incidence of Nontarget Wound Infections Between Baseline and Day 90

Wounds that met target criteria but were not selected as target wound were considered 'additional' wounds and wounds that did not meet target wound criteria were considered 'other' wounds.

The incidence of infections in nontarget wounds between baseline and Day 90 was assessed. Very few (3 [1.3%]) subjects had infections in 'additional' wounds that met target wound criteria within Day 90: 2 (1.8%) subjects in the Oleogel-S10 group and 1 (0.9%) subject in the control gel group.

Thirty subjects (13.5%) had wound infections in 'other' wounds within Day 90: 12 (11.0%) subjects in the Oleogel-S10 group and 18 (15.8%) subjects in the control gel group. Eleven of the 12 other wound infections in subjects treated with Oleogel-S10 were evidenced by AEs and 5 were bacteriologically confirmed. All but one (n=11) of the other wound infections in Oleogel-S10 subjects were treated with concomitant medications.

Maximum Severity of EB Target Wound Infection Between Baseline and Day 90

Based on AE reporting of PTs for wound infection only, 5 subjects had a target wound infection between baseline and Day 90. Of these, the infection reported by the 1 subject who received Oleogel-S10 was classified as mild, and those reported by subjects who received control gel were moderate (3 subjects) or severe (1 subject)). Each of these wounds was treated with a concomitant medication.

Maximum Severity of Non-target Wound Infections Between Baseline and Day 90

Based on AE reporting of PTs for wound infection only, the maximum severity of infections in 'additional' wounds that met target wound criteria was mild (n=1) or moderate (n=1), both in subjects in the Oleogel-S10 group.

For other wounds (that did not meet target wound criteria), the maximum severity of infections was mostly mild (8 [7.3%] Oleogel-S10 subjects; 6 [5.3%] control gel subjects), with moderate wound infections in 2 (1.8%) Oleogel-S10 subjects and 6 (5.3%) control gel subjects, and severe wound infections in 1 (0.9%) subject in the Oleogel-S10 group and 3 (2.6%) subjects in the control gel group.

Change from Baseline in Total Body Wound Burden at Day 90

The evaluation of TBWB was based on clinical assessment using Section I (skin) of the EBDASI. The key secondary efficacy endpoint for change from baseline in TBWB was assessed at Day 90. The EBDASI skin activity score (Section I skin activity: blistering/erosions/crusting) was scored from 0 to 10 for each of 10 anatomical locations (the anogenital and buttocks regions were excluded); therefore, the skin activity score could range from 0 to 100, with lower scores indicative of less wound burden.

For the key secondary efficacy endpoint analysis at Day 90, a reduction from baseline in the EBDASI skin activity score was observed in both groups (-0.44 Oleogel-S10 and -0.56 control gel); the difference between the treatment groups was negligible (0.12; p=0.887). Results across all time points in Table 13 suggest that there was reduction in the TBWB earlier in the course of treatment with Oleogel-S10, with a negligible difference observed at Day 90 compared to the control gel group.

Table 13. Change from Baseline in Total Body Wound Burden Based on EBDASI Skin Activity Score at Day 90 – ANCOVA Model (Full Analysis Set)

Visit	Statistics[a]	Oleogel-S10 (N=109)	Control Gel (N=114)
Day 30	n	99	99
	LS Mean (SE)	-0.64 (0.84)	-0.59 (0.81)
	95% CI of LS Mean	[-2.30, 1.02]	[-2.19, 1.01]
	Oleogel-S10 compared to Control Gel		
	Difference in LS Means (SE)	-0.06 (0.87)	
	95% CI of Difference in LS Means	[-1.76, 1.65]	
	p-value	0.949	
	p-value		
	Treatment group	0.949	
	EB subtype	0.036	
	Target Wound Size class	0.022	
	EBDASI score at baseline	<0.001	
Day 60	n	91	96
	LS Mean (SE)	-1.08 (0.91)	0.09 (0.87)
	95% CI of LS Mean	[-2.88, 0.72]	[-1.63, 1.82]
	Oleogel-S10 compared to Control Gel		
	Difference in LS Means (SE)	-1.17 (0.92)	
	95% CI of Difference in LS Means	[-2.98, 0.63]	
	p-value	0.202	
	p-value		
	Treatment group	0.202	
	EB subtype	0.007	
	Target Wound Size class	0.085	
	EBDASI score at baseline	<0.001	

Visit	Statistics[a]	Oleogel-S10 (N=109)	Control Gel (N=114)
Day 90	n	84	85
	LS Mean (SE)	-0.44 (0.90)	-0.56 (0.85)
	95% CI of LS Mean	[-2.22, 1.35]	[-2.25, 1.12]
	Oleogel-S10 compared to Control Gel		
	Difference in LS Means (SE)	0.12 (0.86)	
	95% CI of Difference in LS Means	[-1.58, 1.83]	
	p-value	0.887	
	p-value		
	Treatment group	0.887	
	EB subtype	<0.001	
	Target Wound Size class	0.050	
	EBDASI score at baseline	<0.001	

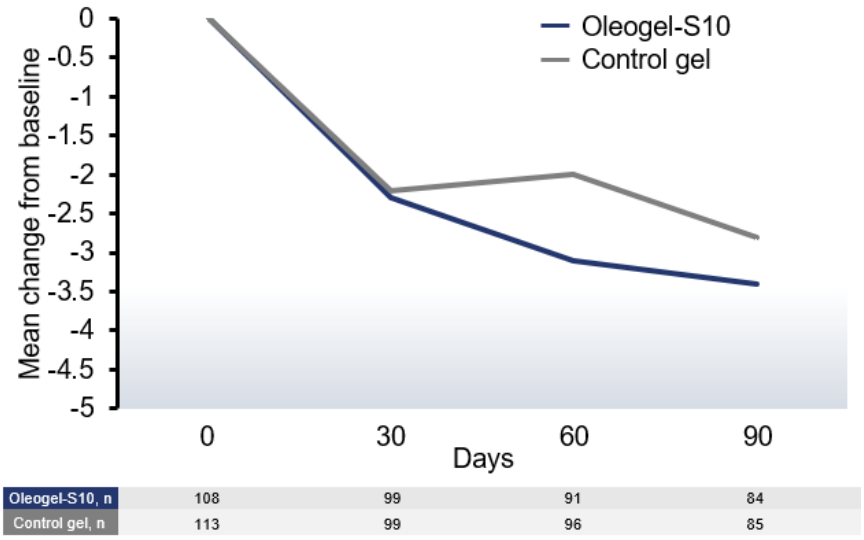
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; DEB=dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; EBDASI=Epidermolysis Bullosa Disease Activity and Scarring Index; JEB=junctional epidermolysis bullosa; LS Mean=least squares mean; SE=standard error of LS Mean

[a] Parameter and model estimates based on ANCOVA on the change from baseline with treatment group, EB subtype, and target wound size class as fixed effects and corresponding EBDASI score at baseline as covariate.

Note: 'EB subtype' included in the model as per the stratification factor groups: JEB/Kindler and DEB. Subjects with EB simplex (EBS) subtype were included in the strata defined by the DEB subtype.

At baseline, the mean EBDASI skin activity score was 19.6 in each treatment group. Overall, reductions in the EBDASI skin activity score were observed in both treatment groups throughout the DBP (i.e., Days 30, 60, and 90). For the secondary efficacy endpoint analysis at Day 90, EBDASI skin activity mean scores for the Oleogel-S10 group and control gel group both showed an improvement from baseline (reductions of -3.4 and -2.8, respectively).

Figure 9. Change from Baseline in Total Body Wound Burden Based on the Mean EBDASI Skin Activity Score by Study Visit



Abbreviations: EBDASI=Epidermolysis Bullosa Disease Activity and Scarring Index; n=number of subjects in the analysis

Change from Baseline in Itching at Day 90

Itching was evaluated as a key secondary endpoint (at Day 90) with assessments completed before wound dressing change. Different instruments were used based on the subject's age: the Itch Man Scale for subjects ≥4 to 13 years of age (N=106) and the Leuven Itch Scale for subjects ≥14 years of age (N=100).

For this key secondary efficacy endpoint at Day 90, subjects 4 to 13 years of age using the Itch Man Scale showed slight improvements (i.e., mean changes) from baseline in both groups (-0.44 Oleogel-S10 group vs. -1.0 control gel group; p=0.182).

Results for subjects ≥14 years using the Leuven Itch Scale were presented according to 6 domains rather than an overall score. Some sites used a VAS of incorrect length for the severity and distress domains of the Leuven Itch Scale, so an additional corrected analysis was performed. Across each of the 6 domain scores at Day 90, a reduction in itching from baseline was observed for subjects treated with Oleogel-S10; this was not observed for subjects who received control gel. At Day 90, greater mean reductions in the duration (-0.93 Oleogel-S10 vs. 0.98 control gel), consequence (-4.39 Oleogel-S10 vs. -3.54 control gel), distress (-0.44 Oleogel-S10 vs. -0.26 control gel), and surface areas (-1.54 Oleogel-S10 vs. 0.68 control gel) of itching were observed for the Oleogel-S10 group than the control gel group, while greater mean reductions from baseline in the frequency (-8.13 Oleogel-S10 vs. -10.14 control gel) and severity (-4.95 Oleogel-S10 vs. -10.76 control gel) of itching were observed in the control gel group compared to the Oleogel-S10 group at Day 90.

Additional Secondary Endpoints

The p-values for these additional secondary efficacy analyses were not adjusted for multiplicity.

Change from Baseline in Procedural and Background Pain

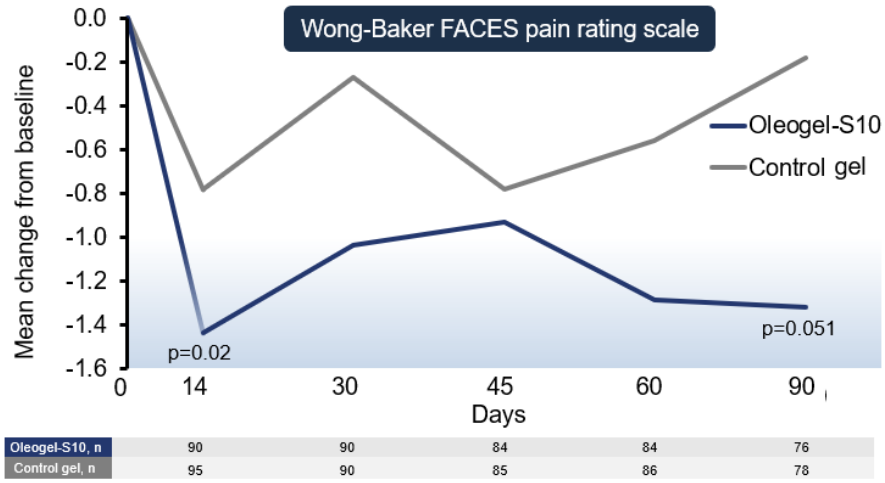
At baseline, subjects in both groups had similar levels of pain resulting from removal of wound dressings and application of new dressings (i.e., procedural pain) and pain experienced between dressing changes (i.e., background pain). In older subjects (≥4 years), the mean procedural pain score at baseline was 3.7 in the Oleogel-S10 group and 3.0 in the control gel group; the mean background pain score was 3.2 in each treatment group. Pain in younger subjects (<4 years) was assessed using the FLACC Pain Rating Scale but was not discussed due to small sample size (N=17).

In subjects ≥4 years, mean improvements compared to baseline in procedural and background pain were observed in both treatment groups throughout the DBP. For procedural pain, these improvements were greater in the Oleogel-S10 group compared to the control gel group starting at Day 14, when the mean change from baseline in the procedural pain score was –1.44 in the Oleogel-S10 group and –0.78 in the control gel group (p=0.022).

At Day 90, the mean change from baseline in the procedural pain score was -1.32 in the Oleogel-S10 group and -0.18 in the control gel group (p=0.051).

For background pain, at most visits in the DBP, marginally more improvement was reported by the control gel group than the Oleogel-S10 group. At Day 90, mean change from baseline in the background pain score was -0.94 in the Oleogel-S10 group and -1.11 in the control gel group.

Figure 10. Change from Baseline in Procedural Pain by Visit



Abbreviations: n=number of subjects in the analysis

Proportion of Subjects with First Complete Wound Closure using Blinded Evaluation of Photographs

In the Oleogel-S10 group, the results were consistent with those observed based on the clinical assessment. In the control gel group, 1 less closure was observed within the first 45 days and 2 less closures were observed within the first 90 days compared to the clinical assessment.

Change from Baseline in Body Surface Area Percentage affected by Partial-Thickness Wounds by Visit

At baseline, the mean total BSAP affected by EB partial-thickness wounds was 12.1% in the Oleogel-S10 group and 12.2% in the control gel group. Mean decreases from baseline (i.e., reductions in the percentage of skin area affected by wounds) in total BSAP were observed in both treatment groups throughout the DBP. On Day 30, the mean change from baseline in total BSAP was -2.6% in the Oleogel-S10 group and -2.6% in the control gel group. At Day 60, these values were -2.9% and -1.7%, respectively, and at EDBP (Day 90), the values were -4.3% and -2.5%, respectively.

Overall, none of the defined six 'key' secondary endpoints could formally be declared positive as the results for the first key secondary endpoint were not statistically significant. In some cases, and at some time points during the DBP, the results were numerically in favour of Oleogel-S10, whereas for other comparisons no difference was observed. Thus, no formally demonstrated effects on wound infections, total body wound burden or itch can be claimed.

For pain, which can be of great importance in EB, (denoted as an additional secondary endpoint), some mean improvements that were greater in the Oleogel-S10 group compared to the control gel group were observed, mainly for procedural pain with a statistically significant difference in favour of Oleogel-S10 at Day 14 (nominal p-value 0.022) and also a larger difference at Day 90 (nominal p-value 0.051). For endpoints relating to sleep, number of days missed from school or work due to EB and overall treatment satisfaction, no clear beneficial effects of Oleogel-S10 vs. control gel could be observed.

- **Ancillary analyses**

Analysis taking sustained healing into account

Subjects who had first complete closure of the target wound during the DBP were to have a confirmation of complete closure (CCC) assessment after 7 days (CCC assessment by the investigator at the site or investigator assessment of the photograph obtained at a CCC home visit).

Additional analyses of the primary endpoint were performed for subjects with first complete closure of the EB target wound within 45 days confirmed by a CCC observation after 7 days. Forty-four subjects in the Oleogel-S10 group and 34 subjects in the control gel group had a CCC visit during the DBP. For this analysis of the primary endpoint, the first wound closure within 45 days was only considered a success if both the clinical assessment and the CCC observation assessed the wound as closed. Within 45 days, a higher number of subjects in the Oleogel-S10 group achieved first complete closure which was confirmed by a CCC observation than subjects in the control gel group (19/109 vs. 10/114, respectively); the difference in proportions between the 2 treatment groups was statistically significant based on the CMH test stratified by EB subtype and target wound size class (p=0.048).

Table 14. Proportion of Patients with First Complete Closure of EB Target Wound within D45±7, Clinical Assessment Confirmed by a Second Observation after 7+2 Days - stratified CMH test (Full Analysis Set)

Statistics [1]	Oleogel-S10 (N=109)	Control Gel (N=114)
n (Closure n / %, Non-Closure n / %)	109 (19/ 17.4%, 90/ 82.6%)	114 (10/ 8.8%, 104/ 91.2%)
DEB 10 to <20 cm² (Closure, Non-Closure)	62 (14, 48)	66 (7, 59)
DEB 20 to <30 cm² (Closure, Non-Closure)	22 (3, 19)	21 (1, 20)
DEB 30 to 50 cm² (Closure, Non-Closure)	14 (1, 13)	12 (0, 12)
JEB/Kindler 10 to <20 cm² (Closure, Non-Closure)	7 (1, 6)	9 (2, 7)
JEB/Kindler 20 to <30 cm² (Closure, Non-Closure)	1 (0, 1)	3 (0, 3)
JEB/Kindler 30 to 50 cm² (Closure, Non-Closure)	3 (0, 3)	3 (0, 3)
Relative Risk	2.03	
95% Confidence Interval for Relative Risk	[0.99, 4.18]	
Odds Ratio	2.29	
95% Confidence Interval for Odds Ratio	[1.00, 5.26]	
CMH Test Statistic	3.90	
p-value	0.048	

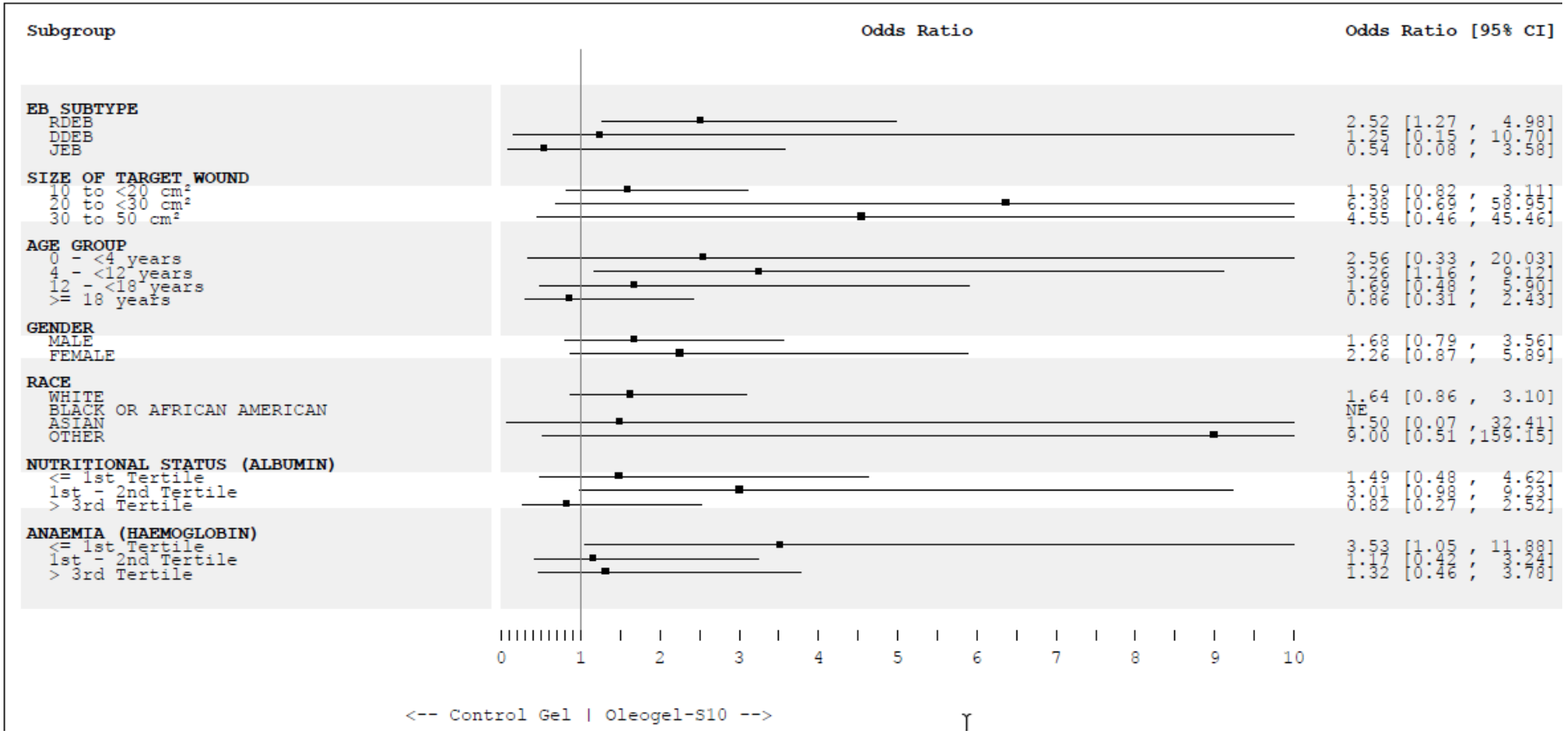
Most of these target wound closures within 45 days confirmed by a CCC observation occurred in the DEB 10 to <20 cm^2 group (14/19 Oleogel-S10; 7/10 control gel). When analysed using a Fisher's exact test, the OR for the comparison between treatment groups was 2.20 (95% CI: 0.91, 5.56). Analysis according to a Pearson's chi-square test also resulted in an OR of 2.20 (95% CI: 0.97, 4.97).

Thus, the sensitivity analysis for the primary endpoint taking sustained healing of the target wound at 7 days after the first healing into account, resulted in fewer subjects rated as 'success' for both groups, with 17.4% achieving confirmed closure in the Oleogel-S10 group vs. 8.8% in the control group. This difference was borderline significant (p=0.048).

Sub-group analyses in study BEB-13

For the primary efficacy endpoint, subgroup analyses for EB subtype, age group, gender, race, size of target wound, contact layer/dressing, baseline nutritional status, baseline anemia, and baseline renal function were performed for the FAS (Figure 11). Ranges for baseline nutritional status (albumin), baseline anemia (hemoglobin), and baseline renal function (eGFR) were divided into tertiles.

Figure 11. Proportion of Subjects with First Complete Closure of EB Target Wound within Day 45 ±7 Based on Clinical Assessment. According to the Stratified CMH Test -Summary of Subgroup Analyses (FAS)



EB subtypes

With respect to EB subtypes, there was a large difference in the numbers included with different subtypes, with the RDEB subtype group being largest (n=175 subjects), while the DDEB (n=20 subjects) and JEB subtype groups (n=26 subjects) were much smaller. This is likely a reason for differing results for the primary endpoint, where an effect could be shown for the RDEB group (44.0% vs. 26.2%, respectively; CMH p=0.008), but not for the two other subtypes (same rates of closure in both groups for DDEB and higher rate of closure for control gel vs. Oleogel-S10 for JEB). There were some imbalances in numbers randomised to Oleogel-S10 vs. control gel and also imbalances with respect to wound size and age, that may have contributed to the differences seen. The applicant initially proposed an indication covering both dystrophic and junctional EB. This was questioned on the basis of these results. It was acknowledged that due to the even higher rarity of the DDEB and JEB sub-types, it may not be realistic to recruit enough patients to enable a demonstration of statistically significant effect within each sub-type. However, further justification for the proposed indication covering both DEB and JEB subtypes, with large heterogeneity in severity and presentation, was considered necessary.

For the JEB subgroup, it was clarified that of the 26 subjects with JEB subtype, most had generalised disease (19 subjects) and would therefore represent the severe end of the spectrum. Six subjects had target wounds aged over 9 months (such long-lasting wounds were later excluded in a protocol amendment) and none of these subjects achieved closure. Several subjects also had large wounds (30-50 cm2), for which healing also was poor. There was no treatment effect observed in the primary endpoint and active treatment had lower rate of healing than control (18.2% Oleogel-S10 vs. 26.7% control gel; p=0.522). The applicant referred to modest reductions in procedural pain during the DBP, however, the reductions were indeed modest and non-significant vs. control gel.

JEB is mainly classified into two main types: JEB generalised severe (formerly known as Herlitz JEB) and JEB generalised intermediate (formerly known as non-Herlitz JEB). Non-generalised severe JEB is the milder form. Blistering may be limited to the hands, elbows, and feet, and often improves in infancy. Whereas generalised severe JEB is evident at or shortly after birth, blistering is widespread in the body, affecting the mucosal lining of the mouth and digestive tract, and the ability to eat and digest food. Chronic malnutrition and stunted growth can result, and these children usually have a poor life expectancy. Therefore, the JEB is quite heterogeneous, and the applicant's opinion was that as an increase in epithelisation is seen this is relevant no matter what subtype is involved. This was not agreed as it would seem more appropriate for the milder form of this disease, which is limited more to skin compared to the generalised junctional EB.

While the trial included a limited number of JEB patients there was no treatment effect observed in the primary endpoint (p=0.522); however, target wounds that closed was swifter in the Oleogel-S10 group (29 vs. 48 days) in the DBP and a very modest improvement in procedural pain. Following the oral explanation, the remaining issue concerning the clinical robustness of the efficacy data were considered to be resolved by the CHMP and an indication covering both DEB and JEB subtypes was considered acceptable given the demonstrated clinical effect in the overall study population, with added information in section 4.4 of the SmPC about limited data in the JEB and DDEB subtypes. Further, the applicant is planning to collect additional data in particular to assess effectiveness of Filsuvez in patients with DEB and JEB as part of the planned PASS (AEB-21), see RMP section 2.7.

Age group

With respect to age, the largest part of the study population was aged below 18 years with the largest sub-group being those aged 4 to <12 years, comprising 38% overall. The subgroup 0 - <4 years was very small (n=17 in total, <7% of the total population). It was in the 4 to <12 years age subgroup that the most pronounced difference between treatments in favour of Oleogel-S10 was observed. Results for the other age groups below 18 years were numerically in favour of Oleogel-S10 while this was not the case for patients aged ≥ 18 years (odds ratio and 95% CI 0.86, 0.31; 2.43). Hence, the youngest age group (0-<4 years) was very small and for the oldest age group (≥18 years, i.e. adults) the results were not in favour of Oleogel-S10. The applicant was asked to discuss and justify the initially applied indication covering all ages.

The age distribution in the 0-<4 years group was presented upon request from the CHMP. There were no Oleogel-S10-treated subjects aged 6-11 months (2 in the control arm), 3 were aged 12-17 months, 3 were aged 2 years and one was aged 3 years. Thus, no patient < 1 year was exposed to Oleogel-S10. From an efficacy perspective, the applicant presented the results for the primary endpoint in the ⩾21 days and <4 years subgroup and 71% reached closure in the Oleogel-S10 group vs. 40% in the control group. This is however based on very small numbers. No firm conclusions can be made regarding procedural pain assessed by the FLACC pain score. There was some initial improvement in procedural pain however this was not sustained over the duration to day 90. There was some improvement again at day 90 but the results were not significant.

The applicant also referred to safety results, showing no major concerns in comparison with the overall study population, but again, the small number of young children make conclusions difficult. Further, in the 7 subjects receiving Oleogel-S10 the applicant stated that 2 patients experienced an SAE. Therefore, this could be higher than patients > 4 years if more patients < 4 years were to receive treatment. Efficacy-wise, there seems to be no reason to expect a different response with Oleogel-S10 in the youngest, compared with older children, adolescents and adults. The treatment is topical and thus a need for a specific systemic exposure to achieve an effect is not relevant. The overall benefit-risk for this age group is discussed further below, see section 2.6.6.

Concerning adults, comprising 30% of the study population, a subgroup analysis did not show favourable results for Oleogel-S10 vs. control gel (odds ratio and 95% CI 0.86, 0.31; 2.43). It is acknowledged that the sample size for this group was small (n=67) and that many adult patients had large wounds. Similar to children, reductions in procedural pain were numerically larger for Oleogel-S10 vs. control gel, without being statistically significant. Overall, no specific pattern pointing to a worse safety profile compared with the overall study population could be observed. The challenges of performing studies in a rare disease like EB are noted and subgroup analyses are not likely to demonstrate statistically significant effects. Therefore, the CHMP considered that, there was no obvious reason to exclude adult EB patients from the indication. This relates also to a potential need for an upper age limit. Even if there were very few EB patients aged >65 years (n=3 according to BEB-13 CSR), an upper age limit did not seem warranted based on efficacy (or safety).

Gender

Results for male and female subgroups were similar to the results of the overall analysis. Gender subgroups included 134 males and 89 females. A higher proportion of both males and females who were treated with Oleogel-S10 achieved the primary endpoint than subjects who received control gel (males: 39.7% vs. 27.3%; females: 43.9% vs. 31.3%, respectively); these differences were not statistically significant (p=0.167 and p=0.097, respectively). Male and female subjects who received Oleogel-S10 were 39% and 56% more likely to achieve the first complete closure of the EB target wound within 45 days than male and female control gel subjects.

Race

Results for White subjects were similar to the results of the overall analysis. In this study, 83.4% of subjects were White therefore, the only race subgroup that included a sufficient number of subjects for meaningful analysis was White subjects (n=186).

Size of Target Wound

Subjects treated with Oleogel-S10 were more likely to achieve first complete closure of the EB target wound within 45 days than subjects who received control gel regardless of the size of the target wound (10 to <20 cm2 [n=144], 20 to <30 cm2 [n=47], and 30 to 50 cm2 [n=32]) (50.7% vs. 40.0%; 26.1% vs. 8.3%; 23.5% vs. 6.7%, respectively); none of these differences were statistically significant (p=0.171; p=0.076; and p=0.180, respectively)

Permitted Contact Layer/Dressing Used

The subgroup including subjects who used a permitted contact layer/dressing included 174 subjects and the subgroup including subjects who did not use a permitted contact layer/dressing included 49 subjects. Subjects treated with Oleogel-S10 were more likely to achieve the primary endpoint than subjects who received control gel regardless of whether a permitted contact layer/dressing was used (41.4% vs. 31.0%) or not used (40.9% vs. 22.2%), respectively; these differences were not statistically significant (p=0.096 and p=0.226, respectively).

Upon request from the CHMP, the applicant provided further clarification on the protocol deviations related to use of prohibited dressings. The numbers of subjects with the deviation were generally similar between treatment groups within each of the subtype groups. Therefore, no issue arises. Prespecified analyses were outlined in the BEB-13 protocol and SAP to evaluate if use of permitted vs. non-permitted dressings affected results of the primary or the first key secondary efficacy analyses. The results of these sensitivity analyses were consistent with the primary efficacy analysis and similar to the first key secondary efficacy endpoints. The applicant also provided a rationale for the decision on classification of the protocol deviations as minor, and as the sensitivity analysis did not show any differences the issue is considered resolved.

Nutritional status

Results for subjects with lower baseline albumin levels (first and second tertile subgroups) were generally similar to the results of the overall analysis.

In the third tertile (normal albumin levels), a higher proportion of subjects who received control gel achieved the primary endpoint than subjects in the same category who received Oleogel-S10 (44.7% control gel vs. 37.5% Oleogel-S10); this difference was not statistically significant (p=0.743).

Baseline characteristics showed that a much higher % of the control group (40.4%) had poor nutritional status Albumin 13.5 to 33 g/l compared to Oleogel-S10 cohort (29.4%). The applicant was asked to clarify why this occurred and whether this may have favoured Oleogel-S10 arm in the efficacy analysis.

The subjects in tertile 1 (albumin $\leq$ 33g/L) had a lower proportion of subjects with first complete target wound closure than observed in the overall study population. It is noted that there was a higher proportion of Control gel subjects in tertile 1 (+ 14 subjects) and tertile 3 (+14 subjects) and a higher proportion of Oleogel-S10 subjects in tertile 2 (+20 subjects). However, the mean level of albumin was slightly higher in Oleogel-S10 compared to placebo which may have slightly favoured the treatment arm. As the median baseline albumin was the same in the 2 treatment groups, the applicant did not

consider that the nutritional status of the study population favoured the Oleogel-S10 group. This was not entirely agreed as the mean level was higher, however this issue was not further pursued.

Baseline Anaemia

Results for subjects with baseline haemoglobin levels in all 3 tertiles were generally similar to the results of the overall analysis. A higher proportion of subjects who received Oleogel-S10 across all tertiles (first tertile [lowest baseline haemoglobin levels – below normal]; second tertile [below normal levels]; third tertile [normal levels]) achieved the primary endpoint than subjects in those categories who received control gel (first tertile: 38.2% vs. 16.2%; second tertile: 37.5% vs. 33.3%; third tertile: 38.9% vs. 35.7%); the difference between treatment groups in the first tertile was statistically significant (p=0.039).

Baseline Renal Function

Results for subjects with normal baseline eGFR values (second and third tertile subgroups) were generally similar to the results of the overall analysis. In the first tertile of subjects with a reduced baseline eGFR level, a slightly higher proportion of subjects who received control gel achieved the primary endpoint than subjects in the same tertile who received Oleogel-S10 (38.9% control gel vs. 34.3% Oleogel-S10); this difference was not statistically significant (p=0.596).

Post hoc Analyses by EB Subtype and Age Group

A post hoc analysis of the proportion of subjects with first complete closure of the EB target wound within 45 days in subjects with RDEB by age group using a Fisher's exact test was performed.

Results in each of the 3 paediatric subgroups (0 to <4 years [n=17], 4 to <12 years [n=85], 12 to <18 years [n=54]) were similar to the overall analysis with higher proportions of subjects who received Oleogel-S10 achieving target wound closure within 45 days than subjects who received control gel.

The difference in the 4 to <12 years age group was statistically significant (p=0.022).

However, a higher proportion of subjects who received control gel in the ≥18 years age group (n=67) achieved first complete closure of the EB target wound within 45 days than subjects who received Oleogel-S10 (43.8% control gel group vs. 34.6% Oleogel-S10 group); the difference was not statistically significant (p=0.745).

When the subset of subjects with generalised severe RDEB (n=124) were evaluated in a post hoc analysis of the proportion of subjects with first complete closure of the EB target wound within 45 days using the CMH test statistic stratified by target wound size class, results were similar to the overall population with a higher proportion of subjects in the Oleogel-S10 group achieving closure (45.2% Oleogel-S10 vs. 19.4% control gel; CMH p=0.001).

Furthermore, of these subjects with generalised severe RDEB, higher proportions of Oleogel-S10 subjects achieved first complete closure within 45 days than control gel subjects regardless of wound size.

Table 15. Proportion of patients with first complete closure of EB target wound within D45 ±7, clinical assessment – stratified CMH test – RDEB generalised severe patients (Full Analysis Set)

EB Subtype = RDEB Generalised Severe

Statistics [1]	Oleogel-S10 (N=62)	Control Gel (N=62)
n (Closure n / %, Non-Closure n / %)	62 (28/ 45.2%, 34/ 54.8%)	62 (12/ 19.4%, 50/ 80.6%)
10 to <20 cm² (Closure, Non-Closure)	36 (21, 15)	37 (11, 26)
20 to <30 cm² (Closure, Non-Closure)	16 (5, 11)	14 (0, 14)
30 to 50 cm² (Closure, Non-Closure)	10 (2, 8)	11 (1, 10)
Relative Risk	2.38	
95% Confidence Interval for Relative Risk	[1.36, 4.16]	
Odds Ratio	4.08	
95% Confidence Interval for Odds Ratio	[1.71, 9.74]	
CMH Test Statistic	10.47	
p-value	0.001	

Additionally, the CHMP recommended, at the time of scientific advice/protocol assistance, considering seasonal change, since this may affect the EB condition. This aspect was not addressed, and the applicant was asked to do so. In the response, it was stated that seasonal effect in EB was mainly described for the EB Simplex subtype, even if changing symptoms and complications of EB have been rarely reported also in other EB subtypes, e.g., related to heat and humidity during the summertime. The lowest number of subjects was enrolled into the BEB-13 study during summer and with a very similar proportion in the treatment arms (13-14%). It is agreed that the number of patients enrolled into both Oleogel-S10 and placebo arms was very similar during summertime, which is expected to cause itch among children. For the other seasons there were some 'imbalances', however, no major impact on results is expected, even if no specific analyses were presented.

- **Summary of main efficacy results**

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 16. Summary of efficacy for trial BEB-13

Title: Double-Blind, Randomised, Vehicle-Controlled, Phase III, Efficacy and Safety Study with 24-Month Open-Label Follow-Up of Oleogel-S10 in Subjects with Inherited Epidermolysis Bullosa	
Study identifier	Study no: BEB-13 EUDRACT no: 2016-002066-32
Design	This is a 2-part, Phase 3 study with a completed double-blind, randomised, controlled phase to compare the efficacy, safety, and tolerability of Oleogel-S10 versus control gel and to assess betulin exposure in subjects with inherited EB. At the end of the 90-day double blind phase (DBP), subjects in both treatment arms entered the single-arm, open label phase (OLP) with Oleogel-S10 for 24 months.

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		DBP: 90 days N/A OLP: 24 months
Hypothesis	Superiority		
Treatments groups	Oleogel-S10		Oleogel-S10 (and standard of care non-adhesive wound dressing) was to be applied during all dressing changes (at least every 4 days) until the end of DBP (EDBP) (Day 90), 109 patients randomised
	Control gel		Control gel (and standard of care non-adhesive wound dressing) was to be applied during all dressing changes (at least every 4 days) until the end of DBP (EDBP) (Day 90), 114 patients randomised
Endpoints and definitions	Primary endpoint	Proportion of subjects with first complete closure of the EB target wound within 45 days based on clinical assessment by the investigator	Proportion of subjects with first complete closure of the EB target wound (defined as EB partial-thickness wound of 10 cm^2 to 50 cm^2 in size and ≥21 days to <9 months in age) in subjects with inherited EB (subtypes DEB, JEB, or Kindler syndrome) within 45 days of treatment with Oleogel-S10 compared with control gel based on clinical assessment by the investigator (the wound was to be rated as "closed" at first appearance of complete re-epithelialisation without drainage).
	Key secondary endpoint	Time to first complete closure of the EB target wound until Day 90	Time to first complete closure of the EB target wound as evidenced by clinical assessment until EDBP (Day 90).
	Key secondary endpoint	Proportion of subjects with first complete closure of the EB target wound at Day 90	Proportion of subjects with first complete closure of the EB target wound at Day 90 based on clinical assessment by the investigator.
	Key secondary endpoint	Incidence of wound infection between baseline and Day 90	The incidence of wound infection between baseline (DBP Day 0) and Day 90 as evidenced by AEs and/or use of topical and/or systemic antibiotics (related to wound infection).

	Key secondary endpoint	Maximum severity of wound infection between baseline and Day 90	The maximum severity of wound infection between baseline (DBP Day 0) and Day 90 as evidenced by AEs and/or use of topical and/or systemic antibiotics (related to wound infection).
	Key secondary endpoint	Change from baseline in TBWB at Day 90	Change from baseline (DBP Day 0) in total body wound burden (TBWB) as evidenced by clinical assessment using Section I (assessment of the skin except for the anogenital region) of the EB Disease Activity and Scarring Index (EBDASI) at Day 90.
	Key secondary endpoint	Change from baseline in itching at Day 90	Change from baseline (DBP Day 0) in itching using the Itch Man Scale in subjects ≥4 years and up to 13 years of age and the Leuven Itch Scale in subjects ≥14 years of age, before wound dressing changes at Day 90.
	Other secondary endpoint	Change from baseline in procedural pain	Change from baseline (DBP Day 0) in "procedural" pain using the FLACC scale in subjects <4 years of age and the Wong-Baker FACES Pain Rating Scale in subjects ≥4 years of age after wound dressing changes at Days 7, 14, 30, 45, 60, and 90.
	Other secondary endpoint	Proportion of subjects with first complete closure of the EB target wound based on blinded evaluation of photographs	Proportion of subjects with first complete closure of the EB target wound at Days 7, 14, 30, 45, 60, and 90 based on blinded evaluation of photographs
Database lock	26 August 2020		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS): all randomised subjects treated at least once with study medication First complete closure within 45 days		
Descriptive statistics and estimate variability	Treatment group	Oleogel-S10	Control gel
	Number of subjects	109	114
Effect estimate per comparison	Proportion of subjects with first complete closure of the EB target wound within 45 days based on clinical assessment by the investigator	Comparison groups	Oleogel-S10 vs control gel

		Relative Risk		1.44
		95% Confidence Interval		1.02, 3.30
		P-value CMH test adjusted with CHW		P=0.013
Notes	The final statistical analysis of the primary efficacy endpoint was performed based on the Cui, Hung, Wang (CHW) approach to adjust the estimates provided by the CMH test following a planned unblinded interim analysis. The primary efficacy endpoint was also analysed using the Completer Analysis Set (CAS) and the Per Protocol Set (PPS). The results were similar in all analysis sets.			
Analysis description	**Secondary analysis** Pre-specified key secondary endpoints and selected other secondary endpoints			
Analysis population and time point description	Full Analysis Set (FAS): all randomized subjects treated at least once with study medication Key secondary endpoints: Until or at EDBP (Day 90) Other secondary endpoints: Days 14, 30, 45, 60 and 90			
Descriptive statistics and estimate variability	Treatment group		Oleogel-S10	Control gel
	Number of subjects		All ages: 109 <4 years: 7 ≥4 years: 102 ≥4 – 13 years: 50 ≥14 years: 52	All ages: 114 <4 years: 10 ≥4 years: 104 ≥4 – 13 years: 56 ≥14 years: 48
	Key secondary endpoint: Time to first complete closure of the EB target wound until EDBP	Median time to first complete closure	92.0 days	94.0 days
		95% Confidence Interval	50.0 days, NE	89.0 days, NE
	Key secondary endpoint: Change from baseline in TBWB at Day 90	Mean change from baseline	-3.4	-2.8
		95% Confidence Interval	-4.9, -1.8	-4.4, -1.2
	Key secondary endpoint: Change from baseline in itching at Day 90	Mean change from baseline ≥4 – 13 years ≥14 years:	-0.4	-1.0

		Frequency	-8.1	-10.1
		Duration	-0.9	1.0
		Severity	-4.9	-10.8
		Consequences	-4.4	-3.5
		Distress	-0.4	-0.3
		Surface area	-1.5	0.7
		95% Confidence interval		
		≥4 – 13 years	-0.9, 0.0	-1.4, -0.6
		≥14 years:		
		Frequency	-16.5, 0.2	-19.2, -1.0
		Duration	-12.8, 11.0	-12.9, 14.9
		Severity	-11.5, 1.6	-22.2, 0.6
		Consequences	-9.2, 0.4	-10.3, 3.2
		Distress	-8.3, 7.4	-12.4, 11.9
		Surface area	-5.8, 2.7	-5.3, 6.6
	Other secondary endpoint:	Mean change from baseline		
	Change from baseline in procedural pain	<4 years		
		Day 14	-2.6	-0.9
		Day 30	-2.0	-2.1
		Day 45	-1.6	-2.0
		Day 60	-2.0	-1.6
		Day 90	-2.6	-1.2
		≥4 years		
		Day 14	-1.4	-0.8
		Day 30	-1.0	-0.3
		Day 45	-0.9	-0.8
		Day 60	-1.3	-0.6
		Day 90	-1.3	-0.2
		95% Confidence interval		
		<4 years		
		Day 14	-5.1, -0.1	-4.0, 2.2
		Day 30	-4.6, 0.6	-5.6, 1.3
		Day 45	-5.3, 2.1	-5.4, 1.4
		Day 60	-6.5, 2.5	-5.1, 1.8
		Day 90	-5.3, 0.1	-3.7, 1.4

		≥4 years		
		Day 14	-1.9, -0.9	-1.3, -0.2
		Day 30	-1.7, -0.4	-0.9, 0.3
		Day 45	-1.6, -0.2	-1.4, -0.1
		Day 60	-1.9, -0.6	-1.2, 0.1
		Day 90	-2.0, -0.6	-0.8, 0.5
Effect estimate per comparison	Key secondary endpoint: Time to first complete closure of the EB target wound until Day 90	Comparison groups	Oleogel-S10/ Control gel	
		Median time to first complete closure	92.0 days/ 94.0 days	
		Confidence Interval	50.0 days, NE/ 89.0 days, NE	
		P-value Log rank test	0.302	
	Key secondary endpoint: Proportion of subjects with first complete closure of the EB target wound at Day 90	Comparison groups	Oleogel-S10/ Control gel	
		Relative Risk	1.16	
		95% Confidence Interval	0.88, 1.52	
		P-value: CMH test	0.296	
	Key secondary endpoint: Incidence of wound infection between baseline and Day 90	Comparison groups	Oleogel-S10/ Control gel	
		Relative Risk	0.44	
		95% Confidence Interval	0.08, 2.34	
		P-value: CMH test	0.326	
	Key secondary endpoint: Maximum severity of wound infection between baseline and Day 90	Comparison groups	Oleogel-S10 vs Control gel	
		van Eltern test statistic	NE	
		Variability statistic	N/A	
		P-value: Wilcoxon rank sum test	P=NE	
	Key secondary endpoint: Change from baseline in TBWB at Day 90	Comparison groups	Oleogel-S10 vs Control gel	
		Difference in least squares means	0.12	
		95% Confidence interval	-1.58, 1.83	
		P-value: ANCOVA	0.887	

Key secondary endpoint: Change from baseline in itching at Day 90	Comparison groups	Oleogel-S10 vs Control gel
	van Eltern test statistic ≥4 – 13 years	20.58
	≥14 years:	
	Frequency	16.98
	Duration	16.76
	Severity	15.80
	Consequences	16.58
	Distress	16.78
	Surface area	17.08
	Variability statistic	N/A
	P-value: Wilcoxon rank sum test ≥4 – 13 years	0.182
	≥14 years:	
	Frequency	0.344
	Duration	0.779
	Severity	0.528
	Consequences	0.940
	Distress	0.797
	Surface area	0.598
Other secondary endpoint: Change from baseline in procedural pain	Comparison groups	Oleogel-S10 vs Control gel
	van Eltern test statistic <4 years	
	Day 14	NE
	Day 30	NE
	Day 45	NE
	Day 60	NE
	Day 90	NE
	≥4 years	
	Day 14	40.84
	Day 30	42.38
	Day 45	41.56
	Day 60	39.03
	Day 90	34.72
	Variability statistic	N/A

		P-value:	
		Wilcoxon rank sum test	
		<4 years	
		Day 14	NE
		Day 30	NE
		Day 45	NE
		Day 60	NE
		Day 90	NE
		≥4 years	
		Day 14	0.022
		Day 30	0.152
		Day 45	0.805
		Day 60	0.095
		Day 90	0.051
	Other secondary endpoint: Proportion of subjects with first complete closure of the EB target wound based on blinded evaluation of photographs	Comparison groups	Oleogel-S10 vs Control gel
		Relative risk	
		Day 14	1.22
		Day 30	1.79
		Day 45	1.37
		Day 60	0.53
		Day 90	0.76
		95% Confidence Interval	
		Day 14	0.63, 2.36
		Day 30	0.92, 3.50
		Day 45	0.54, 3.52
		Day 60	0.17, 1.59
		Day 90	0.27, 2.13
		P-value:	
		CMH test	
		Day 14	0.546
		Day 30	0.080
		Day 45	0.507
		Day 60	0.244
		Day 90	0.607

Notes	Selected endpoints were also analysed using the CAS and PPS. The results were similar in all analysis sets. Assessments for some endpoints included a Day 7 assessment. Efficacy assessments scheduled for Day 7 were not performed if the visit was conducted by phone. A large proportion of subjects had the Day 7 visit conducted by phone (45.3%), therefore, Day 7 results are not reported. As different outcome measures are used for pain and itch based on patient age, the number of patients in the analyses for these endpoints varies. In some cases, a visual analog scale that was shorter than the standard scale was used in error for subject assessment of severity and distress of itch for the Leuven Itch Scale. To account for this, analysis for the Leuven Itch Scale was repeated as a supportive analysis using scaled-up versions of the itch severity and distress scores. The scaled-up scores are reported here.

2.6.5.3. Clinical studies in special populations

There were no dedicated studies in special populations. Sub-group analyses from study BEB-13 are commented below, *Ancillary analyses*. There were very few elderly subjects included in study BEB-13. For completeness, however, the applicant was asked to complete the table below as per usual requirements and has provided the following table:

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	128/707	91/707	10/707
Non Controlled Trials	0/0	0/0	0/0

The applicant has completed the table, as requested, however with inclusion also of non-EB trials, e.g., BAK-08, BSH-10, BBW-11, BSG-12 and BSH-12. For EB only, no such table was available, however, according to the BEB-13 CSR, only 3 subjects > 65 years were included.

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

There was only one pivotal study in the EB population (BEB-13). The small Phase 2 study BEB-10 had another type of design (intra-individual comparison). Hence, it was not considered relevant to pool efficacy results from these two EB studies.

Studies submitted in the Episalvan MAA to support the STSG wound indication were included in this submission as supportive studies (see below). The applicant's decision not to pool the efficacy data from the two EB studies and the three STSG studies was based on differences across the studies including number of subjects, treated population, design/use of control, exposure, treatment administration and wound dressings, wound characteristics, and choice of study endpoints. The reasons for not pooling studies within the EB indication and across EB and STSG studies were endorsed by the CHMP.

2.6.5.5. Supportive studies

Study BEB-10

Methods

This was a Phase 2 open-label, prospective, blindly evaluated controlled case series documentation to intra-individually compare the efficacy and tolerance of Sericare (Oleogel-S10) versus non-adhesive wound dressing alone in accelerating the epithelialisation of skin lesions in patients with inherited EB. The study was conducted as a single centre in Germany, between 3 November 2010 and 14 June 2011.

Patients were eligible for this study if they met the following main inclusion criteria:

- Patients aged 1-95 years
- Patients with inherited EB with at least 1 skin lesion between 10 cm^2 and 200 cm^2 (alternatively 2 comparable lesions of at least 5 cm^2 each)
- Patient and/or his/her legal representative was able and willing to follow study procedures and instructions including application of Sericare on (1 half of) the wound at every wound dressing change and conduct regular visits during the treatment period
- Negative pregnancy test and use of an effective method of contraception in women of childbearing potential; men of procreative capacity should also agree to use an effective method of contraception

Patients were not eligible for this study if any of the following criteria applied:

- Systemic treatment with steroids during the last 30 days
- Uncontrolled diabetes mellitus or diabetic ulcers
- Diseases or conditions that could, in the opinion of the investigator, interfere with the assessment of safety, tolerance or efficacy
- Skin disorders adversely affecting wound healing or involving the areas eligible for study treatment.

The primary objective of the study was to compare wound re-epithelialisation of that half of the skin lesion, which was treated with Oleogel-S10 + non-adhesive wound dressing to that part of the wound, which was covered by non-adhesive wound dressing only (intra-individual comparison).

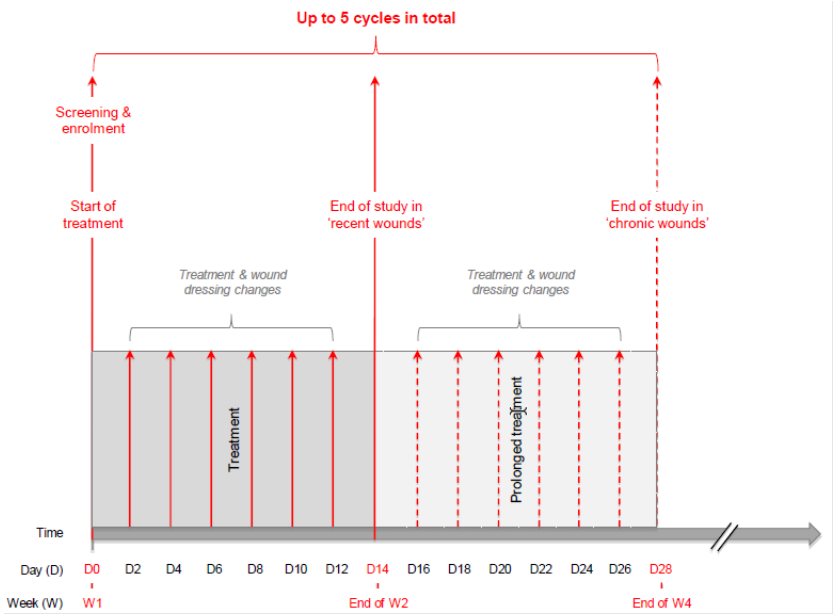
The primary efficacy variable was the progress of re-epithelialisation from baseline to either D14 or D28 of that half of the wound treated with Oleogel-S10 + non-adhesive wound dressing (Mepilex) compared to the other part of the wound covered with non-adhesive wound dressing only (intra-individual comparison). Alternatively, percentage change of re-epithelialisation from baseline to D14 or D28 of 2 comparable lesions of at least 5 cm^2 each was evaluated.

Secondary objectives were to evaluate percentage of wound epithelialisation, touch sensitivity, itching, exudation, and assessment of efficacy (evaluated by both the investigators and patients and/or his/her legal representative) and assessment of tolerance (evaluated by both the investigators and patients and/or his/her legal representative). Incidence, severity and causality of AEs were also evaluated.

The investigator either identified 1 skin lesion eligible for study treatment and divided it into 2 halves or selected 2 comparable lesions of at least 5 cm^2 each eligible for study treatment. One half of the wound was to be treated with the investigational product Oleogel-S10 (1 cm or 125 µL or 115 mg/cm^2) and covered by a non-adhesive wound dressing (Mepilex). The other half of the lesion was covered by a non-adhesive wound dressing only (Mepilex, standard of care) as control. Both primary dressings

were to be kept in place by an additional conventional dressing. If the investigator had identified 2 comparable lesions, they were to be treated correspondingly. Wound dressings were to be changed based on the study flow chart (about every 24 to 48 hours) until discharge from hospital or until the end of treatment at D14 in 'recent wounds' or at D28 in 'chronic wounds'. Before start of treatment and at every wound dressing change photographs of the respective wounds were to be taken.

Figure 12. Study Schema (Visual Representation of Study Periods)



Two independent efficacy assessment experts were assigned to blindly evaluate the progress of wound epithelialisation in serial listings by patient.

The statistical analyses were based on the Safety population (SP; all patients who received at least 1 dose of Oleogel-S10), Intent-to-treat population (ITT; all patients from the SP also constituted the ITT and the Per-protocol population (PP; all patients from the ITT who reasonably adhered to all protocol conditions belonged to the PP). Binomial analysis for superiority of test treatment was used for the primary efficacy variable; all other analyses were explorative. Missing values were not replaced.

This was a very small (n=10) study of Oleogel-S10 in EB patients, seen as evaluation of proof-of-concept in this target population. The study had an intra-individual comparative design, which is rather common in early, explorative studies for locally applied dermatological products. The study had a wide age range for inclusion (1-95 years). Based on the original CSR it was not clear if EB patients of any sub-type could be included. In a CSR amendment, it was clarified that 9 patients diagnosed with RDEB and 1 patient with DDEB were included. In the amended CSR, the applicant chose to present only the results for the RDEB sub-group, without the patient having DDEB. In this report, however, the original results including both RDEB and DDEB patients are presented. The patients were to have either at least 1 skin lesion between 10 and 200 cm^2 or 2 comparable lesions of at least 5 cm^2 each.

Both the Oleogel-S10-treated wound half and the control half of the lesion (or the second wound) were covered by a standard non-adhesive wound dressing, Mepilex. Thus, the control treatment was the standard dressing only and not another applied gel or ointment (placebo/vehicle). Wound dressings

were changed every 24 to 48 hours, which is reasonable, and the duration of treatment depended on whether wounds were 'recent wounds' (14 days) or 'chronic wounds' (28 days).

This study design is reasonable for an early study and an intra-individual design has its pros and cons. One advantage is that the wound halves (or wounds, in case two different wounds are compared) are more likely to be comparable, which may not be the case if a conventional, parallel group design is chosen where wounds on different individuals are compared. Underlying factors affecting wound healing like nutritional status and general health status are thus the same for the wounds being compared. Disadvantages can be a risk of contamination of the untreated wounds half with active product from the treated wound half and that blinding can be impaired if the product is visible.

The study was conducted open-label. Hence, the investigator, the patient and the sponsor knew the identity of the treatment. A blinded assessment of efficacy was to be conducted by 2 independent experts based on chronological series of photographs by patient taken before start of treatment, during wound dressing changes and at the end of treatment on D14/D28. The assessors did not know which (half of the) wound was treated with Oleogel-S10 + non-adhesive wound dressing and which one with non-adhesive wound dressing only.

Results

Ten patients were enrolled into the study and all of them were treated with study medication. Eight patients received 1 and 2 patients were administered 2 cycles of study treatment, 12 wounds were treated with study medication. None of the patients terminated the treatment prematurely.

There was neither any deviation from inclusion nor from exclusion criteria. Treatment deviated from protocol once in 1 patient, whose wound was additionally treated with Lavasept cream (polyhexanid) on both areas (Oleogel-S10 + non-adhesive wound dressing and non-adhesive wound dressing only) due to a suspected super-infection.

All patients completed study treatment and data on the primary efficacy variable was available in all patients. Hence, no patient was excluded from PP analyses and the ITT and PP populations were identical.

The overall median age of patients was 20 years (range 6-48 years); 7 were male, 3 were female. It was clarified that a total of 5 of the 10 subjects (50%) enrolled in BEB-10 were paediatric subjects (<18 years). These subjects were aged 5 years, 8 years, 9 years, 15 years, and 17 years. Most patients had skin type I according to the Fitzpatrick classification (n = 6), while the remaining patients equally had skin type II (n = 2) and skin type III (n = 2), respectively. Medical history revealed pre-existing diseases in 5 of 10 patients; 8 conditions in 7 body systems; all of them stable.

In 7 of 12 cases, 1 skin lesion was treated; 9 of 12 wounds (75%) were 'recent wounds'. Most commonly, wound size was measured using a computer (11 of 12 cases). If 1 wound was treated it had a median size of 35.2 cm^2; in case 2 wounds received treatment they were nearly evenly large with median sizes of 10.3 and 10.5 cm^2, respectively. The maximum wound size in the study was 90 cm^2. Single wounds were located at the lower left extremities in 4 of 7 cases, while 2 comparable wounds were most commonly located at the trunk (8/10).

Efficacy results

For the primary efficacy variable, Oleogel-S10 + non-adhesive wound dressing (Mepilex) significantly accelerated the re-epithelialisation (8 of 8 decided cases; p=0.0078, binomial test) of wounds in inherited EB compared to non-adhesive wound dressing only (0 of 8 decided cases).

As the efficacy of study treatments was either evaluated controversially in patients 1 and 8, or as being equal in patients 5 and 7, the applicant excluded these 4 wounds from the analysis of the primary efficacy variable. Evaluating both reviewer results independently, 'Reviewer 1' scored in favour of Oleogel-S10 + non-adhesive wound dressing (Mepilex) in 8 of according to his view 9 decided cases, 'Reviewer 2' in 7 of based on his estimation 8 decided cases, with the remaining case scored in favour of non-adhesive wound dressing only ('Reviewer 1' in 1 of 9 decided cases, 'Reviewer 2' in 1 of 8 decided cases).

Both efficacy assessment experts were in full agreement in 7 of 12 cases, of which 5 cases were scored in favour of Oleogel-S10 + non-adhesive wound dressing, 2 cases were scored as equal, and none was scored in favour of non-adhesive wound dressing only.

Table 17. Results of Blinded Efficacy Evaluation by Patient and Wound

Patient (wound #)	Blinded efficacy assessment experts		Result	Winner	
	Reviewer 1	Reviewer 2		Oleogel-S10	Wound dressing
1	Non-adhesive wound dressing	Oleogel-S10	Controversial	-	-
2	Oleogel-S10	Equal	Oleogel-S10	1	0
3	Oleogel-S10	Oleogel-S10	Oleogel-S10	1	0
4	Oleogel-S10	Equal	Oleogel-S10	1	0
5	Equal	Equal	Undecided	-	-
6	Oleogel-S10	Oleogel-S10	Oleogel-S10	1	0
7	Equal	Equal	Undecided	-	-
8	Oleogel-S10	Non-adhesive wound dressing	Controversial	-	-
9 (1)	Oleogel-S10	Oleogel-S10	Oleogel-S10	1	0
9 (2)	Equal	Oleogel-S10	Oleogel-S10	1	0
10 (1)	Oleogel-S10	Oleogel-S10	Oleogel-S10	1	0
10 (2)	Oleogel-S10	Oleogel-S10	Oleogel-S10	1	0
Total				**8**	**0**

For the primary endpoint assessment, the evaluation was based on cases classified as 'decided cases'. The applicant then concluded that Oleogel-S10 + non-adhesive wound dressing significantly accelerated the re-epithelialisation (8 of 8 decided cases; p=0.0078) of wounds in inherited EB compared to non-adhesive wound dressing only (0 of 8 decided cases). Thus, those cases were 'Reviewer 1' and 'Reviewer 2' came to different conclusions were denoted as 'controversial' and those were both reviewers considered the wound half results as 'equal' were not included. Those wounds were one of the reviewers considered the results as 'equal' while the other reviewer considered Oleogel-S10 to be the best, were on the hand included. This approach may be questioned. In an estimation per reviewer were *all* wounds are included, the results for Oleogel-S10 as a 'winner' would be 8 of 12 (67%) for 'Reviewer 1' and 7 of 12 (58%) for 'Reviewer 2'. For those cases were both experts were in full agreement (7 of 12 cases), 5 cases were scored in favour of Oleogel-S10 (42%) while none scored in favour of non-adhesive wound dressing only. Thus, Oleogel-S10 showed the majority of positive results whereas the 'Non-adhesive wound dressing' alone was found the best in only two instances; with conflicting results between the reviewers for those cases.

The DDEB patient (#7), excluded from analyses in the amended CSR as described above (however, not excluded in the results presented in this report), had a diagnosis of localised DDEB with blistering on lower legs and nail dystrophy. For this patient, both experts rated the wound halves as 'equal' and the patient was among those classified as 'undecided'.

Concerning *secondary efficacy variables*, the areas treated with Oleogel-S10 + non-adhesive wound dressing (Mepilex) re-epithelialised faster and to a higher degree as their median percentages of epithelialisation were higher on day 7±1 (69.7% vs. 57.4%, p=0.21, Wilcoxon-test) and on day 14±1 (87.7% vs. 79.2%, p=0.33, Wilcoxon-test) than those of areas treated with non-adhesive wound dressing only. Thus, somewhat faster and larger degree of re-epithelialisation was observed for Oleogel-S10 vs. non-adhesive wound dressing alone, although not statistically significant.

Overall, 3 of 24 areas re-epithelialised completely by the end of treatment; all of them had been treated with Oleogel-S10 + non-adhesive wound dressing. The median time to complete wound closure in these 3 areas was 13 days (min. 9 days; max. 15 days).

Touch sensitivity, itching, exudation, and efficacy as rated by investigators and patients were comparable for the treatments.

The efficacy results from this very small, intra-patient, open-label (but claimed reviewer-blinded) study are not strong, however, they provide limited support for a proof-of-concept and beneficial effects of Oleogel-S10 + non-adhesive wound dressing vs. non-adhesive wound dressing alone in the re-epithelialisation of EB wounds. The majority of patients had RDEB.

Study AHV-18 A

Methods
This was an exploratory, randomised, intrasubject-controlled study of the cutaneous healing properties of petrolatum versus the control gel for Oleogel-S10 (developed for use in study BEB-13) versus no treatment, when applied topically to mechanically induced partial-thickness wounds in healthy adult subjects. The study was conducted at a single centre in Germany between 23 January 2020 and 04 March 2020. The results from this study were to be used to inform the design of a confirmatory, Phase 2 study (Study AHV-18-B), including calculation of an appropriate sample size.

Twelve adult healthy volunteers (male or female) aged 18 to 45 years with skin Type II to III according to the Fitzpatrick classification were enrolled. Exclusion criteria included known or suspected defect of wound healing, any kind of skin barrier impairment, sunburn, or scars/tattoos/other skin signs that may have interfered with study procedures/measurements. Subjects who planned to undergo ultraviolet light sessions or sun exposure of the arms during the study were also excluded. Subjects with known or suspected hypersensitivity to one of the components of the investigational medicinal product or an allergy to the dressing to be used were not permitted to enrol in the study. Other exclusion criteria included: use of any treatment which may have affected blood coagulation and haemostasis, any physical treatment (like laser or surgery) on the arms in the six months prior to the study, use of topical or systemic treatments on the investigational areas within four weeks prior to the study, use of systemic antibiotics, systemic or topical steroids within two weeks of Day 1, and medical history of skin cancer.

Randomised subjects had 3 abrasive wounds of approximately 8 mm diameter in 3 mini-zones (A, B, and C) created on the non-dominant volar forearm. The distance between the wounds was 3 cm. Abrasive wounds were created using a sterile scrub brush using moderate pressure until the first signs of epidermal removal and punctuate bleeding were visible. The 3 wounds were labelled as A, B, and C using a skin marker.

Each subject's 3 wounds received either treatment with petrolatum (ALLERGIKA – BASISSALBE, ingredients per 100 g: white petrolatum 95 g, liquid paraffin 5 g), the control gel for Oleogel-S10, or no treatment (one treatment per wound area [A, B, and C]) once daily for 21 days according to their randomly assigned treatment sequence. Petrolatum was chosen as it was considered an example of a

standard topical product to promote cutaneous healing in the management of wounds caused by EB. All mechanically induced wounds were covered with non-adhesive wound dressing (Mepitel Film) from Day 1 through Day 10. The untreated control had no topical treatment applied but was also covered with a non-adhesive wound dressing. Neither the study personnel who created the abrasive wounds and administered treatment nor the subjects were blinded. However, the investigators and study staff who performed the wound assessments were blinded to treatment.

Wound healing was assessed using clinical assessment of cutaneous wound healing, measurement of wound area (planimetry), assessment of transepidermal water loss (TEWL), and clinical assessment of local intolerance from Day 1 through Day 28. A 6-category clinical score was used to assess the degree of epithelialisation (0=0% [no healing], 1=1 to 25% re-epithelialisation, 2=26 to 50% re-epithelialisation, 3=51 to 75% re-epithelialisation, 4=greater than 75% re-epithelialisation, but not complete healing, 5=100% re-epithelialisation [complete healing]).

For measurement of wound area, standardised photographs of each wound were taken on Day 1, then every 2 days through Day 23, and on Day 28. At least 2 photographs were obtained at each timepoint, and the best image (after assessment for clarity and quality) was stored for subsequent image analysis. Wound healing measurements (planimetry) were performed by computerised image analysis using the software ImageJ. Transepidermal water loss was measured according to international guidelines (Rogiers 2001).

The primary efficacy endpoints were days until complete healing according to clinical score and days until complete healing according to planimetry.

Secondary efficacy endpoints were mean clinical score per day, mean wound surface area in mm^2, and mean TEWL per wound in $g/h/m^2$.

This was an exploratory study; hence, only descriptive statistical methods were applied. The investigational medicinal products (IMPs) and the untreated control were not compared using a statistical test; no null hypotheses were tested.

Results

A total of 12 subjects were randomised in this study. Of the 12 subjects randomised, 11 subjects (91.7%) completed the study. One subject discontinued after Day 13 as he failed to return at Day 14. As this subject had achieved complete wound healing according to planimetry (all wounds) prior to his withdrawal, he was included in the analyses based on planimetry data but was excluded from the analyses based on clinical score due to missing data. Planimetry measurements (Day 11 to Day 13) were missing for another subject who did complete the study; this subject was included for analyses based on clinical score but excluded from analyses based on planimetry data.

Twelve subjects (6 male and 6 female) aged 20 to 41 years were randomized and treated. Prior to wound induction, mean baseline TEWL was 7.5 $g/m^2/h$ (SD: 0.7). Baseline TEWL for all subjects ranged from 6.4 to 8.8 $g/m^2/h$.

Primary Endpoint

Mean days to complete wound healing according to clinical score were similar for all treatments (13.3 days for untreated wounds and wounds treated with control gel, 13.4 days for wounds treated with petrolatum). All wounds were considered healed according to clinical score within 16 days.

Table 18. Days to Complete Wound Healing According to Clinical Score

	Untreated Control	Petrolatum	Control Gel
N[a]	11	11	11
Mean	13.3	13.4	13.3
95% CI	12.3-14.3	12.4-14.3	12.3-14.2
SD	1.5	1.4	1.4
Minimum	11	11	11
Maximum	16	16	15

Abbreviations: CI=confidence interval, N=number of subjects, SD=standard deviation.

[a] Subject 01/05 was excluded as no data were available from Day 14 to Day 23 for the untreated control wound. Complete wound healing had not been achieved prior to Day 14.

Mean days to complete wound healing according to planimetry were similar for all treatments (10.6 days for untreated wounds and wounds treated with control gel and 10.5 days for wounds treated with petrolatum). All wounds were considered healed according to planimetry by Day 13.

Secondary Endpoints

Time to complete wound healing according to clinical score was similar for all treatments. Median clinical scores for untreated wounds and wounds treated with control gel or petrolatum were 5 (100% re-epithelialisation/complete wound healing) by Day 14 and all wounds were considered healed according to clinical score within 16 days.

On Day 1 (following wound induction), mean wound surface area according to planimetry was similar for the 3 treatments (42.9, 44.2 and 43.2 mm^2 for the untreated wounds, wounds treated with petrolatum, and wounds treated with control gel, respectively). From Day 13 onwards, mean wound surface area was 0 mm^2 for untreated wounds and those treated with petrolatum or control gel. Mean wound surface areas on Days 3 to 11 were similar for untreated wounds and those treated with petrolatum or control gel. Area under the curve for wound surface area according to planimetry was also similar for all treatments.

On Day 1 (following wound induction), mean TEWL was similar in wound areas for the 3 treatments (77.4, 75.5, and 76.2 $g/m^2/h$ for the untreated wounds, wounds treated with petrolatum, and wounds treated with control gel, respectively). Mean TEWL decreased over time for untreated wounds and those treated with petrolatum or control gel; there were no clinically relevant differences in mean TEWL per day between untreated wounds and wounds treated with petrolatum or control gel.

Study AHV-18-B

Methods

Study AHV-18-B was conducted at the phase 1 unit in the Charité Universitätsmedizin Berlin, Germany and enrolled 16 subjects. The [AHV-18-B protocol] was submitted and approved by BfArM on 29 September 2020 and by the Ethics Committee of the 'Landesamt für Gesundheit und Soziales, Berlin' on 02 October 2020, however, the global COVID-19 pandemic had a major impact. This trial was not permitted to commence by the host institution until late April 2021 with a reduced rate of enrolment in order to comply with site COVID-19 mandated restrictions. Subject enrolment has been completed and all subjects completed the follow-up visit on 16 June 2021. The database was locked on 12 July 2021. The final study report was included in the Day 180 response, as requested.

The primary objective was to demonstrate that the control gel was non-inferior to petrolatum with regards to time to achieve cutaneous healing of mechanically induced partial thickness wounds in healthy volunteers.

Secondary objectives were to evaluate the change in cutaneous healing per day of mechanically induced wounds following application of control gel and petrolatum, and to assess the safety and

tolerability of control gel and petrolatum as assessed by the incidence, severity, and relatedness of adverse events (AEs) in healthy volunteers with mechanically induced wounds.

Subjects provided written informed consent before any study procedures were performed. A medical examination was performed within 2 weeks but no less than 3 days before inclusion in the study. This examination included a review of the subjects' medical history, a physical examination, clinical laboratory tests, and serology tests to confirm eligibility.

The investigational area was identified on the nondominant forearm. Two minizones (A and B) of approximately 8 mm diameter were defined using standardised templates. Two abrasive wounds were created on the 2 minizones. The selected skin areas were disinfected and a flexible template with 2 circular holes of 8 mm diameter was closely attached to the skin, which should result in a wound surface area ≤ 50 mm2. The distance between the wounds was 5 cm. Abrasive wounds were created using a sterile scrub brush (such as MEDISCRUB) by trained study assistants. The skin areas were uniformly scrubbed using moderate pressure until the first signs of epidermal removal and punctuate bleeding were visible. The template was removed, and the 2 wounds were labelled as A and B using a skin marker.

Each subject received treatment with control gel and petrolatum (1 treatment per wound area [A and B]) once daily for 16 days according to their randomly assigned treatment sequence. A non-adhesive wound dressing with a non-adherent pad was applied to each wound once a day until Day 10. The study was outcome assessor- blinded. Study personnel who administered the intervention and the subjects who received the interventions were not blinded. The Investigators who performed the wound assessments and standardised image analysis were blinded to treatment. To maintain the blind, the data manager, project manager and those preparing the analysis and results (programmers and statisticians) were blinded throughout the study until after database lock.

Wound healing was assessed using clinical score, standardised photography, measurement of wound area, and clinical assessment of local tolerance from Day 1 through Day 16. Clinical assessment: A 6 category clinical score was used to assess the degree of epithelialisation (0=0% [no healing], 1=1 to 25% reepithelialisation, 2=26 to 50% reepithelialisation, 3=51 to 75% reepithelialisation, 4=>75% reepithelialisation, but not complete healing, 5=100% reepithelialisation [complete healing]).

Planimetry assessment: For measurement of wound area, standardised photographs of each wound were taken; at least 2 photographs were taken at each timepoint, and the best image (after assessment for clarity and quality) was stored for subsequent image analysis. Wound healing measurements (planimetry) were performed by computerised image analysis using the software ImageJ. This was performed by 2 trained researchers/study assistants independently based on the Standard Operating Procedure for wound area measurement. The wound area was reported in mm2 and the means of the 2 independent measurements were used. Complete wound healing was defined as a mean wound area of 0 mm2.

Local tolerance was evaluated at every visit according to both the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 and the Grading System of Local Intolerance developed by the Clinical Research Center for Hair and Skin Science. AEs were monitored throughout the study from the time of informed consent through Day 23±2 days.

Study population: It was planned to enroll 16 subjects (8 male and 8 female) aged 18 to 45 years, which allowed for an additional 3 subjects to compensate for possible subject withdrawals.

Adult healthy volunteers (male or female) aged 18 to 45 years with skin Type II to III according to the Fitzpatrick classification were eligible for enrolment. Exclusion criteria included known or suspected defect of wound healing, any kind of skin barrier impairment, sunburn, or scars/tattoos/other skin signs that may have interfered with study procedures/measurements. Subjects who planned to undergo ultraviolet light sessions or sun exposure of the arms during the study were also excluded. Subjects with known or suspected hypersensitivity to 1 of the components of the investigational medicinal product or an allergy to the dressing to be used were not permitted to enroll in the study. Other exclusion criteria included: use of any treatment which may have affected blood coagulation and haemostasis, any physical treatment (like laser or surgery) on the arms in the 6 months prior to the study, use of topical or systemic treatments on the investigational areas within 4 weeks prior to the study, use of systemic antibiotics, systemic or topical steroids within 2 weeks of Day 1, and medical history of skin cancer.

Treatments

Test product=Control Gel. Ingredients: sunflower oil, beeswax yellow, carnauba wax. Applied topically once daily for 16 days at a thickness of approximately 1 mm (0.04 inch) over the wound area (diameter 8 mm to cover the wound edges). The treated areas were covered with a non-adhesive wound dressing with a non-adherent pad (Mepitel Border Lite) from Day 1 through Day 10 immediately after product application.

Reference product = Petrolatum (ALLERGIKA – BASISSALBE). Ingredients per 100 g: white petrolatum 95 g, liquid paraffin 5 g Applied topically once daily for 16 days at a thickness of approximately 1 mm (0.04 inch) over the wound area (diameter 8 mm to cover the wound edges). The treated areas were covered with a non-adhesive wound dressing with a non-adherent pad (Mepitel Border Lite) from Day 1 through Day 10 immediately after product application.

Duration of Treatment: 16 days (with a follow-up visit at day 23 +/-2 days).

Endpoints

Efficacy Endpoints: The primary efficacy endpoint was days until complete healing of mechanically induced wounds in terms of complete re-epithelialisation (assessed by clinical score). Secondary efficacy endpoints were days until complete healing of mechanically induced wounds in terms of complete re-epithelialisation (assessed by planimetry), clinical score per day, and wound surface area in mm2 per day.

Safety Endpoints: Secondary safety endpoints were incidence, severity, and causality of local tolerance AEs, and incidence, severity, and causality of all AEs.

Statistical Methods

The following analysis sets were used:

• Enrolled Set: All subjects who provided informed consent irrespective of whether they received an application of study treatment.

• All Randomised Subjects: All subjects who were assigned a randomisation number, irrespective of whether they received an application of study treatment.

• Full Analysis Set (FAS): All randomised subjects who received at least 1 application of study treatment and who had at least 1 post baseline assessment of clinical scoring of wound healing.

Subjects' wounds were analysed according to the treatment they were assigned to at randomisation, irrespective of the treatment they actually received.

• Per-Protocol Set (PPS): A subset of the FAS that consisted of those subjects who did not have major protocol deviations considered to have a serious impact on the efficacy results. The PPS was used as the primary analysis set for the statistical analysis of the primary and secondary estimands. However, as the PPS and FAS contained identical subject assignments, the FAS was used as the primary analysis set.

• Safety Analysis Set (SAF): All subjects who received at least 1 application of study treatment. Subjects' wounds were analysed according to the treatment actually applied (if different from the randomised treatment). The SAF was used for analysis of safety and tolerability.

The objective of the study was to demonstrate that the control gel was non inferior to petrolatum, based on the primary endpoint of days until complete healing assessed by clinical score. The primary estimand was mean difference in days until complete healing of 2 mechanically induced wounds in terms of complete re-epithelialisation (assessed by clinical score), regardless of the intercurrent events of treatment discontinuation or the assessment of re-epithelialisation being precluded.

The null hypothesis was that the control gel was inferior to petrolatum (i.e., H0: Mean difference $\geq$ NIM) and the alternative hypothesis was that the control gel was non inferior to petrolatum (i.e., H1: Mean difference < NIM), where NIM was the non-inferiority margin which was equal to 1 day, and the difference corresponded to: Control gel petrolatum.

All statistical tests were performed using a 1-sided 2.5% overall significance level and the comparison between the treatments was reported with 97.5% upper confidence limit for the difference. If the upper limit of the 97.5% confidence interval (CI) for the NIM was less than 1 day, then non inferiority was demonstrated. The use of a 1-sided 97.5% confidence limit is equivalent to the use of a 1-sided test at the alpha=0.025 level of significance.

For the primary analysis, a paired samples t test was utilised to conduct the non-inferiority test. This tested if the dependent variable of number of days to wound healing, measured for 2 different treatments (i.e., the 2 paired measurements) were significantly different. Summary estimates for each treatment with corresponding 95% 2-sided CIs and the difference between treatments with corresponding 1-sided 97.5% upper confidence limit, t-value and p-value were presented. The p-value was for the noninferiority test. If the 97.5% upper confidence limit was less than 1 day, then non-inferiority had been demonstrated. This primary analysis was performed for the FAS only as the FAS and PPS contained identical subject assignments.

For the secondary objective of days until complete healing of mechanically induced wounds in terms of complete re-epithelialisation (assessed by planimetry), the primary estimand was mean difference in days until complete healing of 2 mechanically induced wounds in terms of complete re-epithelialisation (assessed by planimetry), regardless of treatment discontinuation or the assessment of re-epithelialisation being precluded. Complete wound healing was defined as a mean wound area of 0 mm2. The number of days until complete healing (according to planimetry) was summarised and statistically analysed for mm^2 only in the same manner as described for the primary endpoint. Mean wound area in mm^2 and pixels were summarised by treatment group. The evaluation of each visit photography was performed by 2 independent assessors and the mean was used.

Results

A total of 16 patients were randomised and all completed the study. Eight subjects were randomised to receive control gel on Wound A and petrolatum on Wound B, and 8 subjects were randomised to receive petrolatum on Wound A and control gel on Wound B. No major protocol deviations were reported.

Eight male and 8 female subjects aged between 19 and 45 years were randomised and treated. All subjects had a Fitzpatrick skin phototype II or III as required by the protocol. None of the reported medical conditions or concomitant medications were considered likely to affect the conduct or results of the study.

On Day 1 (following wound induction), mean wound surface area according to planimetry was similar for wounds treated with control gel and those treated with petrolatum (42.97 mm^2 and 42.15 mm^2, respectively). The degree of variability was high on day 1; wound surface areas ranged from 22.2 mm^2 to 65.5 mm^2 across all wounds, and intra-subject-wound surface area difference was >10mm^2 in 5 subjects.

Efficacy Results

Primary Endpoint: Mean (standard deviation [SD]) days to complete wound healing assessed by clinical score were 14.2 (3.85) days for wounds treated with control gel and 12.5 (1.75) days for wounds treated with petrolatum. The null hypothesis that the control gel is inferior to petrolatum (mean difference ≥ the predefined NIM of 1 day) could not be rejected (upper limit of the 97.5% CI for the difference between treatments was 3.44 days). The maximum number of days to complete wound healing assessed by clinical score was longer for wounds treated with control gel (24 days) compared to those treated with petrolatum (16 days). Two wounds treated with control gel were assessed as not completely healed on Day 16; per protocol, the next assessment of wound healing was performed at the End of Study Visit (Day 23 ± 2 days). Both wounds were assessed as completely healed at the End of Study Visits. All wounds treated with petrolatum were assessed as completely healed by Day 16.

Secondary Endpoints: Mean (SD) days to complete wound healing assessed by planimetry was 8.6 (1.36) days for wounds treated with control gel and 8.9 (0.89) days for wounds treated with petrolatum. Control gel was confirmed to be non-inferior to petrolatum (upper limit of the 97.5% CI for the difference between treatments was <1 day [0.35 days]). The maximum number of days to complete wound healing assessed by planimetry was 11 days for both wounds treated with control gel and those treated with petrolatum. All wounds were considered completely healed as assessed by planimetry within 11 days following treatment with control gel or petrolatum.

Safety results

Six (37.5%) subjects experienced a total of 10 treatment-emergent AEs (TEAEs) during the study. With the exception of a single report of moderate application site pruritus, all TEAEs were mild in severity. No TEAEs led to discontinuation of study treatment, and none were considered serious.

Three (18.8%) subjects experienced a total of 6 TEAEs associated with the wound treated with control gel. These included application site pain (single event), application site pruritus (single event), and application site erosion (4 events described as scratching of wound site [2 events] and excoriation due to scratching [2 events]). With the exception of a single report of application site pruritus, all were considered to have a reasonable causal relationship to investigational medicinal product (IMP).

No subjects experienced a TEAE associated with the wound treated with petrolatum.

The remaining 4 TEAEs reported were not associated with a wound area. One event of pruritus (itching) between the wounds was assessed as having a reasonable causal relationship to IMP. The other 3 events were assessed as having a non-reasonable causal relationship to IMP.

No severe intolerance events were reported. The incidence of erythema, burning, pain, and exudate at the wound sites was low and all cases were mild with the exception of 1 report of moderate erythema at the End of Study Visit. The incidence of pruritus and desquamation was higher for wounds treated with control gel compared with wounds treated with petrolatum. However, the majority of occurrences were mild, and no severe cases were reported.

In accordance with the CHMP advice/protocol assistance (PA) provided in 2018 (EMEA/H/SA/2179/1/FU/2/2018/PA/SME/II), a study was conducted to evaluate a potential detrimental effect of the BEB-13 control gel. In the original dossier, study AHV-A18 was included, however, this was stated to be an exploratory study, to be followed by a confirmatory study (AHV-18-B). The applicant concluded that the results of study AHV-18-A indicated no differences in wound healing of mechanically induced partial-thickness wounds in healthy subjects between control gel, petrolatum, and no topical treatment (untreated). They claimed that this supported the use of the control gel as a blinded comparator for Oleogel-S10 in interventional clinical studies. However, this was just an exploratory study without any statistical hypothesis stated. According to the applicant, initiation of study AHV-18-B was delayed by a surge in the COVID-19 pandemic, however, upon request from the CHMP the final CSR was submitted.

In the 2018 PA procedure, it was stressed that the study should have a clear test hypothesis (superiority, non-inferiority vs. no treatment) and be powered for this. It should not be just an exploratory study. Further, there should be a justification of the extrapolation of the results observed in the skin of healthy volunteers to the skin in patient with EB, taking aspects like wound area and treatment duration into account. It was however agreed that for several reasons, performing the study in EB patients would not be feasible. The Sponsor was asked to define in the protocol what will constitute 'no difference in wound healing' and 95% confidence intervals for the pairwise comparisons needed to be presented, not only the p-values, which are of less interest/value for the interpretation.

It was also stated that the Sponsor needed to provide convincing arguments that the experimental wound study in healthy volunteers is sensitive enough to detect differences in wound healing. For instance, if the study can show that the petrolatum product is significantly superior to the untreated control and that the "placebo product" and petrolatum are similar, this can provide support for the notion that the vehicle used in the pivotal study will not have a detrimental effect on wound healing.

Study AHV-18-B had a very similar design as the AHV-18-A study, but with a somewhat larger sample size (n=16 vs. n=12). In contrast to the AHV-18-A study, there was no untreated control wound in the AHV-18-B study. Also based on the final results, it could not be demonstrated that the control gel was non-inferior to petrolatum according to clinical score (primary endpoint). The study showed that the control gel was non-inferior to petrolatum according to planimetry score (secondary endpoint/ mean score from 2 independent assessors).

Thus, it is concluded that based on the primary evaluation based on clinical assessment, the observed difference between the two treatments was *1.7 days*, which is very similar to the magnitude of effect observed for the similar endpoint (time to first complete closure of the EB target wound by clinical assessment; median 92 days for Oleogel-S10 and 94 days for control gel, the first key secondary endpoint) in the pivotal EB study, i.e. *2 days*. Hence, these results could not alleviate the concern that the difference observed for the primary endpoint in study BEB-13 could actually be due to an impaired

wound healing caused by the control gel. In view of the modest beneficial effect perceived to be due to Oleogel-S10, this may at least in part contribute to the observed small difference between treatments.

The applicant argued that although the evaluation of time to complete wound healing by clinical (naked eye) examination in the AHV-18-B study did not provide statistical evidence of non-inferiority using the pre-specified criteria, this observation was isolated as inconsistent with all others made in the same model (planimetry evaluations of wound healing in AHV-18-A and AHV-18-B, and clinical evaluations in AHV-18-A).

In the Day 180 response, the applicant further discussed and tried to find reasons for study AHV-18-B not showing formal non-inferiority. For instance, some practical issues were experienced when inflicting the standardised wounds, i.e., that the templates used needed to be re-attached in some cases which may have resulted in different wound surface areas and thus high variability in baseline wound area size. In study AHV-18-B, there were two wounds per subject and not three as in the exploratory AHV-18-A study, in which a third wound was also inflicted but was left untreated. The applicant also discussed whether a comparison of two wounds in the 18-B study ('best-in-two') would be more likely to result in a worse outcome for one of the two as compared to a comparison of three wounds in the 18-A study ('best-in-three'). For the latter, the claimed bias when comparing wounds side by side would be more diluted compared with the situation in the confirmatory 18-B study. The presence of two subjects in the 18-B study with wounds not healed by Day 16 based on clinical assessment (but assessed as healed with planimetry on Day 8 and 9, respectively) was also mentioned. Reasons for the planimetry assessment being more objective and reliable vs. the clinical assessment were also brought forward. These different factors may or may not have affected the outcomes.

Study AHV-18-B was designed to be the confirmatory study, with an increased number of subjects and optimised design, e.g., with respect to frequency of evaluations, etc. Further, the applicant chose to have the clinical assessment and not the planimetry as the primary endpoint for non-inferiority assessment. Thus, even if potential reasons for not showing non-inferiority for the control gel vs. petrolatum in the primary clinical assessment are noted and acknowledged, it must still be noted that the study could not formally fulfil its aim; to ascertain that the BEB-13 control gel did not impact wound healing in a negative way.

The applicant made a reference to the 'mean time to complete closure of the target wound' in the BEB-13 study. However, when presenting these figures, only the figures for those achieving wound closure were used. This led to a complete target wound closure of 37.7 (21.65) days for Oleogel-S10 and 44.5 (26.15) days (mean (SD)) for the control gel, thus, a difference of 6.8 days. This was misleading as it only included those subjects reaching wound closure. For the first key secondary endpoint in BEB-13 (time to first complete closure of the EB target wound as evidenced by clinical assessment within 90 days), the difference between the 2 treatment groups was not statistically significant (p=0.302). The median time to closure within 90 days was similar between treatment groups (92 days Oleogel-S10 and 94 days control gel).

Supportive external data

As additional support, the applicant referred to a study with a different product, however, in a similar setting (randomised, vehicle-controlled study of a topical treatment in different EB subtypes). The aim was to provided support for the 'natural history' of wound healing in EB patients.

In this study, no difference between the vehicle and active treatment could be demonstrated. However, the main purpose of referring to this study was to show a similar rate of wound closure with this vehicle as for the BEB-13 control gel. In this external study, the proportion of subjects who achieved the first target wound closure within 45 days on the vehicle was 24.05% and for the total population it was 27.15%. In BEB-13, 28.9% of subjects on control gel achieved complete wound

healing within D45. Nevertheless, between-study comparisons should be made with caution and no detailed display on differences or similarities in e.g., DEB/JEB distribution, age and co-morbidities was included. Still, the data may provide some support that the BEB-13 control gel behaved as expected and not obviously worse, although this study did not constitute a strong part of the justification for the control gel.

Literature review

The applicant has also provided a literature review aimed to support that ingredients in the control gel are not associated with negative effects on wound healing.

A number of authorised topical products contain these excipients. According to the applicant, there was no evidence found for these products of a detrimental effect on wound healing.

It was also referred to antioxidant and anti-inflammatory effects as well as healing properties of beeswax. For carnauba wax it was mentioned that a silk fibroin-based bi-layered wound dressing coated with carnauba wax was demonstrated to promote wound healing in full-thickness wounds with a greater extent of wound size reduction, epithelialisation, and collagen formation.

A literature review on sunflower oil was also performed, based on which it was concluded that it was used as standard of care in paediatric skin care, as it enhanced skin hydration, skin barrier development, function, and recovery and reduced transepidermal water loss. The sunflower oil *per se* is however not at question here, since it is included in both Filsuvez and the control gel.

Both beeswax and carnauba wax are present in topical medicinal products and are thus not unknown excipients. The applicant was also asked to provide any supporting literature data on the effects of topical products containing the same components as the control gel on wound healing, in general and in EB patients. This has been performed and a number of products and publications were referred to.

The applicant concluded that none of the 11 yellow wax-containing products listed has been shown to have adverse effects on wound healing. For 3 products, no information regarding effects on wound healing could be identified. In 3 further products, the use on wounds was not recommended. It was stated that their respective SmPCs did not provide a detailed rationale, but the likely reason was to minimize systemic absorption through application of e.g., a potent corticosteroid on open wounds.

The applicant made efforts to identify products containing the two waxes of interest, which is appreciated. The claimed lack of adverse effects on wound healing was complicated by several aspects. Firstly, a lack of *reported* negative effects on wound healing does not mean that there is none. Secondly, many products containing the waxes are products not indicated for use on open wounds, either because this is not the primary use or due to risk of adverse effects, e.g., systemic absorption of the active substance. Thirdly, when the waxes are used as excipients in topical products containing e.g., a topical corticosteroid, the effect of the steroid can mask potential negative effects, e.g. local irritant effects. Nevertheless, the applicant has fulfilled the requirement to compile literature data on the control gel components. Firm conclusions on lack of negative effects are difficult to draw from this data, although the presence of beeswax and carnauba wax in several topical medicinal products suggest that these components have no obvious harmful effects.

A justification was also requested for the extrapolation of the results observed in the skin of healthy volunteers to the skin in patient with EB, taking aspects like wound area and treatment duration into account. This part of the question has rather limited relevance, since the pivotal HV study could not demonstrate non-inferiority for control gel vs. petrolatum. Hence, a conclusive 'lack of negative effect' cannot be extrapolated to EB patients. It was however acknowledged that healthy volunteers and not

EB patients as a model for wound healing is preferred for the control gel assessment. While use of partial thickness wounds in healthy volunteers did remove the potential confounders seen in EB wounds, it may not be possible to extrapolate the results to patients with EB for that same reason. In addition, the size of wounds treated in the healthy volunteer studies versus the pivotal studies was different.

Interestingly, the applicant also mentioned that "petrolatum (the 'reference product' in the healthy volunteer wound healing studies) has been widely used on PTWs of different aetiology including EB wounds for decades, even if there's still no conclusive evidence of its effects on wound healing". If petrolatum would have a demonstrated, indisputable *positive* effect on wound healing, a smaller effect of the BEB-13 control gel would not have been surprising. If on the other hand, petrolatum has a modest, inconclusive effect, the observed longer time to wound healing for the control gel would be more concerning.

Overall, the applicant referred to the collective information from the *literature* review, the *AHV-18-A results* (clinical score and planimetry), the *AHV-18-B planimetry results* and the comparison with the *ESSENCE study* as evidence for the control gel not having a detrimental effect on wound healing.

It is acknowledged that these different pieces of evidence suggested no existence of an obvious harmful effect of the control gel. The carefully designed confirmatory study AHV-18-B could not conclude on non-inferiority for the control gel vs. petrolatum for its primary endpoint. Some degree of uncertainty still exists; however, the applicant has made efforts to discuss and explain this issue to the extent possible and further data and/or justifications were not deemed necessary.

Studies in partial-thickness wounds other than EB (Episalvan studies)

The three studies in partial-thickness wounds (STSG donor site wound studies BSG-12 and BSH-12, and Grade 2a burn wound study BBW-11) were assessed in depth in the Episalvan MAA. A summary of the main design elements can be found in Table 19.

The study results are summarized in Table 19. In these three non-EB studies in subjects with STSGs and Grade 2a burn wounds, a global assessment of efficacy was performed by both investigators and subjects throughout treatment until the end of treatment (EoT) using a questionnaire. At the EoT, Oleogel-S10 was assessed as more effective or much more effective than control for the majority of subjects in both the investigator and subject assessments.

Table 19. Overview of Efficacy Results for Non-EB Phase 3 Studies, BSH-12, BSG-12, BBW-11 (ITT)

		Split-thickness skin graft donor site wound studies		**Grade 2a burn wound study**
		BSH-12, N=107	**BSG-12, N=110**	**BBW-11, N=57**
Blinded reader assessments (mean expert evaluation)				

		Split-thickness skin graft donor site wound studies		Grade 2a burn wound study
		BSH-12, N=107	**BSG-12, N=110**	**BBW-11, N=57**
Primary endpoint for BSH-12, BSG-12 (2° for BBW-11)	Mean intrasubject difference in time to wound closure between the wound halves -using conservative "+1 day approach" for censored values	-1.4 days in favor of Oleogel-S10 p<0.0001, 2-sided paired t-test	-0.8 days in favor of Oleogel-S10 p=0.0232, 2-sided paired t-test	-1.0 day in favor of Oleogel-S10 p<0.0001, 2-sided paired t-test
Sensitivity analysis	Mean intrasubject difference in time to wound closure between the wound halves -using "+ MTWDC approach" for censored values	-2.0 days in favor of Oleogel-S10 p<0.0001, 2-sided paired t-test	-1.1 days in favor of Oleogel-S10 p=0.0063, 2-sided paired t-test	n. d.
Follow-up result (secondary endpoint)	Pigmentation: Wound half more similar to healthy skin, 3 months after injury	41% of subjects Oleogel-S10 vs. 7% standard of care	33% of subjects Oleogel-S10 vs. 14% standard of care	38% of subjects Oleogel-S10 vs. 0% standard of care
	Pigmentation: Wound half more similar to healthy skin, 12 months after injury	21% of subjects Oleogel-S10 vs. 8% standard of care	28% of subjects Oleogel-S10 vs. 9% standard of care	21% of subjects Oleogel-S10 vs. 0% standard of care
Direct assessments (not blinded)				
Global assessments	Global assessment of efficacy by investigators / subjects (at EoT)	More (or much more) effective: 68.2% / 62.5% of Oleogel-S10 subjects, vs. 2.9% / 2.9% standard of care	More (or much more) effective: 52.4% / 51.0% of Oleogel-S10 subjects, vs. 10.5% / 9.8% standard of care	More (or much more) effective: 87.5% / 85.4% of Oleogel-S10 subjects, vs. 2.1% / 0.0% standard of care

		Split-thickness skin graft donor site wound studies		Grade 2a burn wound study
		BSH-12, N=107	**BSG-12, N=110**	**BBW-11, N=57**
Follow-up result (secondary endpoint)	Scar score (POSAS, patient and observer scar assessment scale)	n.d.	n.d.	Oleogel-S10=24 at 3 months, and 18 at 12 months Standard of care=33 at 3 months, and 22 at 12 months

Abbreviations: EB=epidermolysis bullosa; EoT=end of treatment, *i.e.*, last study visit in the treatment period; ITT=Intention-to-treat set; MTWDC=mean time to wound dressing change, *i.e.*, the mean interval between dressing changes; N=number of subjects in the analysis set; n.d.=not done; POSAS=Patient and Observer Scar Assessment Scale

Statistically significant results in favour of Oleogel-S10 were demonstrated in the pivotal studies supporting the partial-thickness wound indication for Episalvan. The effect size was however not large with a difference in time to wound closure between the wound halves generally being one day.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical efficacy data supporting an EB indication for Filsuvez is the phase 3 study BEB-13, with some support also from a small phase 2 study in EB patients, BEB-10. In addition, the studies included in the submission for Episalvan in the indication Treatment of split-thickness skin graft (STSG) donor site wounds were included in the dossier as supportive data. Furthermore, Phase 2 healthy subject studies with the control gel (AHV-18-A and AHV-18-B) were referred to in support of the EB application.

No specific pharmacodynamic studies (*ex vivo* or *in vivo*) in EB patients have been performed to support a positive effect of Oleogel-S10 in the acceleration of wound healing in EB skin. The postulated beneficial effects relied on the assumption that wound healing processes were similar in skin of healthy, non-EB subjects and EB patients. The mechanism of action is thus more of a general support to achieve a faster wound healing rather than a specific mechanism of action targeting specific EB sub-types.

There is no European guideline available for medicinal products indicated for the treatment of wounds, including wounds associated with EB.

The applicant overall followed the CHMP Scientific Advice/Protocol Assistance received except in terms of dossier content. A number of issues were raised, in particular regarding the justification for the control gel used in the pivotal study. This is further discussed below.

Study BEB-10

Study BEB-10 was a very small (n=10) Phase 2 study of Oleogel-S10 in EB patients, seen as evaluation of proof-of-concept in this target population. The study had an intra-individual comparative design, commonly seen in early, explorative studies for locally applied dermatological products. The control treatment was the standard dressing only and not another applied gel or ointment (placebo/vehicle). The study was conducted open-label, with blinded assessment of efficacy by 2 independent experts based on photographs. The analyses of this study had methodological flaws as it favoured the IMP with limited justification, in case the two reviewers disagreed.

Study BEB-10 did not include dose finding and no other dose finding study has been performed for Filsuvez/Oleogel-S10 in the EB indication. Since the effect is local, PK/PD modelling is not applicable. The applicant was of the view that a clinical dose-finding study was not performed because lower or higher concentrations of the drug substance would have negatively impacted the characteristics of the gel. This is acknowledged. In the Episalvan EPAR, it was also concluded that no conventional dose-response studies were performed and the CHMP considered that the provided information was sufficient for the selection of the chosen concentration. The same concentration (10%) and formulation is used in both products. Therefore, there was no issue raised by the CHMP related to the dose finding.

Study BEB-13

Study design

This was a randomised, controlled, 90-day double-blind phase 3 study, with a 24-month open-label follow-up of Oleogel-S10 in subjects with inherited EB. Each subject was to participate for 90 days in the randomised DBP. At the end of the DBP (Day 90), subjects in both treatment arms were invited to enter the single-arm OLP with Oleogel-S10 treatment of all wounds for 24 months.

Study population

The inclusion and exclusion criteria were overall found acceptable and were endorsed by the CHMP in scientific advice (EMEA/H/SA/2179/1/2011/PA/III and EMEA/H/SA/2179/1/FU/1/2016/PA/SME/III). Following a protocol amendment, patients with the milder EB subtype EBS (EB Simplex) were not to be included. This is acknowledged and the proposed indication wording does not include EBS.

It was not stated in the inclusion criteria how the EB diagnosis should have been confirmed, e.g., if genetic testing was needed or if immunofluorescence mapping or electron microscopy or a clinical EB diagnosis only would suffice. This is further discussed below.

A target wound was defined as having a size 10 cm^2 to 50 cm^2, aged ≥21 days but less than 9 months, and should be present outside of the anogenital region. This is endorsed. Following discussions in the CHMP Protocol assistance in 2017 (EMEA/H/SA/2179/1/FU/1/2016/PA/SME/III), an upper size limit of 50 cm^2 was set. The target wound should not have clinical signs of local infection. An upper age limit of 9 months for the target wound was included following an amendment.

The study had broad age inclusion criteria; subjects from the age of 21 days could be included. The inclusion of children below 4 years of age was only made after confirmation by the IDMC upon review of the safety and PK (betulin levels) data at the interim safety review. This approach is reasonable, and the inclusion of children and infants is relevant due to the unmet need also in this group of EB patients.

Treatments

The subjects were randomized 1:1 to receive either Oleogel-S10 or control gel respectively on top of the standard of care (non-adhesive wound dressing). The control gel used in this study was not the gel vehicle without the active substance (the extract). Due to the galenical properties, with the betulin extract and sunflower oil forming an 'oleogel', it was not possible to use the gel vehicle in this case, i.e., pure sunflower oil (with different viscosity etc. vs the active product). Therefore, a dedicated 'control gel' was developed and used in the study. This approach was extensively discussed in the scientific advice procedures (EMEA/H/SA/2179/1/FU/1/2016/PA/SME/III, EMEA/H/SA/2179/1/FU/2/2018/PA/SME/II). There was a concern that in case a beneficial effect of the active treatment (Oleogel-S10) was observed, sufficient reassurance would be needed to establish that this was not merely due to a detrimental effect on wound healing caused by the 'control gel'. To overcome this concern, the applicant conducted study AHV18-A and subsequently study AHV18-B (see below).

Oleogel-S10 or the control gel were applied on the EB target wound and also to all areas on the subject's body that were affected by EB partial-thickness wounds. No maximum body surface area to be covered was specified in the protocol.

The attempts to standardise the type of wound dressings to be used, to the extent possible in a global study, was acknowledged. However, some subjects still used Vaseline gauze or other dressings containing topical emollients, although these were not permitted per the protocol. A subgroup analysis of these subjects was performed and is discussed below.

Objectives and endpoints

The primary objective of the DBP was to compare the efficacy of Oleogel-S10 with vehicle (control gel) in the promotion of healing of EB partial-thickness wounds.

The primary efficacy endpoint of the DBP was the proportion of subjects with first complete closure of the EB target wound in subjects with inherited EB within 45 days of treatment with Oleogel-S10 compared with control gel based on clinical assessment by the investigator (the wound was to be rated as "closed" at first appearance of complete re-epithelialisation without drainage). The choice of this endpoint was discussed and agreed in the CHMP protocol assistance in 2017 (EMEA/H/SA/2179/1/FU/1/2016/PA/SME/III). Assessing the proportion of patients achieving wound closure within a period of 45 days, rather than time to first wound closure within 90 days was found adequate. In addition, the time point 45 days was preferred to the initially proposed 60 days, since assessment at an earlier time point would be relevant to address acceleration of wound healing.

A *re-opening* of a closed target wound is however also of great interest since EB skin is very fragile and a benefit of a healed wound would be larger if the healing is sustained. This was discussed in the PA procedure (EMEA/H/SA/2179/1/FU/1/2016/PA/SME/III) and it was considered that the incidence of re-injury of the target wound should be reported. Confirmation of complete closure was assessed by a site study team member (e.g., study nurse) at home 7 days (±2 days) after first clinical assessment of complete closure of the EB target wound. This was assessed in a supportive analysis.

A large number of secondary endpoints have been evaluated, six of them being classified as key secondary efficacy endpoints and included in the multiple testing procedure. If the primary analysis of the primary efficacy endpoint demonstrated superiority at the 5% significance level, hierarchical confirmatory testing of the 6 key secondary endpoints was planned on the FAS. These endpoints reflect other aspects of wound healing, the incidence and severity of wound infections, change from baseline in total body wound burden (TBWB) and change from baseline in itching. In addition to the key secondary endpoints a range of other secondary endpoints were also evaluated, e.g., addressing "procedural" pain and "background" pain, evaluating target wound closure at other time points, TBWB, change from baseline in body surface area percentage affected by EB partial-thickness wounds and itch. These were considered as relevant efficacy endpoints in an EB study.

Randomisation and blinding

A 1:1 randomisation to Oleogel-S10 or control gel was used, stratified for EB subtype and size of target wound (cm^2) in six different strata. The stratification factors were considered adequate. The sample size was increased following an unblinded sample size re-estimation. This was pre-planned and described in detail in the SAP and the final analysis was adequately adjusted.

Adequate procedures and measures have been taken to ensure blinding. As described above, using the pure vehicle (sunflower oil) was not considered possible in this case due to different galenic properties, e.g., viscosity, that would have led to unblinding. Nevertheless, the use of a different 'control gel' can impact the interpretation of a difference observed between treatment arms. This is discussed further below in relation to the assessment of the supportive studies AHV-18-A and AHV18-B.

Statistical analysis

The primary endpoint was analysed with Cochran-Mantel-Haenszel (CMH) test, stratified by EB subtype and target wound size class. The primary analysis of the primary endpoint used the Cui, Hung, Wang (CHW) approach to adjust the estimates provided by the CMH test for the sample size re-estimation.

Concerns were raised related to the type I error control using this approach, however adequate justification for using this method has been provided.

Missing data was imputed as failures in the primary analysis. Since more subjects discontinued the double-blind phase in the control treatment group than in the Oleogel-S10 treatment group this was not considered to be a conservative approach for the treatment comparison. Hence the sensitivity analyses were of importance. Of particular interest for assessing the robustness of the results was the tipping point analysis challenging the MAR assumption (see further below).

Study AHV-18-A

This was an exploratory, randomised, intrasubject-controlled study of the cutaneous healing properties of petrolatum versus the control gel for Oleogel-S10 (used in BEB-13) versus no treatment, when applied topically to mechanically induced partial-thickness wounds in 12 healthy adult subjects. The results from this study were to be used to inform the design of a confirmatory, Phase 2 study (Study AHV-18-B), including calculation of an appropriate sample size. Randomised subjects had 3 abrasive wounds (created using a sterile scrub brush) of approximately 8 mm diameter in 3 mini-zones and the three wounds were treated with either of the three treatments, randomly assigned.

The primary efficacy endpoints were days until complete healing according to clinical score and days until complete healing according to planimetry. Secondary efficacy endpoints were mean clinical score per day, mean wound surface area in mm^2, and mean TEWL per wound.

This was an exploratory study; hence, only descriptive statistical methods were applied, treatments were not compared using a statistical test; no null hypotheses were tested.

Study AHV-18-B

This study had a very similar design as study AHV-18-A, but it did not include an untreated wound area, only a comparison of the control gel vs. petrolatum. The sample size was larger compared with AHV-18-A (n=16 vs. n=12).

The primary objective was to demonstrate that the control gel was non-inferior to petrolatum with regards to time to achieve cutaneous healing of mechanically induced partial thickness wounds in healthy volunteers. The primary efficacy endpoint was days until complete healing of mechanically induced wounds in terms of complete re-epithelialisation assessed by clinical score. The first secondary efficacy endpoint was days until complete healing of mechanically induced wounds in terms of complete re-epithelialisation assessed by planimetry. A non-inferiority margin of 1 day was used.

Efficacy data and additional analyses

Study BEB-10

In the comparison of wound halves, Oleogel-S10 showed the majority of positive results whereas the 'non-adhesive wound dressing' alone was found the best in only two instances (with conflicting results between the reviewers for those). The efficacy results from this very small, intra-patient, open-label (but reviewer-blinded) study were not strong and provided limited support for a proof-of-concept and beneficial effects of Oleogel-S10 in the re-epithelialisation of EB wounds. The majority of patients had RDEB. The open label nature was considered a limitation and there were flaws in the applicant's interpretation/presentation of the efficacy results for the primary endpoint. The study may have benefitted from three blinded experts assessing the wounds to lessen ambiguity regarding efficacy results. In any case, the results seen for the primary, key and other secondary endpoints were not overly compelling and thus are considered to provide limited support for this application.

Study BEB-13

A total of 252 subjects were screened and of these, 223 subjects were randomised to Oleogel-S10 (N=109) or control gel (N=114). Randomised subjects were enrolled across 49 sites in 26 countries and geographic regions, including the US, Europe, South America, and Rest of World. Overall, 199

(89%) subjects completed the DBP of the study (92%, Oleogel-S10 vs. 87%, control gel), and 24 (11%) subjects discontinued. Thus, the rate of completion in the double-blind part of the study was high. The most common reasons for discontinuation were reasons classified as Other and withdrawal of consent. Upon request from the CHMP, the applicant provided updated data from the OLP. The final CSR will be submitted once available (i.e., by Q1 2023).

There were several amendments to the protocol. These included for instance exclusion of subjects with EB Simplex, sample size re-estimations, definition of the EB target wound and clarification of the primary endpoint (confirmation of closure no longer required). More than 60% of the subjects overall had at least one major protocol deviation during the DBP of the study. The major reasons were related to the investigational product (e.g., non-compliance with administration regimen), use of prohibited concomitant treatment / prohibited dressings or due to missed visits / visits outside window.

Wound dressings that were prohibited according to the protocol were used in a large proportion of subjects. These included both dressings with emollients and in some cases also dressings containing an active ingredient, e.g., silver or PHMB. It was finally decided that non-permitted dressings were to be considered as minor protocol deviations for defining the PPS. The use of prohibited wound dressings occurred in both treatment arms (31 Oleogel-S10 vs. 37 control gel). A subgroup analysis has been performed, see below. The use of prohibited dressing occurred in a higher percentage of patients in the control arm versus the treatment arm. The applicant has provided further detail on the underlying EB type that this occurred in or whether it was for all EB subtypes and also provided a further analysis on the primary and key secondary endpoints removing these patients. No concerns regarding the impact of the above findings on the study results remain based on the additional data provided.

Compliance, defined as actual treatment duration in days / treatment duration in days * 100, was high in both treatment arms, being >98%.

Overall, the demographics were well balanced between the two treatment groups. 60% of subjects were male and 40% were female. The median age was 12 years (range 6 months to 81 years). Divided by age categories, 8% of subjects were 0 to <4 years of age, 38% were 4 to <12 years, 24% were 12 to <18 years, and 30% were ≥18 years of age. Of the 67 subjects who were ≥18 years of age, 3 subjects were 65 years of age or older. Thus, the majority of subjects were in the age range 4-12 years and very few subjects were elderly (only three aged above 65 years). This reflected a population with severe EB, i.e., that the condition was present from birth and that many EB patients with severe forms like DEB or JEB have a limited life span.

The majority (>80%) of subjects were White. Geographic regions in which subjects were enrolled included Europe (46%), South America (30.5%), Rest of World (17%), and the US (6%).

The mean BMI of subjects was 16.2 kg/m^2. Approximately half (52%) of subjects were underweight; 39% had normal weight; 5% were overweight; and 5% were obese. This also reflected a severely affected EB population, where many patients have nutritional problems.

In the Safety Analysis Set, 87% subjects had the EB subtype of DEB; of these, 175 (78.5%) subjects had RDEB and 20 (9%) subjects had DDEB. Twenty-six (11.7%) subjects had JEB. Two (0.9%) subjects had EBS, since with implementation of Version 4.0 of the protocol, subjects with EBS were excluded from study participation. None of the subjects had Kindler syndrome.

EB subtype identification was based on genetic testing in 129 (57.8%) subjects, clinical diagnosis only in 49 (22.0%) subjects, immunofluorescence mapping or electron microscopy in 41 (18.4%) subjects, and method classified as Other in 4 (1.8%) subjects.

Justifications for clinical diagnosis only was requested. The applicant clarified that additional subjects had or were planned to undergo genetic testing prior to final database lock. It was anticipated that for the final CSR, the proportion of subjects with clinical diagnosis only will be reduced to approximately 12%, which is acknowledged by the CHMP. It was also noted that according to both previous and current EB consensus, classification of inherited EB is still primarily clinically oriented, as the EB

classification is complex. It is acknowledged that a specific diagnosis of EB subtype can be challenging, and it is agreed that the risk of misdiagnosis or misclassification is low. Hence, for a topical treatment which is not specifically developed to target specific mutations causing EB, it does not seem critical to require genetic confirmation prior to initiation of treatment in the SmPC. Based on this, a requirement for restricted medical prescription is also not considered warranted.

The DEB and JEB disease subtypes and methods of diagnosis were generally well balanced between the 2 treatment groups. However, within the DEB subtype, the Oleogel-S10 group had a higher proportion of subjects with RDEB compared to the control gel (83.5%, Oleogel-S10 vs. 73.7%, control) and a lower proportion of subjects with DDEB (5.5%, Oleogel-S10 vs. 12.3%, control).

Concerning the target wound characteristics, the majority (65%) of subjects had a target wound between 10 to <20 cm^2; 21% between 20 to <30 cm^2, and 14% between 30 to 50 cm^2. The median wound size was about 16 cm^2. The overall median wound age was 35.5 days. The target wounds were most commonly located on the lower leg (20%), knee (13.5%), and thigh (13.5%).

The target wound size was well balanced between the treatment groups; however, the median wound age was slightly greater in the Oleogel-S10 group (39 days, Oleogel-S10 vs. 32 days, control gel). It was not fully clear how large body surface area in total that was treated, but clarification has been provided in a safety question and relevant information was adequately reflected in SmPC section 5.1.

Comorbidities observed (e.g., gastrointestinal disorders, blood and lymphatic system disorders, skin disorders other than EB, metabolism and nutrition disorders, infections) were those generally anticipated in subjects with EB and were related to the disease and its complications. Medical and surgical histories were generally well balanced between the treatment groups, with some imbalances in pruritus and pain. Prior and concomitant medication use were overall well balanced between treatment groups.

All of the randomised subjects (N=223) were included in the Safety Analysis Set and the FAS; 185 (83%) subjects were included in the PPS (84.4% Oleogel-S10 vs. 81.6% subjects, control).

Efficacy results

Primary endpoint

The primary efficacy endpoint was met as the proportion of subjects with first complete closure of the EB target wound within 45 days of initiating treatment was higher in the Oleogel-S10 group (41.3%) compared to the control gel group (28.9%). This finding was statistically significant in favour of Oleogel-S10 based on the CHW method using the CMH test statistics (p=0.013) and based on the unadjusted CMH test (p=0.041). The difference between treatments was considered by the CHMP to be small (12.4 % units) and the results were not of high statistical significance (SmPC section 5.1). Results for the PPS population did not reach statistical significance (p=0.151) even if the magnitude of the difference was almost similar to the FAS.

Since the primary analysis used a non-responder imputation for missing data and the amount of missing data was larger in the control treatment group than in the Oleogel-S10 treatment group this was not considered a sufficiently conservative analysis. The tipping point analysis described in the SAP using multiple imputation (MI) was considered of particular interest. The MI analysis without tipping gave borderline significant results and switching the result for only one control patient resulted in a non-significant p-value. Hence, the robustness of the results was initially questioned, and a discussion was requested by the CHMP.

Upon request from the CHMP, the applicant provided further information on amount of missing data at the day 45 visit arguing that the amount and reasons of missing data was similar in the two treatment groups. This wa agreed to by the CHMP. However, this is no guarantee that data are Missing at Random (MAR). The CHMP was of the view that there could still be mechanisms deviating from the

MAR assumption that would create bias in the comparison. Hence, the tipping point analysis evaluating robustness to any such bias was still considered important.

The applicant argued that the CMH (Cochran-Mantel-Haenszel) test did not work well with small strata and has provided post hoc analyses combining or removing the three JEB/Kindler strata. In those analyses the p-value was slightly smaller and switching one subject did not yield non-significant results (however switching two subjects did). The applicant hence considered that the primary analysis was robust and driven by the largest cohort, namely the dystrophic EB subtype. This was not agreed by the CHMP. Those analyses were performed post-hoc and were not prespecified in the SAP. A major objection was therefore raised by the CHMP regarding the robustness of the results for the primary endpoint.

Further justifications for the robustness of results were presented by the applicant. Based on the response provided, it can be agreed that the results for the primary endpoint (which used the clinical assessment of the target wound by the investigator) and an assessment using standardised photographs (evaluated by an independent blinded expert panel) were consistent. The effect size was also similar, with a difference of 12.4% units (Oleogel-S10 vs. control gel) for the primary endpoint and 13.2% units for the blinded expert panel photo evaluation.

To try to strengthen the evidence from the primary analysis the applicant has gone through subjects with missing data in the primary endpoint and discussed whether each subject could have been a responder. Since this subject-by-subject evaluation was performed post hoc on fully unblinded results and was not conclusive in its result it was not considered to add any information to the assessment. The fact pointed out by the applicant that the tipping point analysis was performed with the Cochran-Mantel-Haenszel (CMH) test and not the Cui-Hung-Wang (CHW) test used for the primary analysis was also not considered to weaken the tipping point analysis. The fact remained, the primary analysis was statistically significant with a p-value of 0.013, however, most sensitivity analyses were not statistically significant, and the tipping point analysis showed that changing the result of one single patient gave a non-significant result. Nevertheless, at the oral explanation and upon request by the CHMP, the applicant presented results of the primary efficacy analysis switching this one single patient from non-responder to responder using the CHW methodology. In contrast to the tipping point analysis performed with the CMH test, this analysis demonstrated that the p-value remained statistically significant (i.e., p-value=0.021). The CHMP was therefore of the view that the results for the primary endpoint can be considered as robust from a statistical viewpoint.

The applicant also referred to the importance of evaluation of both *complete wound closure* and *reduction in wound size* as key efficacy measures and that there can be a benefit even if a wound has not yet achieved one hundred percent wound closure at time of evaluation for EB patients.

The target wound showed a reduction in size in both treatment groups from a mean of 19.14 cm2 at baseline to 7.65 cm^2 by Day 45 -11.49 cm^2 for Oleogel-S10, compared to a reduction from 19.6 cm^2 at baseline to 9.26 cm^2 by Day 45 -10.34 cm^2 for the control gel arm. For a comparison of the mean AUCs using a two-sided two-sample t-test, the Oleogel-S10 mean was significantly lower than the control mean (p=0.017). It should be noted that this was not the analysis pre-planned and reported in the study report. Analyses presented in the study report did not show statistically significant treatment difference. Furthermore, this was not a multiplicity-controlled secondary endpoint, hence the p-value must be seen as 'nominal'. Also, the difference between treatments was overall considered to be small by the CHMP; the difference in change from baseline in mean wound size at Day 45 was 1.15 cm^2.

For the presentation based on stratification factors, the DEB strata showed higher rates of wound closure for Oleogel-S10 vs. control gel across wound size. In the largest stratification group of 128 subjects (DEB 10 to <20 cm^2), the proportion of subjects with first complete closure of the EB target wound within 45 days of treatment was higher in the Oleogel-S10 group (54.8%) compared to the control gel group (39.4%). In the second largest stratification group of 43 subjects (DEB 20 to <30 cm2), these proportions were 27.3% and 9.5%, respectively; a similar trend was observed for subjects

with DEB 30 to 50 cm2 (21.4% and 8.3%, respectively). For the JEB/Kindler sub-types, however, the patient numbers were much smaller (n=26 in total; no subject in BEB-13 had Kindler syndrome) and conclusions were difficult to make.

In a sensitivity analysis, results for the primary endpoint was assessed based on confirmed, sustained healing of the target wound, at 7 days after the first healing was observed. This resulted in fewer subjects rated as 'success' for both groups, with 17.4% achieving confirmed closure in the Oleogel-S10 group vs. 8.8% in the control group. This difference was borderline significant (p=0.048).

Secondary endpoints

The applicant had defined six 'key' secondary endpoints of the total 18 secondary endpoints in the protocol. The results for the first key secondary endpoint were not statistically significant, hence, the results for the key secondary endpoints were not confirmatory. The p-values reported for other analyses of the key secondary endpoints were not adjusted for multiplicity.

Regarding the first key secondary endpoint, the median time to closure was similar between treatment groups (92 days Oleogel-S10 and 94 days control gel) and the difference was not statistically significant (p=0.302).

The second key secondary endpoint was the proportion of subjects with first complete closure of the EB target wound within 90 days of treatment based on clinical assessment by the investigator. A higher proportion of subjects in the Oleogel-S10 group (50.5%) achieved first EB target wound closure than subjects in the control gel group (43.9%) by Day 90, however, the difference was not statistically significant (p=0.296).

Two subjects treated with Oleogel-S10 (1.8%; actually 1 based on a misclassification, thus 0.9%) experienced a target wound infection between baseline and Day 90 compared with five subjects treated with control gel (4.4%). Overall, the number of wound infections was low and no statistically significant treatment difference was observed. The same applied to infections in non-target wounds. Not much could be said about the severity of wound infections; the infection reported by the 1 subject who received Oleogel-S10 was classified as mild. Overall, the CHMP considered that the rates were too low to assess whether there was a difference between Oleogel-S10 and control gel.

For pain, which can be of great importance in EB, (denoted as an additional secondary endpoint), some mean improvements that were greater in the Oleogel-S10 group compared to the control gel group were observed, mainly for procedural pain with a statistically significant difference in favour of Oleogel-S10 at Day 14 (nominal p-value 0.022) and also a larger difference at Day 90 (nominal p-value 0.051). However, the differences between treatments were very small.

For endpoints relating to sleep, number of days missed from school or work due to EB and overall treatment satisfaction, no clear beneficial effects of Oleogel-S10 vs. control gel could be observed.

Thus, no formally demonstrated positive effects on wound infections, total body wound burden, itch, pain or sleep can be claimed for Filsuvez.

In order to address the CHMP's concerns regarding the clinical relevance of the effects seen with Filsuvez to patients and carers of EB patients, further argumentation was provided by the applicant.

One new aspect was a review of subjects who had daily dressing changes at baseline, which showed that the proportion who had reduced frequency at subsequent visits was larger in the Oleogel-S10 arm than in the control gel arm. At Day 90/end of DBP, 14.7% of subjects on Oleogel-S10 no longer required daily dressings compared to 6.1% of subjects on control gel. Although the difference between treatments was considered to be small by the CHMP and this was not a formal endpoint in the study, this may be of benefit since changing dressings in EB patients is time consuming and painful. However, these analyses were not pre-planned, and as such were considered by the CHMP of limited value for the present application.

The applicant also referred to testimonies from the EB patient community and an EB expert statement. These statements and testimonies were acknowledged, and it is understandable that in a condition like EB, there is a tolerance towards a degree of uncertainty for a treatment benefit and also an acceptance of a higher level of risk for even the chance of a potential benefit. The benefits of a local treatment without systemic risks and without need for check-ups was also referred to. The applicant also provided information from the use of Oleogel-S10 via 'Temporary Authorisation for Use' (ATU) in France. Between 25 August 2020 and 06 October 2021, 31 patients at 5 sites have been granted access to Oleogel-S10 within the ATU, the majority being children (74%) and with the subtype RDEB (74%). The youngest participant is less than 1 year old. In terms of safety data from the ongoing ATU, as of 23 Nov 2021, 4 of the 31 subjects enrolled had discontinued the ATU prematurely of which 2 discontinued due to AEs, but in general, the product was well tolerated. These data were noted but did not provide further support for the effect of Oleogel-S10.

To conclude on the results from secondary endpoints in study BEB-13, even if there was largely a consistency in the direction of improvement, the differences between Oleogel-S10 and control gel were very modest. It is acknowledged that in rare diseases, secondary endpoints may not be powered for formal statistical testing. It was unclear if the minor differences compared to control with respect to total wound burden, itch and pain are clinically meaningful. At the AHEG meeting, it was however confirmed by both physicians treating EB patients and by EB patients/caregivers that any effect, no matter how small, would be of clinical benefit in this condition.

Overall, even if the statistical robustness of the analysis of the primary endpoint has been questioned during the procedure, the CHMP is of the view, in line with the recommendation of the AHEG, that an effect of Filsuvez has been established in the overall study population considering that some of the sensitivity analyses supported the primary analysis of the primary endpoint. This effect was also considered to be clinically relevant for the EB patients and carers.

Sub-group results

With respect to *EB subtypes,* there was a large difference in the numbers included with different subtypes, with the RDEB subtype group being largest (n=175 subjects), while the DDEB (n=20 subjects) and JEB subtype groups (n=26 subjects) were much smaller. This is likely a reason for differing results for the primary endpoint, where an effect could be shown for the RDEB group (44.0% vs. 26.2%, respectively; CMH p=0.008), but not for the two other subtypes (same rates of closure in both groups for DDEB and higher rate of closure for control gel vs. Oleogel-S10 for JEB). There were some imbalances in numbers randomised to Oleogel-S10 vs. control gel and also imbalances with respect to wound size and age, that may have contributed. The applicant initially proposed an indication covering both dystrophic and junctional EB, which was questioned on the basis of these results. It was acknowledged that due to the even higher rarity of the DDEB and JEB sub-types, it may not be realistic to recruit enough patients to enable a demonstration of statistically significant effect within each sub-type. However, especially in JEB, the results were still deemed questionable as this EB subtype has large heterogeneity in severity and presentation. In an attempt to address the CHMP's concerns, the applicant initially proposed to remove the JEB subgroup from the indication based on a sub-group analysis only on the RDEB subject population. However, in the new subgroup analysis, the DEB subgroup did not include the DDEB sub-type even if the revised proposed indication included both RDEB and DDEB, which was questioned by the CHMP.

It is agreed that the presented subgroup analysis for the RDEB sub-population had a larger treatment effect and a stronger significance level (nominal p-value) than the analysis of the FAS dataset as pointed out by the applicant. Since the presented sub-group analysis was considered post-hoc and data-driven, it was not accepted as confirmatory evidence of efficacy by the CHMP.

At the AHEG meeting, the experts considered that one cannot infer that a drug that works in DEB would work in JEB as well, while the patients' representatives considered that any drug that overall works in EB would be considered as important for the EB patients. It was finally considered acceptable by the CHMP to include also the JEB subtype in the indication given the demonstrated effect of Filsuvez

in the overall study population (i.e., DEB and JEB) and the unspecific mechanism of action which does not target specific EB sub-types. However, a cautionary statement was included in SmPC section 4.4 clarifying the limited data available in the JEB and DDEB subtypes.

With respect to *age*, the largest part of the study population was aged below 18 years with the largest sub-group being those aged 4 to <12 years, comprising 38% overall. The subgroup 0 - <4 years was very small (n=17 in total, <8% of the total population). In the 4 to <12 years age subgroup, the most pronounced difference between treatments in favour of Oleogel-S10 was observed. Results for the other age groups below 18 years were numerically in favour of Oleogel-S10 while this was not the case for patients aged ≥ 18 years (odds ratio and 95% CI 0.86, 0.31; 2.43). Hence, the youngest age group (0-<4 years) was very small and for the oldest age group (≥18 years, i.e., adults) the results were not in favour of Oleogel-S10. The applicant was asked to discuss and justify the applied indication covering all ages.

The age distribution in the 0-<4 years group has been presented and there were no Oleogel-S10-treated subjects aged 6-11 months (2 in the control arm), 3 were aged 12-17 months, 3 were aged 2 years and one was aged 3 years. Thus, no patient < 1 year was exposed to Oleogel-S10. From an efficacy perspective, the applicant presented the results for the primary endpoint in the ⩾21 days and <4 years subgroup and 71% reached closure in the Oleogel-S10 group vs. 40% in the control group. This was however based on very small numbers. No firm conclusions can be made regarding procedural pain assessed by the FLACC pain score. The applicant also referred to safety results, showing no major concerns in comparison with the overall study population, but again, the small numbers made conclusions difficult. Efficacy-wise, there seems to be no reason to expect a different response with Oleogel-S10 in the youngest, compared with older children, adolescents and adults. The treatment is topical and thus a need for a specific systemic exposure to achieve an effect is not relevant. Nevertheless, from a safety viewpoint, considering the very limited data in the youngest age group, an indication from birth onwards was not supported by the CHMP and a lower age limit of 6 months has been introduced by the applicant. See section 2.6.9 discussion on clinical safety.

Concerning adults, there is no obvious reason to exclude adult EB patients from the indication (even if a subgroup analysis did not show favourable results for Oleogel-S10 vs. control gel). Even if there were very few EB patients aged >65 years (n=3), an upper age limit does not seem warranted based on efficacy (or safety).

Regardless of *target wound size* and *gender*, the results tended to favour Oleogel-S10.

Concerning *permitted vs. non-permitted contact layer/dressings*, subjects treated with Oleogel-S10 were more likely to achieve the primary endpoint than subjects who received control gel regardless of whether a permitted contact layer/dressing was used. Further analyses and clarifications have been provided and no issues remained.

Results with respect to *race* are difficult to make since 83.4% of subjects were White.

No obvious differences in effect for Oleogel-S10 vs. control gel were observed for the factors *baseline nutritional status, anemia and renal function* (although in the third tertile, having normal albumin levels, a higher proportion of subjects who received control gel achieved the primary endpoint than subjects who received Oleogel-S10).

In the CHMP scientific advice, CHMP recommended considering seasonal change as the disease course and severity of EB may differ with season. The applicant was asked to address this, e.g., describe which season(s) the DBP was performed in and whether there were differences between the two treatment groups, and a discussion on a potential impact on the results. This has been provided; few patients were included during summertime (13-14% of subjects in each arm) and no concerns were raised.

Concerns related to the control gel in study BEB-13

Study AHV-18-A

Mean days to complete wound healing according to planimetry were similar for all treatments (10.6 days for untreated wounds and wounds treated with control gel and 10.5 days for wounds treated with petrolatum). All wounds were considered healed according to planimetry by Day 13. The applicant thereby concluded that the results of study AHV-18-A indicated no differences in wound healing of mechanically induced partial-thickness wounds in healthy subjects between control gel, petrolatum, and no topical treatment (untreated). The applicant claimed that this supported the use of the control gel as a blinded comparator for Oleogel-S10 in interventional clinical studies. However, this was an exploratory study without any statistical hypothesis stated.

In the 2018 PA procedure, it was stressed that the study should have a clear test hypothesis (superiority, non-inferiority vs. no treatment) and be powered for this and thus not be an exploratory study. Further, there should be a justification for the extrapolation of the results observed in the skin of healthy volunteers to the skin in patient with EB, taking aspects like wound area and treatment duration into account. It was however agreed that for several reasons, performing the study in EB patients would not be feasible. The Sponsor was asked to define in the protocol what will constitute 'no difference in wound healing' and 95% confidence intervals for the pairwise comparisons needed to be presented, not only the p-values, which are of less interest/value for the interpretation.

It was stated that in a MAA, the Sponsor needed to provide convincing arguments that the experimental wound study in healthy volunteers was sensitive enough to detect differences in wound healing. For instance, if the study can show that the petrolatum product was significantly superior to the untreated control and that the "placebo product" and petrolatum were similar, this can provide support for the notion that the vehicle used in the pivotal study will not have a detrimental effect on wound healing.

Study AHV-18-B

Initiation of the confirmatory study AHV-18-B was delayed by a surge in the COVID-19 pandemic, but final results have been presented upon request by CHMP. The study had a very similar design as the AHV-18-A study, but with a slightly larger sample size (n=16 vs. n=12) and there was no untreated control wound in the AHV-18-B study. Based on the results, it could not be demonstrated that the control gel was non-inferior to petrolatum according to clinical score (primary endpoint). The study showed that the control gel was non-inferior to petrolatum according to planimetry score (secondary endpoint/ mean score from 2 independent assessors).

Thus, it was concluded that based on the primary evaluation based on clinical assessment, the observed difference between the two treatments was *1.7 days*, which is very similar to the magnitude of effect observed for the similar endpoint (time to first complete closure of the EB target wound by clinical assessment; median 92 days for Oleogel-S10 and 94 days for control gel, the first key secondary endpoint) in the pivotal EB study, i.e. *2 days*. Hence, these results could not fully alleviate the concern that the difference observed for the primary endpoint in study BEB-13 may partly be due to an impaired wound healing caused by the control gel.

Supportive external data

As additional support, the applicant referred to a study with a different product, however, in a similar setting (randomised, vehicle-controlled study of a topical treatment in different EB subtypes). The aim was to provide support for the 'natural history' of wound healing in EB patients. In the study provided, the proportion of subjects who achieved the first target wound closure within 45 days on the vehicle was 24.05% and for the total population it was 27.15%. In BEB-13, 28.9% of subjects on control gel achieved complete wound healing within D45. Nevertheless, between-study comparisons should be made with caution and no detailed display on differences or similarities in e.g., DEB/JEB distribution,

age and co-morbidities was included. Nevertheless, the data may provide some support that the BEB-13 control gel behaved as expected and not obviously worse, although this study did not constitute a strong part of the justification for the control gel.

Literature review

The applicant also provided a literature review aimed to support that ingredients in the control gel are not associated with negative effects on wound healing. A number of authorised topical products contain beeswax and carnauba wax, thus, these are not unknown excipients. The applicant was also asked to provide any supporting literature data on the effects of topical products containing the same components as the control gel on wound healing, in general and in EB patients. This has been performed and a number of products and publications were referred to.

The applicant concluded that none of the yellow wax- or carnauba wax-containing or products identified have been shown to have adverse effects on wound healing, however, this conclusion was complicated by several aspects. Firstly, a lack of *reported* negative effects on wound healing does not mean that there is none. Secondly, many products containing the waxes are products not indicated for use on open wounds, either because this is not the primary use or due to risk of adverse effects, e.g., systemic absorption of the active substance. Thirdly, when the waxes are used as excipients in topical products containing e.g., a topical corticosteroid, the effect of the steroid can mask potential negative effects, e.g., local irritant effects. Nevertheless, the CHMP considered that the applicant has fulfilled the requirement to compile literature data on the control gel components. Firm conclusions on lack of negative effects were difficult to draw from this data, although the presence of beeswax and carnauba wax in several topical medicinal products suggest that these components have no obvious harmful effects.

A justification was also requested for the extrapolation of the results observed in the skin of healthy volunteers to the skin in patient with EB, taking aspects like wound area and treatment duration into account. The pivotal HV study could not demonstrate non-inferiority for control gel vs. petrolatum. Hence, a conclusive 'lack of negative effect' was difficult to extrapolate to EB patients. It is however acknowledged that healthy volunteers and not EB patients as a model for wound healing is preferred for the control gel assessment.

In conclusion, based on the final AHV-18-B study results, the concern related to the BEB-13 control gel cannot be completely dismissed. However, collectively the information from the *literature* review, the *AHV-18-A results* (clinical score and planimetry), the *AHV-18-B planimetry results* and the comparison with the *external study* suggest that the control gel did not have a detrimental effect on wound healing. The confirmatory study AHV-18-B could not conclude on non-inferiority for the control gel vs. petrolatum for its primary endpoint. However, the applicant has made efforts to discuss and explain this issue and further data and/or justifications were not requested by the CHMP.

Episalvan MA data

The three studies supporting the approval of the partial-thickness wound indication for Episalvan showed statistically significant results in favour of Oleogel-S10. The relevance of the observed efficacy data for adults in acquired STSG donor site wounds or burn wounds to patients with inherited EB is unclear but likely to be limited, given the genetic basis for EB. During the assessment of Episalvan, the CHMP noted the small effect size in the Phase 3 studies in acquired wounds. However, in acquired wounds a reduction in time to wound closure or healing was considered clinically relevant by CHMP due to the potential for reduction of complications (infection, scarring, lengthy hospital stays) or avoidance of surgery. While the MAH has submitted the previous studies which were pivotal for the authorisation of Episalvan in the treatment of superficial burns, these cannot be accepted as pivotal to EB. EB is an entirely different condition, characterised by underlying chronic inherited blistering disease of skin and mucous membranes. Therefore, the effects seen in adults with acquired STSG donor site wounds or

burn wounds cannot be inferred for paediatric and adolescent patients with EB. Post-marketing efficacy (and safety) data are extremely limited for Episalvan.

Additional expert consultations

The position of the BSWP was sought on whether or not the application of the Cui, Hung, Wang (CHW) approach was appropriate as the primary test in the single pivotal phase 3 study BEB-13 (EASE) in the context of the Filsuvez MAA and on whether the type I error was appropriately controlled. The answer from the BSWP is presented below.

Answer from BSWP to the Question by CHMP
BSWP assessed the acceptability of the CHW-method as primary test in the BEB-13 study with one interim analysis including sample size re-estimation and whether BSWP considers that the type I error is adequately controlled in the context of the Filsuvez MAA.

For continuous endpoints, the CHW-method is constructed to strictly control the type I error for an interim analysis with sample size re-assessment as in study BEB-13. For a binary endpoint as in the BEB-13 study, type I error control is based on asymptotic convergence which is sufficiently satisfied in the study BEB-13 with a sample size of 223 subjects. Overall, the CHW-method is considered adequate as primary test for the BEB-13 study and considered to methodologically control the type I error. In the following the risk of introducing bias, and hence endangering type I error control, due to the procedural step of sample size re-estimation and potential risk of unblinding is discussed.

As the study is double-blind there is no direct suspicion that the outcome of the sample size re-estimation may have influenced the decision-making process. To assess the risk of bias introduced through unblinding following the interim analysis, results including only subjects enrolled before and after sample size re-estimation were requested from the applicant. These results show an estimated treatment effect of OR=1.96, CI=(1.03, 3.74), in the first 192 subjects recruited as compared to an estimated treatment effect of OR=1.5, CI=(0.29, 7.85), in the 31 subjects recruited after sample size re-estimation. Of note, the observed closure rate in subjects recruited after sample size re-estimation is slightly higher in both treatment groups. The estimated treatment effect does not increase after sample size re-estimation and the results do not immediately raise the suspicion that interim results may have influenced the recruitment or outcome assessment of subjects after sample size re-estimation. Consequently, there is no direct evidence that bias was introduced because of the sample size re-estimation.

Based on the above considerations, it is concluded that assessment of the Filsuvez MAA application can be based on the submitted data which show an estimated treatment effect that is smaller than was assumed for the initial sample size estimation when planning the trial. The clinical relevance of the estimated treatment effect should be considered with the remainder of the evidence in the in-depth benefit-risk assessment.

Summary of BSWP opinion
BSWP is of the opinion that the CHW-method is appropriate as the primary test in the BEB-13 study and adequately controls the type I error in the context of the Filsuvez MAA.

Need for additional expert consultation

Considering the issues raised on robustness of the results of the primary endpoint with poor support from secondary endpoints, as well as the rarity of the disease without any approved therapies, consultation of external EB experts was considered necessary to assist CHMP to conclude on the benefit/risk. Upon request from the CHMP, an *ad hoc* expert group meeting was convened on 15 March 2022.

1. **Given the results of study BEB-13, does the AHEG consider that an effect of Filsuvez has been established in the studied population?**

The experts and the patients' representatives acknowledged that EB is a very rare and complex disease with very high burden for patients affecting their daily lives. There are currently no approved treatment and thus the unmet medical need is very high. The standard of care is symptomatic aiming at preventing complication and improving the patients' quality of life. Filsuvez is not a disease modifying agent. It is a symptomatic treatment.

Given the results of study BEB-13, the majority of the experts considered that an effect has been established in the studied population for Filsuvez. The majority of the experts also agreed that the primary endpoint (i.e., % with first complete closure of EB target wound within 45 days) was met and is considered as clinically relevant and statistically significant. Further, although the other (secondary) endpoints were not statistically significant, their findings were considered to be clinically relevant by all patients' representatives and by the majority of the experts too, especially the effects regarding reduction in pain and in frequency of dressing changes. However, one expert was not convinced by the Filsuvez's effect based on all the data provided by the Applicant. This expert considered that although short term observations of benefit on clinical symptoms could be considered as good results; they do not demonstrate the long-term effect of the drug in re-epithelialisation as indeed there were no differences demonstrated on the long term as at Day 90 the following key secondary endpoint '% with first complete closure of EB target wound within Day 90' and other secondary endpoints did not reach statistical significance. Further, the variability between the time points for some of the endpoints was also considered to be an issue for this expert.

Overall, the majority of the experts and all the patients' representatives considered that an effect with Filsuvez has been shown even if considered to be modest. It was mentioned that a high level of effect could not be expected to be observed with a topical formulation used in a very rare condition and for which the mechanism of action is not well determined. Therefore, one could not expect more convincing results. The majority of the experts agreed that the results showed an acceleration of wound healing, improvements on itching and pain, which are considered very important factors for EB patients.

2. **If it can be concluded that an effect of Filsuvez in epidermolysis bullosa (EB) has been demonstrated, is this effect considered to be of clinical relevance for EB patients?**

The patients' representatives and the majority of the experts considered that any effect/improvement would be of clinical relevance for EB patients and would be considered important especially due to the rarity of the disease and the very high unmet medical need for those patients. The reduction of time for dressing, the reduction of frequency of the dressing as well as the reduction of pain were particularly discussed and the majority of the experts agreed that results presented, although limited, showed to be beneficial and of clinical relevance for the EB patients. The expert, who did not consider that an effect was shown, was of the view that there was no clinical relevance for EB patients.

3. **As the mechanism of action has not been proven, the view of the experts is sought on whether there is a biological rationale to expect a difference in response to treatment with Filsuvez in different EB subtypes, e.g. dystrophic epidermolysis bullosa (RDEB and DDEB) and junctional epidermolysis bullosa (JEB)?**

It was highlighted that the precise mechanism of action of the drug in wound healing is not clearly known. It was also stated that the product has anti-inflammatory effects and that those were shown in different studies not only in EB.

There was a consensus amongst the experts that based on biological differences in the EB sub-types of the disease, the wounds would be expected to behave differently. Indeed, the experts considered that JEB wounds would be more difficult to heal than the DEB wounds due to the involvement of different

proteins (e.g., laminin 332, its absence causes tissue separation along the lamina lucida of the dermal-epidermal basement membrane of the skin)/genes in JEB compared to DEB. Further, given the small number of patients that is considered to be too low for the JEB sub-type, that no better clinical efficacy data were provided for the JEB subtype and taking into consideration the above-mentioned biological consideration; the experts considered that it will be inappropriate to extrapolate the efficacy results observed in DEB to the JEB subtype without further supporting data. Some experts also considered that a difference is not only expected from a biological viewpoint but also from the putative mechanism of action of Filsuvez such as the anti-inflammatory effect of the drug.

Overall, the experts considered that one cannot infer that a drug that works in DEB would work in JEB as well.

The patients' representatives considered that any drug that overall works in EB would be considered as important for the EB patients.

Third party intervention during the evaluation of Filsuvez

The CHMP received, during the assessment of this application, a correspondence from the EB patient community (hereinafter referred to as "third party") expressing the third party' views about the perspective and experience of people affected by EB, and the unmet medical need of EB patients. The CHMP considered this intervention in the context of its assessment and concluded that the observations put forward by the EB patient community were already known by CHMP, and as such had no impact on the CHMP assessment or its conclusions.

2.6.7. Conclusions on the clinical efficacy

The conduct of a randomised controlled study in the rare and severe condition EB was acknowledged and appreciated. The study was fairly large considering the orphan condition, with 223 patients randomised. The overall design of the study was endorsed. The issues related to the control gel (which is not the pure vehicle of Oleogel-S10, i.e., sunflower oil) have to the extent possible been alleviated by results from the healthy volunteer studies AHV-18-A and AHV-18-B and by literature data.

As a single pivotal study has been conducted, the corresponding EMA guideline would be applicable, although the rarity of the EB condition needs to be taken into consideration. The efficacy of Oleogel-S10 in the pivotal study BEB-13 was modest, with 41.3% of subjects achieving complete target wound closure within 45 days vs. 28.9% for the vehicle but considered clinically relevant by the CHMP. Even if the statistical robustness of the analysis of the primary endpoint has been questioned during the procedure, the CHMP is of the view, in line with the recommendation of the AHEG, that an effect of Filsuvez has been established considering that some of the sensitivity analyses supported the primary analysis of the primary endpoint.

The support from secondary endpoints was considered to be limited by the CHMP, but demonstration of statistical significance for secondary endpoints is not a strict regulatory requirement.

The majority of the experts and all patient representatives at the AHEG meeting considered that an effect with Filsuvez has been shown, even if considered to be modest. The enormous unmet medical need described by the EB community was acknowledged and the position at the AHEG meeting was that any effect/improvement would be of clinical relevance for EB patients. This was supported by the CHMP.

In conclusion, the CHMP considered that the totality of evidence is supportive of a beneficial treatment effect of Filsuvez. The difference, albeit modest, was considered clinically meaningful in the following indication:

Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.'

2.6.8. Clinical safety

In Table 20 an overview of all completed or ongoing clinicals studies of Oleogel-S10 is presented.

Table 20. Overview of Completed or Ongoing Clinical Studies of Oleogel-S10

Study Number & Phase **Country** **Study Status**	**Study Population/ Indication**	**Study Design**	**Study Treatment(s) and Duration of Treatment** **Duration of Follow-Up**	**Number of Study Subjects** **Demographics**
Treatment of epidermolysis bullosa (EB) skin wounds				
BEB-13 (EASE Study) Phase 3 Argentina, Australia, Austria, Brazil, Chile, Colombia, Czech Republic, Denmark, France, Georgia, Germany, Greece, Hong Kong, Hungary, Ireland, Israel, Italy, Romania, Russia, Serbia, Singapore, Spain, Switzerland, Ukraine, United Kingdom, United States (26 countries) Double-blind phase (DBP) completed Open-label phase (OLP) ongoing	Subjects ≥21 days of age with **inherited EB** (subtypes JEB, DEB, or Kindler syndrome)[a] with EB partial-thickness wound of 10 cm^2 to 50 cm^2 in size, aged ≥ 21 days and <9 months	Double-blind, randomized, controlled, efficacy and safety study with 24-month open-label follow-up of Oleogel-S10 with pharmacokinetic sampling to determine systemic concentration of Betulin	Oleogel-S10 plus non-adhesive wound dressing vs. control gel plus non-adhesive wound dressing applied directly to the wound or wound dressing every 1 to 4 days during dressing changes for **90 days** (DBP). Target wounds and all other EB partial-thickness wounds were treated during the DBP. If a wound was confirmed as closed, it was not necessary to continue to apply study medication to that wound. Oleogel-S10 was applied in the same manner to all EB partial-thickness wounds for up to **24 months** during OLP. Subjects were followed during the 24-month OLP (Follow-up period).	223 subjects enrolled: 109 Oleogel-S10 114 Control gel (At the time of data cut-off, 11 Jun 2020, 134 subjects remained in the OLP). 60% Male Median age 12 years (range 6 months to 81 years) Race: 83% White 5% Not reported 5% Asian 1% Black Fitzpatrick skin type: 6% Type I, 49% Type II, 34% Type III, 9% Type IV, 2% Type V, <1% Type VI

Study Number & Phase Country Study Status	Study Population/ Indication	Study Design	Study Treatment(s) and Duration of Treatment Duration of Follow-Up	Number of Study Subjects Demographics
BEB-10 (EBCS Study) Phase 2 Germany Completed	Subjects 1 to 95 years of age with **inherited EB** and at least 1 skin wound between 10 and 200 cm^2 or 2 similar wounds of at least 5 cm^2 each	Open-label, blindly evaluated, prospective, intra-individually controlled study	Oleogel-S10 plus non-adhesive wound dressing vs. non-adhesive wound dressing alone. The eligible wound (half) was topically treated with Oleogel-S10 and covered with wound dressing (Mepilex®) on Day 0. Wound dressings were changed about every 24 to 48 hours until discharge from hospital or until the end of treatment at **Day 14** in 'recent wounds' or **Day 28** in 'chronic wounds.' No follow-up beyond Day 14 or 28.	10 subjects enrolled and treated (12 wound pairs, as 2 subjects received 2 cycles of treatment) 70% male Median age 20 years (Range: 6 to 48 years) Race: not collected Fitzpatrick skin type: 60% Type I, 20% Type II, 20% Type III
Treatment of split-thickness skin graft donor site wounds				
BSH-12 Phase 3 Austria, Bulgaria, Czech Republic, Finland, Germany, Poland Completed	Subjects ≥18 years of age with a **split-thickness skin graft donor site wound** of a minimum size of 15 cm^2 and a minimum width of 3 cm.	Open, blindly evaluated, prospective, intra-individually controlled, randomized, multicenter study with pharmacokinetic sampling to determine systemic concentration of Betulin	Oleogel-S10 plus non-adhesive wound dressing vs. non-adhesive wound dressing alone at each dressing change (every 3 to 4 days) until full wound closure or up to **28 days**. Treatment allocation to the halves of the wound was randomly assigned. Subjects attended follow-up visits at 3 and 12 months post treatment.	111 subjects enrolled 107 subjects treated 64% male Median age 56 years (range: 18 to 86 years) 100% Caucasian Fitzpatrick skin type: 3% Type I, 77% Type II, 18% Type III, 3% Type IV
BSG-12 Phase 3 France, Greece, Latvia, Spain Completed	Subjects ≥18 years of age with a **split-thickness skin graft donor site wound** of a minimum size of 15 cm^2 and a minimum width of 3 cm.	Open, blindly evaluated, prospective, intra-individually controlled, randomized, multicenter study with pharmacokinetic sampling to determine systemic concentration of Betulin	Oleogel-S10 plus non-adhesive wound dressing vs. non-adhesive wound dressing alone until full wound closure or up to 28 days. Treatment allocation to the halves of the wound was randomly assigned. Subjects attended follow-up visits at 3 and 12 months post treatment.	113 subjects enrolled 112 subjects treated 66% male Median age 49 years (range: 19 to 90 years) Race: 88% Caucasian 10% Not reported 2% Other 1% Black Fitzpatrick skin type: 1% Type I, 29% Type II, 36% Type III, 17% Type IV, 18% Type V

Study Number & Phase **Country** **Study Status**	**Study Population/ Indication**	**Study Design**	**Study Treatment(s) and Duration of Treatment** **Duration of Follow-Up**	**Number of Study Subjects** **Demographics**
Treatment of Grade 2a thermal burn wounds				
BBW-11 Phase 3 Germany, Sweden, Switzerland, United Kingdom Completed	Subjects ≥18 years of age with **Grade 2a burn wounds** between 80 cm^2 and <25% of total body surface area (TBSA) or 2 comparable wounds with size >40 cm^2 each and <12.5% of TBSA each.	Open, blindly evaluated, prospective, intra-individually controlled, randomized, multicenter study with pharmacokinetic sampling to determine systemic concentration of Betulin	Oleogel-S10 plus fatty gauze dressing vs. Octenilin® plus fatty gauze dressing applied every other day until full wound closure or for up to **21 days**. Treatment allocation to the 2 halves of the wound (or 2 comparable wounds) was randomly assigned. Subjects attended follow-up visits at 3 and 12 months post treatment.	66 subjects enrolled 61 subjects treated 69% male Median age 41 years (range: 18 to 79 years) Race: 84% Caucasian 8% Asian 7% Black 2% Other Fitzpatrick skin type: 12% Type I, 49% Type II, 21% Type III, 8% Type IV, 3% Type V, 7% Type VI
Other Phase 2 Non-EB Studies				
BSH-10 (OleoSplit Study) Phase 2 Germany Completed	Subjects ≥18 years of age with **split-thickness skin graft donor site wounds** who required skin grafting due to burns, trauma, chronic venous ulcers, or surgical removal of cutaneous malignancies, with a donor site of between 8 cm^2 and 200 cm^2 on a nonarticulated site	Open, blindly evaluated, prospective, intra-individually controlled, randomized, multicenter study	• 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 wound areas at the upper leg were divided into 2 equal halves, 1 proximal and 1 distal. The treatment allocation to the 2 halves of the wound was determined by randomization. Follow-up at 3 months.	24 subjects enrolled and treated

Study Number & Phase Country Study Status	Study Population/ Indication	Study Design	Study Treatment(s) and Duration of Treatment Duration of Follow-Up	Number of Study Subjects Demographics
BAK-08 (BETA Study) Germany, Greece Completed	At least two mild to moderate **actinic keratoses**	Phase 2, double-blind, placebo-controlled, prospective, parallel group, randomized, multicenter study	• Oleogel-S10 once a day • Oleogel-S10 twice a day • Placebo (petroleum jelly) once a day • Placebo (petroleum jelly) twice a day Treatment period: 12 weeks Application at the total target area on all actinic keratosis lesions of the face and head and other regions of the body if present. Follow-up at 18 weeks.	169 subjects enrolled 165 subjects treated (111 with Oleogel-S10)

Abbreviations: DEB=dystrophic epidermolysis bullosa; DBP=double-blind phase; EB=epidermolysis bullosa; EBS=epidermolysis bullosa simplex; JEB=junctional epidermolysis bullosa; OLP=open-label phase; TBSA=total body surface area.

[a]Subjects with the EBS subtype were originally enrolled in the study but removed from eligibility criteria in Protocol Version 4.0 (2 EBS subjects enrolled).

The phase 3 study BEB-13 was considered pivotal for the safety assessment of Oleogel-S10 in EB patients. In the BEB-13 study, 223 patients were enrolled for the 90-day double-blind phase (DBP) with EB subtypes JEB and DEB and a median age of 12 years (range 6 months to 81 years). The 24-month open-label follow-up phase of the BEB-13 study was still ongoing.

The applicant has presented the data from the phase 2 study (BEB-10) in subjects with EB separately, without a pooled safety analysis for the EB indication or across indications. This approach was considered acceptable given differences in study design and duration.

Oleogel-S10 was approved under the trade name Episalvan on 14 January 2016 in the EU for the treatment of partial-thickness wounds in adults for up to four weeks. In the three pivotal studies for the Episalvan MAA, two studies investigated split-thickness skin graft donor site wounds (BSG-12 and BSH-12), and one study investigated patients with Grade 2a burn wounds (BBW-11). It has been concluded that Episalvan gel has a mild safety profile with adverse events limited to local application reactions. Listed undesirable effects associated with the use of Oleogel-S10 included wound complication, wound infections, and application/administration site reactions as these named identified events are listed as adverse reactions in the SmPC section 4.8 of Episalvan. However, Episalvan gel is not intended for long-term treatment in EB patients and the safety data from the authorised Episalvan was thus considered supportive only, taking into account uncertainties concerning long-term treatment, larger wound size area and a different target population in EB. The additional studies presented i.e., BEB-10, BSH-10 and BAK-08, were also considered supportive of the safety of this topical product. The CHMP agreed that pooling of the safety results from all studies was not required.

2.6.8.1. Patient exposure

In Table 21, an overview of exposure data from completed or ongoing clinicals studies of Oleogel-S10 is presented. Overall, EB is a rare, designated orphan disease and the constraints in recruitment due to

the rare condition is acknowledged. However, the sample size of long-term exposure and the characteristics of patients exposed is essential for an initial MAA also for an orphan disease such as EB. The application was submitted before the end of OLP of pivotal study BEB-13 and contained only interim data relating to the OLP.

From the small short-term BEB-10 study, additional data from 10 patients were made available. Out of the 10 patients enrolled and completed the study, 9 subjects had been diagnosed with RDEB and 1 subject with DDEB. The mean age of these 10 patients was 21.6 years (range, 6-48 years). More subjects were male (70.0%) than female (30.0%). Race was not collected in this study. The majority of subjects (60.0%) had a Fitzpatrick skin type of I. The median wound size when 1 wound was treated was 31.0 cm^2; when 2 wounds were treated, the median wound sizes were 11.3 and 15.8 cm^2. The patients were exposed to a 1 cm string of Oleogel-S10 gel (or 115 mg) per cm^2 of wound eligible for study treatment for 13 to 29 days. The median calculated cumulative extent of exposure was 4966 mg (min. 1320 mg; max. 23437 mg), while the median daily extent of exposure was 305 mg (min. 88 mg; max. 1594 mg).

In the three pivotal studies for the Episalvan MA, two studies investigated split-thickness skin graft donor site wounds (BSG-12 and BSH-12), which included a total of 219 patients (ITT: N=217), and one further study in 61 patients with Grade 2a burn wounds (ITT: N=57) (BBW-11). However, in the safety data from the non-EB pooled studies no patient <18 years of age was included, and no long-term exposure data was available. The 219 patients with split-thickness skin graft donor site wounds had a mean age of 53 years; their donor site mean wound size was 81.5 cm^2. In the burn wound study with 61 patients, the mean study wound area was 216 cm^2; the total burn injury of these patients was larger and affected 5.8% of the total body surface area. 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 cm^2) in comparison with the burn wound study BBW-11 (85 cm^2). Most patients in the non-EB pooled studies were white (91%) and had a Fitzpatrick skin type of Grade II or III (77%).

Table 21. Oleogel-S10 Exposure by study.

Study Indication	Treatment Area	Control/ Comparator	Planned Treatment Frequency	Mean Dressing Change Interval	Planned Treatment Duration	Mean (SD) Duration of Exposure to Oleogel-S10	Number of Subjects Exposed		
							Oleogel-S10	Control Gel or Comparator	Total
BEB-13 EB	Target wound, additional wound(s), and all other EB wounds	Control gel	At each wound dressing change, at least every 4 days (every 1 to 4 days)	1 to 2 days [a]	Double-blind: 90 days Open-label: 24 months	89 days (18.34) in DBP (OLP ongoing)	DBP:109 OLP: 205[b]	114	223
BEB-10 EB	1 wound (half Oleogel-S10, half control) or 2 wounds (1 Oleogel-S10, 1 control)	Standard of care control non-adhesive wound dressing	Once every 24 to 48 hours (approx.)	2.8 days	Recent wounds: 14 days Chronic wounds: 28 days	18.7 days (6.7)	10	10	10 [c]
BSH-12 STSG donor site wounds	1 wound (half Oleogel-S10, half control)	Standard of care control non-adhesive wound dressing	At each wound dressing change, at least every 3 to 4 days, until full wound closure	3.1 days	28 days (maximum)	18.3 days (7.5)	107	107	107[c]
BSG-12 STSG donor site wounds	1 wound (half Oleogel-S10, half control)	Standard of care control non-adhesive wound dressing	At each wound dressing change, at least every 3 to 4 days, until full wound closure	3.5 days	28 days (maximum)	18.7 days (6.0)	112	112	112[c]

Study Indication	Treatment Area	Control/ Comparator	Planned Treatment Frequency	Mean Dressing Change Interval	Planned Treatment Duration	Mean (SD) Duration of Exposure to Oleogel-S10	Number of Subjects Exposed		
							Oleogel-S10	Control Gel or Comparator	Total
BBW-11 Grade 2a thermal burn wounds	1 wound (half Oleogel-S10, half control) or 2 wounds (1 Oleogel-S10, 1 control)	Octenilin® wound gel	At each wound dressing change, at least every 2 days, until full wound closure	2 days	21 days (maximum)	10.4 days (4.9)	61	61	61 [c]
BSH-10 STSG donor site wounds	1 wound (half Oleogel-S10, half control)	Mepilex® moist dressing only	At each wound dressing change, at minimum every 4 days	4 days	14 days	N/A[d]	24	24	24
BAK-08 Actinic keratosis skin lesions	All lesions on face and head	Placebo (petroleum jelly)	Once or twice per day	Once or twice per day	12 weeks	N/A[e]	111	54	165

Abbreviations: DBP=double-blind phase; EB=epidermolysis bullosa; N/A=not available; OLP=open-label phase; SD=standard deviation; STSG=split-thickness skin graft.
[a]No mean was calculated. Majority of subjects in both treatment groups reported dressing changes and study medication application occurred daily or every 2 days.
[b]Six subjects, all in the control gel group, discontinued the DBP prematurely due to worsening of the EB target wound status or due to EB target wound infection and continued into the OLP prematurely (at the investigator's discretion). Therefore, 100 subjects who received Oleogel-S10 in the DBP continued to the OLP; 105 subjects who received control gel in the DBP (99 plus 6 subjects who discontinued the DBP prematurely) continued to the OLP.
[c]Subjects served as their own controls; subjects are not counted twice.
[d]Each wound dressing change was performed according to the protocol for all subjects. Mean was not calculated.
[e]No mean was calculated.

In the pivotal BEB-13 DBP, 195 (87.4%) of the 223 subjects had the EB subtype of DEB; of these, 175 (78.5%) subjects had RDEB and 20 (9.0%) subjects had DDEB. Twenty-six (11.7%) subjects had JEB, and 2 (0.9%) subjects had EBS. The majority of included patients were male (60.1%), white (83.4%), had Fitzpatrick skin type of Grade Type II or III (83%). The mean age was 16.7 and the majority of patients <18 years of age (70%). An overview of the demographics in the BEB-13 study is presented in Table 22.

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Table 22. An overview of the demographics in the BEB-13 Study

	Oleogel-S10 DBP	Control Gel DBP	All Subjects DPB	Subjects OLP (DLP 21 April 2021)
	N=109	N=114	N=223	N=205
Age groups: n (%)				
0 to <4 years	7 (6.4)	10 (8.8)	17 (7.6)	16 (7.8%)
4 to <12 years	42 (38.5)	43 (37.7)	85 (38.1)	81 (39.5%)
12 to <18 years	25 (22.9)	29 (25.4)	54 (24.2)	50 (24.4%)
≥18 years	35 (32.1)	32 (28.1)	67 (30.0)	58 (28.3%) 3 ≥ 65 y
Gender: n (%)				
Female	41 (37.6)	48 (42.1)	89 (39.9%)	79 (38.5)
Male	68 (62.4)	66 (57.9)	134 (60.1%)	126 (61.4)
Race: n (%)				
Asian	4 (3.7)	7 (6.1)	11 (4.9%)	10 (4.9)
Black	1 (0.9)	2 (1.8)	3 (1.3%)	3 (1.5)
White	95 (87.2)	91 (79.8)	186 (83.4%)	169 (82.4)
Other/NA	9 (8.3)	12 (10.5)	23 (10.3%)	23 (11.2)
Fitzpatrick skin type				
Grade type I	8 (7.3)	6 (5.3)	14 (6.3)	NA
Grade type II	55 (50.5)	54 (47.4)	109 (48.9)	NA
Grade type III	35 (32.1)	40 (35.1)	75 (33.6)	NA
Grade type IV	8 (7.3)	12 (10.5)	20 (9.0)	NA
Grade type V	2 (1.8)	2(1.8)	4 (1.8)	NA
Grade type VI	1 (0.9)	0	1 (0.4)	NA
EB subtype: n (%)				
DEB	97 (89.0)	98 (86.0)	195 (87.4%)	178 (86.8)
JEB	11 (10.1)	15 (13.2)	26 (11.7%)	25 (12.2)
EBS	1 (0.9)	1 (0.9)	2 (0.9%)	2 (1.0)

As all subgroups were small in the BEB-13 study dataset, it was agreed that the interpretation of subgroup data was limited, in particular in the subgroups race and geographic regions. While EB occurs in all races and ethnic groups, Black and Asian patients were underrepresented in the safety analysis. This is reflected in the SmPC section 5.1.

In the BEB-13 study, not only a target wound, but all of a patient's partial thickness EB wounds were treated with Oleogel-S10 or control gel. Oleogel-S10 was to be administered topically at approximately 1 mm (0.04 inch) thickness. Wound areas were then to be covered with a standard of care non-adhesive wound dressing. The mean (SD) duration of treatment in the DBP was 89.0 (18.43) days in the Oleogel-S10 group and 86.8 (23.64) days in the control gel group. Overall treatment compliance, specifically in relation to the target wound, was approximately 99% in both groups. In the DBP the patients used from 18 g to 7830 g of Oleogel-S10 or control gel.

The betulin concentration in capillary and/or venous blood samples in the DBP of BEB-13, has been evaluated in sections related to pharmacokinetics. It has been agreed that the Filsuvez was a locally applied, locally acting product with limited systemic absorption.

From the ongoing long-term exposure OLP of the BEB-13 study, the applicant has provided interim safety data with data lock point of 21 December 2020 and in the 90-Day Safety Update Report with data lock point 21 April 2021. On 21 April 2021, out of 205 patients who entered the ongoing BEB-13 OLP, 144 (70%) had completed the month 12 visit, and 68 patients (33.2%) completed the month 24 visit. In addition, subjects in the so called "former Oleogel-S10 group" have received an additional 3

months of exposure to Oleogel-S10 during the previous DBP. Thus, the 82 patients in the "former Oleogel-S10-group" that completed the month 9 visit, have been exposed to Oleogel-S10 for 12 months in total, i.e., 156 patients have been exposed to Oleogel-S10 for 12 months.

The total quantity of Oleogel-S10 used in the OLP of the BEB-13 study up to 21 April 2021 is displayed in Table 23. As the quantity of product used (and hence the tertile calculation) was only available for subjects who have completed Visit 7 at Day 90 (for the end of the DBP) and Visit 10 at Month 24 (for the end of the OLP), respectively, the subgroups were very small and it was agreed that the interpretation of these data might be limited. Also, the amount of study medication used was only applied to subjects recruited after Protocol Version 4.0. The highest extent of exposure to Oleogel-S10 in a subject was 33.7 kg over a 24-month period, who did not experience any AE.

Table 23. Tertiles for Total Quantity of Study Medication Used, BEB-13 Study in EB; (Safety Analysis Set)

Tertile	Oleogel-S10 / Control Gel Total Quantity
	Double-Blind Phase
1st tertile	18 g to 650 g
2nd tertile	659.8 g to 1555 g
3rd tertile	1560 g to 7830 g
	Open-Label Phase (interim data 21 April)
1st tertile	37.2 g to 2662 g
2nd tertile	2664 g to 7470 g
3rd tertile	7650 g to 33369 g

The applicant has also calculated the daily and cumulative extent of exposure for DBP and OLP combined by age category (Table 24).

Table 24. Median daily and cumulative extent of exposure for DBP and OLP combined - all patients and by age category

	All patients	**0 - <4 years**	**4 - <12 years**	**12 - <18 years**	**≥18 years**
Median daily extent of exposure (grams per day)	10	12	10	11	10
Median cumulative extent of exposure (grams)	1835	1218	2180	2446	1353

A summary of exposure data by age group from the BEB-13 DBP and interim data from the OLP was included in SmPC section 5.1.

In the pivotal BEB-13 study, the majority of the included patients were <18 years of age (Table 22). A total of 17 subjects under 4 years old entered the BEB-13 study of which 14 had RDEB with the majority having generalised severe RDEB. In the Oleogel-S10 arm (n=7), all subjects completed the DBP and then entered the OLP. In the control gel arm (n=10), 7 subjects completed the DBP and entered the OLP; 3 subjects discontinued DBP prior to completion, with 2 of these subjects entering OLP (Figure 13). Hence, 16 subjects entered the OLP.

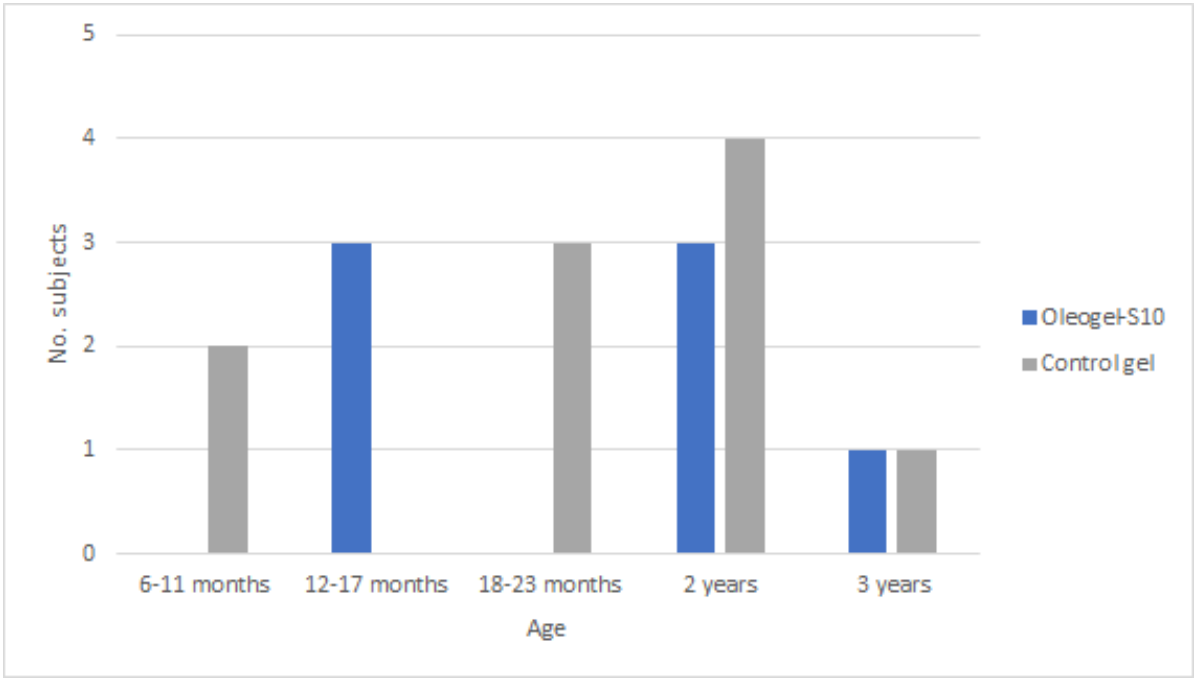

Figure 13. Age distribution: ≥21 days and < 4 years.

In the age group 0 to <4 years, as of the OLP Month 12 Efficacy DBL on 15 July 2021, 3 subjects had withdrawn: 1 former control gel subject withdrew consent after 360 days treatment with Oleogel-S10 in the OLP; 1 former control gel subject withdrew due to an AE after 90 days of treatment with Oleogel-S10 in the OLP; 1 Oleogel-S10 subject withdrew due to worsening of medical condition after 381 days treatment in the DBP and OLP (90 days and 291 days respectively). One subject had completed the OLP and 12 subjects were ongoing.

There were no safety data for children under the age of 6 months. The applicant argued that considering that Oleogel-S10 was a topical treatment and minimally systemically absorbed, the use in children under 6 months was not expected to have any different safety profile to those already seen in the rest of the population. This was not agreed. Since the immune system of newborns and infants is not fully developed, they are more susceptible to infections. Therefore, due to lack of data, it is not known if children under the age of 6 months have a higher risk of for example wound infections when treated with Oleogel-S10. Therefore, at present, the available safety database for Oleogel-S10 in the long-term treatment of JEB and DEB patients under the age of 6 months was considered insufficient. This is also discussed in section 2.6.9.

2.6.8.2. Adverse events

Since the control gel used in clinical studies contained the vehicle of Filsuvez, *i.e.,* sunflower oil, AEs related to the control gel were also considered of importance.

Cumulatively (up to 21 April 2021), nonserious, serious, and severe AEs were reported for a number of subjects. The overall summary of adverse events in the BEB-13 study is presented in Table 25.

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Table 25. Overall Summary of Adverse Events, BEB-13 Study in EB (Safety Analysis Set)

	DBP Oleogel-S10 (N=109) n (%) E	DBP Control Gel (N=114) n (%) E	OLP (N=205) 11 June 2020 n (%) E	OLP (N=205) 21 April 2021 n (%) E
Any AEs	89 (81.7) 282	92 (80.7) 277	132 (64.4) 571	145 (70.7) 687
Any serious AEs	7 (6.4) 10	5 (4.4) 7	40 (19.5) 68	44 (21.5) 85
Any severe AEs	13 (11.9) 19	6 (5.3) 7	23 (11.2) 40	28 (13.7) 58
Any related AEs	27 (24.8) 50	26 (22.8) 49	25 (12.2) 55	26 (12.7) 63
Any serious related AEs	1 (0.9) 1	0	1 (0.5) 1	2 (1.0) 2
Any AEs leading to study withdrawal	3 (2.8) 4	2 (1.8) 2	14 (6.8) 14	14 (6.8) 14
Any serious AEs leading to study withdrawal	2 (1.8) 3	0	3 (1.5) 3	3 (1.5) 3
Any related AEs leading to study withdrawal	2 (1.8) 2	0	10 (4.9) 10	10 (4.9) 10
Any serious related AEs leading to study withdrawal	1 (0.9) 1	0	1 (0.5) 1	1 (0.5) 1
Any serious AEs leading to death	0	0	5 (2.4) 5	5 (2.4) 5
Any AEs due to wound complications[a]	67 (61.5) 100	61 (53.5) 88	78 (38.0) 100	81 (39.5) 103
Any AEs leading to drug withdrawal	3 (2.8) 4	4 (3.5) 4	13 (6.3) 13	13 (6.3) 13

AE=adverse event; E=number of events; EB=epidermolysis bullosa; LLT=Lowest level term; N=number of subjects in specific group; n=number of subjects; Preferred term=PT
[a]Refers to any AEs with PT or LLT 'Wound complication'. Please note there are other AEs involving wounds (e.g., wound hemorrhage, wound secretion) but with a different PT/LLT.
Note: Calculation of percentages is based on N.

In the BEB-13 DBP, the most frequently reported AEs in the Oleogel-S10 group (N=109) and the control gel group (N=114), respectively, were wound complication (61.5% and 53.5%), pyrexia (8.3% and 13.2%), wound infection (7.3% and 8.8%), pruritus (7.3% and 5.3%), anaemia (7.3% and 3.5%), and cough (2.8% and 7.0%) (Table 26).

Of the 205 subjects who have participated in the OLP (all of whom receive Oleogel-S10), a total of 145 (70.7%) subjects have reported at least 1 AE as of the Safety Update cut-off date of 21 April 2021. Up to 21 April 2021, the most frequently reported AEs (≥5% of all subjects) were wound complication (39.5%), anaemia (14.1%), wound infection staphylococcal (9.8%), wound infection (9.3%), oesophageal stenosis (8.8%), pyrexia (8.3%), wound infection bacterial (5.9%), and pruritus (5.9%). Two PTs, malnutrition and vitamin D deficiency, were newly included within the incidence threshold of ≥2% of all subjects (3.4% and 2.0%, respectively) Table 26).

Table 26. Summary of Adverse Events by System Organ Class and Preferred Term with an Incidence ≥2% BEB-13 Study in EB (Safety Analysis Set)

	DBP Oleogel-S10 N=109 n (%) E	DBP Control Gel N=114 n (%) E	OLP N=205 n (%) E DLP 11 June 2020	OLP N=205 n (%) E DLP 21 April 2021
Any AEs	89 (81.7) 282	92 (80.7) 277	132 (64.4) 571	145 (70.7) 687
Injury, poisoning and procedural complications	69 (63.3) 119	66 (57.9) 97	88 (42.9) 121	91 (44.4) 128
Wound complication	67 (61.5) 100	61 (53.5) 88	78 (38.0) 100	81 (39.5) 103
Wound secretion			4 (2.0) 4	4 (2.0) 4
Fall	4 (3.7) 6	1 (0.9) 1		

	DBP Oleogel-S10 N=109 n (%) E	DBP Control Gel N=114 n (%) E	OLP N=205 n (%) E DLP 11 June 2020	OLP N=205 n (%) E DLP 21 April 2021
Infections and infestations	37 (33.9) 51	36 (31.6) 58	56 (27.3) 152	68 (33.2) 188
Wound infection	8 (7.3) 9	10 (8.8) 12	17 (8.3) 27	19 (9.3) 33
Wound infection staphylococcal	4 (3.7) 4	3 (2.6) 3	15 (7.3) 20	20 (9.8) 26
Skin infection				5 (2.4) 9
Wound infection bacterial	3 (2.8) 4	5 (4.4) 6	9 (4.4) 16	12 (5.9) 19
Upper respiratory tract infection	4 (3.7) 4	1 (0.9) 1		
Nasopharyngitis	3 (2.8) 3	7 (6.1) 7	4 (2.0) 5	4 (2.0) 5
Pharyngitis	3 (2.8) 3	0		
Otitis externa			4 (2.0) 4	4 (2.0) 5
General disorders and administration site conditions	21 (19.3) 28	25 (21.9) 36	27 (13.2) 42	30 (14.6) 45
Pyrexia	9 (8.3) 11	15 (13.2) 18	14 (6.8) 21	17 (8.3) 24
Application site pruritus	4 (3.7) 6	1 (0.9) 1		
Administration site pain	3 (2.8) 4	3 (2.6) 3		
Skin and subcutaneous tissue disorders	11 (10.1) 11	15 (13.2) 22	23 (11.2) 34	26 (12.7) 40
Pruritus	8 (7.3) 8	6 (5.3) 7	11 (5.4) 15	12 (5.9) 16
Gastrointestinal disorders	11 (10.1) 13	13 (11.4) 19	37 (18.0) 73	43 (21.0) 95
Oesophageal stenosis			14 (6.8) 16	18 (8.8) 26
Dysphagia			6 (2.9) 9	9 (4.4) 12
Vomiting			5 (2.4) 6	5 (2.4) 6
Diarrhoea			7 (3.4) 9	8 (3.9) 10
Toothache	3 (2.8) 3	0	4 (2.0) 4	5 (2.4) 6
Respiratory, thoracic and mediastinal disorders	9 (8.3) 16	11 (9.6) 15		
Cough	3 (2.8) 3	8 (7.0) 9		
Oropharyngeal pain	3 (2.8) 6	2 (1.8) 2		
Blood and lymphatic system disorders	8 (7.3) 10	6 (5.3) 6	22 (10.7) 31	30 (14.6) 45
Anaemia	8 (7.3) 10	4 (3.5) 4	21 (10.2) 28	29 (14.1) 39
Eye disorders	6 (5.5) 7	2 (1.8) 2	13 (6.3) 24	14 (6.8) 25
Ulcerative keratitis	3 (2.8) 3	0	4 (2.0) 12	4 (2.0) 12
Metabolism and nutrition disorders			13 (6.3) 22	19 (9.3) 35
Hypoalbuminaemia			4 (2.0) 5	7 (3.4) 10
Vitamin D deficiency				7 (3.4) 7
Malnutrition				4 (2.0) 5
Congenital, familial and genetic disorders				7 (3.4) 7
Syndactyly				4 (2.0) 4

Abbreviations: AE=adverse event; E=number of events; EB=epidermolysis bullosa; N=number of subjects in specific group; n=number of subjects.
Note: Calculation of percentages is based on N.

By age group category, the percentage of subjects reporting at least 1 AE was 62.5% (10/16 subjects) in the age group 0 to <4 years, 74.1% (60/81 subjects) in the age group 4 to <12 years, 66.0% (33/50 subjects) in the age group 12 to <18 years, and 72.4% (42/58 subjects) in the age group ≥18 years. In these same 4 age group categories, the most frequently reported AE overall was wound complication (31.3%, 43.2%, 34.0%, and 41.4%, respectively).

The overall incidence of AEs by gender was 65.1% (82/126 subjects) for males and 79.7% (63/79 subjects) for females. In males, the most frequently reported AE was wound complication (36.5%); no other AE was reported at a frequency of ≥10% in males. In females, the most frequently reported AEs were wound complication (44.3%), anaemia (21.5%), wound infection (13.9%), wound infection staphylococcal (13.9%), and pruritus (10.1%). The AE incidence in the Infections and Infestations SOC was lower in males (27.8%) than in females (41.8%); however, this difference was not reflected in any particular PT.

Unless otherwise indicated, "wound complication" referred to AEs with MedDRA Preferred Term (PT) or Lowest Level Term (LLT) of "wound complication" and included e.g. wound re-opening, increase in wound size, wound worsening, increase in wound burden, worsening of EB wound pain, and wound odour, but excluded AEs such as wound haemorrhage, wound secretion, wound pain, wound infection, pruritus, and administration site pain, as these were coded to separate PT/LLT. There were no baseline data available and according to the applicant, no historical data on the incidence of wound complication from standard of care.

The BEB-13 protocol specified that worsening of wound status, increase in wound size, re-opening of wounds, and wound infections should be reported as AEs, following an FDA advice. When the investigators clinically assessed the wound for closure as part of the efficacy endpoint evaluation, they were required to complete a specific case report form (CRF) page with detailed wound closure assessments, and if the investigator marked that the wound had worsened, they were prompted to report an AE. Most wound complication AEs were not assessed as treatment-related by the investigator since changes in wound size from visit to visit, as well as reopening of previously closed wounds, are expected in EB due to the subjects' genetic skin fragility. In this comprehensive evaluation, only wounds that had closed could have met the category of "wound reopening" and only wounds that had decreased in size could have met the category of "increase in wound size compared to the previous visit." Thus, according to the applicant, there was an overlap with facets of the efficacy endpoint assessment of the target and non-target wounds.

In the BEB-13 study, the applicant conducted an important analysis of wound complications which highlighted a higher incidence of wound reopening (which could only occur if a wound had closed during the DBP) and increased in wound size compared to the previous visit in the Oleogel-S10 group as compared to the control gel group (28.4% vs. 17.5% and 11.0% vs 6.1%, respectively) during the DBP of BEB-13. It was also noted that during the DBP the composite events of increase in wound burden, worsening of EB wound pain, and wound odour were also worse for the Oleogel-S10 group (3.7% v 2.6%). During the OLP, the overall incidence of wound complication-related AEs in the OLP was 38.0%. This frequency was lower than in the DBP (65% of Oleogel-S10 group and 53.5% in the control gel) though it was noted that in the OLP (still ongoing) there was only 1 study visit (Month 3) at which target, and additional wounds were required to be clinically assessed for wound closure. The AEs related to wound complication in the ongoing BEB-13 OLP study at cut-off date 11 June 2020 and 21 April 2021 are presented in Table 27

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Table 27. Interim data of Adverse Events Related to Wound Complications, BEB-13 Study in EB; Open-Label Phase (Safety Analysis Set)

	All Subjects N=205 n (%) E DLP 11 June 2020	**All Subjects N=205 n (%) E DLP 21 April 2021**
Subjects with at least one AE with PT/LLT wound complication	78 (38.0) 100	81 (39.5) 103
- Wound reopening	39 (19.0) 44	40 (19.5) 45
- Increase in wound size compared to baseline	29 (14.1) 29	30 (14.6) 30
- Increase in wound size compared to the previous visit	12 (5.9) 12	12 (5.9) 12
- Other (which included increase in wound burden, worsening of EB wound pain, and wound odour)	9 (4.4) 11	9 (4.4) 11
- Wound worsening compared to baseline	3 (1.5) 3	4 (2.0) 4
- Injury to the wound	1 (0.5) 1	1 (0.5) 1

Abbreviations: E=number of events; EB=epidermolysis bullosa; LLT=Lowest Level Term; N=number of subjects in specific group; n=number of subjects; PT=Preferred Term.
Please note there are other AEs involving wounds (e.g., wound haemorrhage, wound secretion) but with a different PT/LLT
Note: Calculation of percentages is based on N.

In terms of wound reopening, the applicant confirmed that reopening occurred for 28.4% of Oleogel-S10 treated patients vs. 17.5% of control patients though the overall incidence of wound complication-related AEs was not substantially different between the treatment groups (61.5% in the Oleogel-S10 group and 53.5% in the control gel group). The applicant argued that as only wounds that had closed during the DBP could reopen; the increased frequency of reopening was viewed as a marker of efficacy. Throughout the DBP there was little difference between the proportions of target wounds assessed as closed for those patients treated with Oleogel-S10 vs control gel. A total of 45 patients out of 109 treated with Oleogel-S10 achieved first complete closure within 45±7 days. One wound reached first closure at day 7 and reopened by day 30, though it was assessed as closed again by day 60. Fifteen first complete wound closures occurred by day 14, with 7 of these assessed as reopened by day 30 (47%). Eighteen wounds reached first complete closure by day 30 with 6 of these reopening by day 45 (33%). Eleven wounds reached first complete closure by day 45 with 5 of these reopening by day 45 (45%). The applicant has previously argued that analysis of sustained closure was less relevant for EB due to nature of the fragile, structurally defective skin of EB patients which remained susceptible to re-opening after the achievement of closure. While this point is acknowledged it appeared that approximately 40% of first complete closures had reopened within 15 days and the clinical relevance of this duration of closure was uncertain.

Wound infections were reported also at baseline in the EB patients i.e., wound infection (5.8%), skin infection (4.5%), staphylococcal skin infection (1.8%) sepsis (1.3%), pseudomonal skin infection (0.9%), skin bacterial infection (0.4%), staphylococcal bacteraemia (0.4%), staphylococcal infection (0.4%), and pseudomonal infection (0.4%). Nevertheless, in case of wound infection the treatment with Filsuvez should be discontinued as recommended in SmPC section 4.4.

In SmPC section 4.4 the applicant has proposed a warning that the product should be removed by eye irrigation in case of exposure to eyes. This warning is considered relevant.

Considering that Filsuvez is a locally applied, locally acting product with limited systemic absorption and taking into account the reported AEs up to now, the statement that Filsuvez has no or negligible influence on the ability to drive and use machines in SmPC section 4.7 was agreed.

Overdosing with Filsuvez is unlikely. No case of overdose has been reported when a maximum amount of 69 g was used on a daily basis for more than 90 days. No data have been generated to establish the effect of accidental ingestion. This is included in SmPC section 4.9.

In SmPC section 4.8, the most frequently observed adverse reactions in EB patients, were wound complication (in 11.6% of patients), application site reaction (5.8%), wound infections (4.0%), pruritus (3.1%) and hypersensitivity reactions (1.3%). In patients with grade 2a burn wounds or split thickness skin grafts, the most frequently observed adverse reactions were wound complication (in 2.9% of patients), pain of skin (2.5%) and pruritus (1.3%).

System organ class	Very common	Common	Uncommon
Infections and infestations		Wound infections	
Immune system disorders		Hypersensitivity reactions*	
Skin and subcutaneous tissue disorders	Wound complication*	Pruritis	
			Dermatitis[a]
			Rash pruritic[a]
			Purpura[a]
General disorders and administration site conditions		Application site reactions* (e.g. application site	Pain[a]

System organ class	Very common	Common	Uncommon
		pain and application site pruritis)	
Injury, poisoning and procedural complications		Wound complication*[a]	Wound secretion

* see Description of selected adverse reactions
[a] adverse reactions observed in studies of patients with grade 2a burn wounds or split-thickness skin grafts

The frequencies of table 1 in SmPC section 4.8 have been updated with the OLP interim safety data as of 21 April 2021 i.e. Table 28) and contained all treatment-emergent AEs assessed as having a causal relationship. The recommendation of the use of the highest frequency has been applied.

Table 28. Summary of OLP Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Interim OLP Data

	N=205 n (%) E
Any AEs	26 (12.7) 63
Injury, poisoning and procedural complications	18 (8.8) 21
Wound complication	15 (7.3) 18
Wound secretion	2 (1.0) 2
Skin laceration	1 (0.5) 1
Skin and subcutaneous tissue disorders	10 (4.9) 13
Pruritus	4 (2.0) 4
Excessive granulation tissue	3 (1.5) 3
Blister	2 (1.0) 2
Rash	2 (1.0) 2
Eczema	1 (0.5) 1
Erythema	1 (0.5) 1
Infections and infestations	8 (3.9) 23
Wound infection	4 (2.0) 9
Wound infection staphylococcal	5 (2.4) 7
Wound infection bacterial	3 (1.5) 5
Bacterial disease carrier	1 (0.5) 1
Staphylococcal skin infection	1 (0.5) 1
General disorders and administration site conditions	5 (2.4) 6
Administration site pruritus	2 (1.0) 2
Administration site erythema	1 (0.5) 1
Administration site pain	3 (1.5) 3

Based on the data submitted for the MA of Episalvan, the applicant has included the following ADRs as uncommon: dermatitis, rash pruritic, purpura and pain; this is agreed.

Wound complication was split in to two different SOCs, i.e., data from non-EB patients in the SOC 'Injury, poisoning and procedural complications' but data from EB-patients was considered more appropriate under the SOC 'Skin and subcutaneous tissue disorders'.

2.6.8.3. Serious adverse event/deaths/other significant events

There were no deaths in the DBP of BEB-13. In the OLP of BEB-13 up to the cut-off date 21 April 2021, 6 patients have died. All deaths were assessed as anticipated with regard to disease course, none of these deaths were considered related to Oleogel-S10:

- disease progression (15-year-old male with RDEB [generalised severe])
- sepsis (10-year-old female with RDEB [generalised severe])

- cardiac failure (11-year-old male with RDEB [generalised severe])
- acute kidney injury (18-year-old female with RDEB [generalised severe])
- pneumonia (52-year-old female with RDEB [generalised severe])
- 6-month-old female with JEB (generalised severe), who died of sepsis with onset >30 days after last date of study medication administration (45 days since date of last dose and date of study discontinuation).

Since the intended action of Filsuvez gel is to promote wound healing, there is a potential proliferative and/or carcinogenic effect of the product, even if there was no evidence of such effects from the currently available data. The applicant planned to further characterise the important potential risk (clinical) and has included pharmacovigilance activities in the RMP which will include both a specific skin malignancies questionnaire and a register-based study (see section on the RMP). It was agreed, considering the chronic nature of the underlying disease and the recommended long-term treatment with Filsuvez, that monitoring of squamous cell carcinoma (SCC) and other skin malignancy events was clinically important. The direct effect of Oleogel-S10 on cell differentiation and/or proliferation, i.e., an underlying potential, local carcinogenic action was also discussed from a non-clinical perspective. Furthermore, in terms of non-clinical characterisation of carcinogenicity, it was noted that so far no carcinogenicity studies have been performed (see Non-clinical sections).

A warning that in the case of diagnosis of SCC or other skin malignancies, treatment to the affected area should be discontinued has been included in SmPC section 4.4.

Up to 21 April 2021, 44 of the 205 subjects (21.5%) have reported a total of 85 SAEs in the OLP (Table 29 and

Table 30). During the reporting period, 11 new SAEs were reported, of which 2 occurred in 2 additional subjects; the remaining 9 SAEs occurred in subjects for whom SAEs had been previously reported. The most common SAEs during the reporting period were oesophageal stenosis (4.4%) and anaemia (3.9%); these were the same 2 most common SAEs at the previous data lock point 11 Jun 2020. The 2 new subjects with SAEs during the reporting period were in the 4 to <12 years category (1 subject; oesophageal stenosis) and in the 12 to <18 years category (1 subject; anaemia). The applicant stated that oesophageal stenosis and anaemia were anticipated with regard to the disease course. Although the number of SAEs were increasing with longer exposure to Oleogel-S10, it was agreed that anaemia, oesophageal stenosis were anticipated with regard to the disease course and the baseline characteristics of the 223 patients included at the start of the BEB-13 study, included anaemia in 33.6% of the patients and oesophageal stenosis in 25.1% of the patients.

Table 29. Summary of Serious Adverse Events (SAEs) by Preferred Term by Age Category Subgroup (BEB-13, Safety Analysis Set)

	OLP N=205 n (%) E DLP 21 April 2021
Age 6 months-<4 y	**16**
Any SAEs	2 (12.5) 4
- Faecaloma	1 (6.3) 1
- Oesophageal stenosis	1 (6.3) 2
- Wound infection	1 (6.3) 1
Age 4-<12 y	**81**
Any SAEs	22 (27.2) 41
- Bacteraemia	2 (2.5) 2
- Wound infection	2 (2.5) 3
- Covid-19	1 (1.2) 1
- Catheter bacteraemia	1 (1.2) 1
- Sepsis	1 (1.2) 1
- Wound infection bacterial	1 (1.2) 1
- Blister infected	1 (1.2) 1
- Erysipelas	1 (1.2) 1
- Oral herpes	1 (1.2) 1
- Pyelonephritis	1 (1.2) 1
- Oesophageal stenosis	4 (4.9) 7
- Dysphagia	1 (1.2) 1
- Rectal haemorrhage	1 (1.2) 1
- Stomatitis	1 (1.2) 1
- Anaemia	4 (4.9) 7
- Dehydration	1 (1.2) 1
- Hypoalbuminaemia	1 (1.2) 1
- Malnutrition	1 (1.2) 1
- Pseudosyndactyly	1 (1.2) 1
- Unintentional medical device removal	1 (1.2) 1
- Gastronomy tube site complication	1 (1.2) 1
- Cardiac failure	1 (1.2) 1
- Talipes	1 (1.2) 1
- Psychomotor hyperactivity	1 (1.2) 1
- Pruritus	1 (1.2) 1
Age 12-<18 y	**50**
Any SAEs	9 (18.0) 19
- Anaemia	4 (8.0) 6
- Oesophageal stenosis	3 (6.0) 4
- Diarrhoea	1 (2.0) 1
- Otitis externa	1 (2.0) 1
- Medical device site infection	1 (2.0) 2
- Disease progression	1 (2.0) 1
- Eschar	1 (2.0) 1
- Malnutrition	1 (2.0) 1

	OLP N=205 n (%) E DLP 21 April 2021
- Weight gain poor	1 (2.0) 1
- Rash	1 (2.0) 1
Age ≥18 y	**58**
Any SAEs	11 (19.0) 21
- Device-related infection	1 (1.7) 3
- Osteomyelitis	1 (1.7) 1
- Septic shock	1 (1.7) 1
- Skin bacterial infection	1 (1.7) 1
- Skin infection	1 (1.7) 1
- Pneumonia	1 (1.7) 1
- Vaginal infection	1 (1.7) 1
- Anal fissure	1 (1.7) 1
- Anal stenosis	1 (1.7) 2
- Haemoperitoneum	1 (1.7) 1
- Oesophageal stenosis	1 (1.7) 1
- SCC	3 (5.2) 3
- Pericarditis	1 (1.7) 1
- Acute kidney injury	1 (1.7) 1
- Syndactyly	1 (1.7) 1
- Pelvic congestion	1 (1.7) 1

Table 30. Interim data of Serious Adverse Events by System Organ Class and Preferred Term Reported for ≥2 Subjects Overall, BEB-13 Study in EB; Open-Label Phase (Safety Analysis Set)

	All Subjects N=205 n (%) E DLP 11 June 2020	**All Subjects N=205 n (%) E DLP 21 April 2021**
Subjects with at least one SAE	40 (19.5) 68	44 (21.5) 85
Infections and infestations	17 (8.3) 22	18 (8.8) 26
Bacteraemia	2 (1.0) 2	2 (1.0) 2
Wound infection	2 (1.0) 2	3 (1.5) 4
Gastrointestinal disorders	12 (5.9) 15	15 (7.3) 23
Oesophageal stenosis	7 (3.4) 8	9 (4.4) 14
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.5) 3	3 (1.5) 3
Squamous cell carcinoma of skin	3 (1.5) 3	3 (1.5) 3
Blood and lymphatic system disorders	6 (2.9) 9	8 (3.9) 13
Anaemia	6 (2.9) 9	8 (3.9) 13
Musculoskeletal and connective tissue disorders	2 (1.0) 2	2 (1.0) 2
Pseudosyndactyly	2 (1.0) 2	2 (1.0) 2
Metabolism and nutrition disorders		3 (1.5) 5
Malnutrition		2 (1.0) 2

Abbreviations: E=number of events; EB=epidermolysis bullosa; N=number of subjects in specific group; n=number of subjects; SAE=serious adverse event.
Note: Calculation of percentages is based on N.

2.6.8.4. Laboratory findings

In the EB studies (BEB-13, BEB-10), there were inherent difficulties in conducting standard clinical safety evaluations such as electrocardiograms (ECGs, which use adhesive standard electrodes) and blood pressure measurements (which typically use arm or wrist cuffs) because of the fragility of the subjects' skin. However, in the pivotal BEB-13 study in EB, blood samples for clinical laboratory tests, ECGs, and vital sign measurements (heart rate, respiratory rate, and body temperature only) were collected per the study's schedule of assessments when feasible.

In the DBP of BEB-13, mean changes from baseline in haematology and biochemistry parameters from baseline to Day 90 were generally small and not clinically relevant. There were no clinically significant mean or median changes from baseline to Day 90 in the DBP vital sign parameters, and no differences were observed between treatment groups.

In the other clinical studies of Oleogel-S10, laboratory testing and measurement of vital signs were not performed.

Taking into account that Filsuvez gel is a locally applied, locally acting product with limited systemic absorption and considering the pain and fragility of the skin of RDEB and JEB patients, the clinical laboratory tests and measurements of vital signs performed in the pivotal BEB-13 study were considered sufficient. No safety issues have been identified from clinical laboratory tests and measurements of vital signs performed in the pivotal BEB-13 study.

2.6.8.5. Safety in special populations

From the BEB-13 study, there were no major differences identified in the nature and incidence of AEs for patients below or above 18 years of age and considering that Filsuvez is a locally applied, locally acting product with limited systemic absorption, it is agreed that no dose adjustment is required in elderly for Filsuvez. For the authorised medicinal product Episalvan, it was concluded that there were

no major differences in the nature and incidence of AEs for patients aged less than 65 years compared with older patients.

Taking into account that Filsuvez gel is a local treatment, and the systemic exposure is limited it is agreed that no dose adjustment or special considerations are anticipated for patients with renal or hepatic impairment. Furthermore, no effects on human fertility are anticipated since the systemic exposure is low. No studies of Oleogel-S10 in pregnant women have been conducted, and it is unknown whether birch bark extract/metabolites are excreted in human milk after the administration of Oleogel-S10.

Animal studies with respect to reproductive toxicity have been assessed in the non-clinical sections. Since there are no data on pregnant women, it was considered appropriate to state in SmPC section 4.6 that there are no data in pregnant women. The additional phrase 'limited amount of data (less than 300 pregnancy outcomes)' was not included, although a standard phrase, since it was considered misleading, in particular since that the total safety database in EB patients was less than 300 patients.

2.6.8.6. Immunological events

Hypersensitivity symptoms have been reported in both BEB-13 subjects and in subjects from the supportive clinical studies for the Episalvan indication of partial-thickness wounds.

The same extract from birch bark and the same vehicle were included in Episalvan and hypersensitivity to the active substance or to the excipient contained in the product is a contraindication for the use of Episalvan. In addition, hypersensitivity and dermatitis are listed in SmPC section 4.8 for Episalvan. It is agreed that the same risk of hypersensitivity reactions is anticipated during the use of Filsuvez in EB patients. Therefore, the proposed contraindication and warning regarding hypersensitivity in the SmPC for Filsuvez is agreed. It is also agreed that hypersensitivity should be listed in SmPC section 4.8.

2.6.8.7. Safety related to drug-drug interactions and other interactions

In the pivotal BEB-13 study, 201 (90.1%) subjects took at least one concomitant product during the DBP, including medicinal products and food supplements. Concomitant products were taken for conditions of the alimentary tract and metabolism (57.8%; mostly laxatives, vitamins and minerals), blood and blood forming organs (49.3%; mostly iron supplements), respiratory system (48.0%; mostly piperazine derivatives and antihistamines), nervous system (42.6%; mostly analgesics), and dermatologicals (39.9%).

Filsuvez is a locally applied, locally acting product with limited systemic absorption. Hence, no systemic drug-drug interactions were expected, and it was accepted that no drug-drug interaction studies were included in the development program. In SmPC section 4.5 of Episalvan, the recommendation is that other topical products should not be concomitantly used together with Episalvan but rather sequentially or alternatively depending on the clinical need. Due to the lack of additional data or other justification for Filsuvez, the text in SmPC section 4.5 was harmonised with the SmPC of Episalvan.

2.6.8.8. Discontinuation due to adverse events

Five patients had AEs leading to study withdrawal during the DBP of BEB-13, three patients in the Oleogel-S10 group and two in the control gel group. The AEs leading to study withdrawal in the Oleogel-S10 group were wound haemorrhage in one patient, procedural pain in one patient and SCC of

the skin (diagnosed upon enrolment and not treated with Oleogel-S10) in one patient. Wound haemorrhage and SCC were considered SAEs.

Cumulatively (up to 21 April 2021), a total of 60 patients have discontinued the OLP. A total of 14 patients have been withdrawn from the OLP because of AEs. Since the time of the previous data cut-off, an additional 4 subjects have discontinued the study (3 who withdrew of consent and 1 who withdrew for other reasons). No new discontinuations due to AEs have occurred to date (Table 31).

Table 31. Subject Disposition, Phase 3 Study BEB-13 in EB

	DBP Oleogel-S10 (N=109) n (%)	**DBP Control gel (N=114) n (%)**	**OLP (N=223) 11 June 2020 n (%)**	**OLP (N=223) 21 April 2021 n (%)**
Subjects who received treatment	109 (100.0)	114 (100.0)	205 (91.9)	205 (91.9)
Subjects who discontinued from the study	9 (8.3)	15 (13.2)	52 (23.3)	60 (26.9)
Reason for discontinuation				
- Withdrawal of consent	2 (1.8)	4 (3.5)	27 (12.1)	33 (14.8)
- AE	3 (2.8)	2 (1.8)	13 (5.8)	14 (6.8)
- Other	3 (2.8)	3 (2.6)	10 (4.5)	11 (4.9)
- Progression of medical condition	0	2 (1.8)	1 (0.4)	1 (0.4)

Abbreviations: AE=adverse event; DBP=double-blind phase; EB=epidermolysis bullosa; N=number of subjects in specific group; n=number of subjects; OLP=Open-label phase.
Note: Calculation of percentages based on N of randomized subjects.

2.6.8.9. Post marketing experience

The post marketing experience with Oleogel-10 is limited. To date, 11 patients (in Colombia and Argentina) have received Episalvan for partial-thickness wounds in EB under a Named Patient Program. An additional 5 patients (not eligible for enrolment in BEB-13 study) received Oleogel-S10 in France and Germany on a compassionate use basis.

2.6.9. Discussion on clinical safety

Oleogel-S10 containing 10% of dry extract from birch bark and with sunflower oil as the only excipient, has already been approved under the trade name Episalvan for the treatment of partial-thickness wounds in adults for up to four weeks. The systemic absorption of betulin has been assessed in the pharmacokinetics sections. It has been agreed that, as also concluded in the MA for the Episalvan gel, that the Oleogel-S10 is a locally applied, locally acting gel with limited systemic absorption.

Episalvan has been placed on the market but has not yet been launched commercially in the EU. Hence, the post marketing experience with Episalvan is limited. The three pivotal studies for the Episalvan MAA included a total of 280 patients. In split-thickness skin graft donor site wounds the mean wound size was 40.7 cm² (range 8-300 cm²) and in the Grade 2a burn wound the mean wound size was 108 cm² (range 23-395 cm²). In the pooled analysis of safety from these non-EB studies, most patients (91%) were white, and 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. It was concluded that Episalvan gel had a mild safety profile for the treatment of partial-thickness wounds in adults for up to four weeks with adverse events limited to local application reactions. Listed undesirable effects associated with the use of Oleogel-S10 include wound complication, wound

infections, and application/administration site reactions as these named identified events are listed as adverse reactions in the SmPC section 4.8 of Episalvan. However, no patient <18 years of age was included, and no long-term exposure data was available from the non-EB pooled studies. Overall, data from the authorised Episalvan were considered supportive only for Filsuvez, taking into account uncertainties concerning long-term treatment, larger wound size area and a different target population in EB.

The phase 3 study BEB-13 was considered pivotal for the safety assessment of Oleogel-S10 in patients with EB. In the BEB-13 study, 223 patients were enrolled for the 90-day DBP with EB subtypes JEB (11.7%) and DEB (87.5%), with a median age of 12 years (range 6 months to 81 years). The majority of patients were <18 years of age (70%), white (83.4%), and had Fitzpatrick skin type of Grade Type II or III (83%). Comorbidities reported in included EB patients were e.g., anaemia, malnutrition, oesophageal stenosis, susceptibility to infections.

In the DBP part of the BEB-13 study, 109 patients were exposed for 90-days only. The Filsuvez MAA was submitted before the end of the 24-month open-label follow up phase (OLP) of the pivotal study BEB-13 and contained only interim data relating to the OLP. The applicant has provided additional safety data with data lock point of 21 December 2020 and a 90-Day Safety Update Report with data lock point 21 April 2021. On 21 April 2021, out of 205 patients who entered the ongoing BEB-13 open label phase (OLP) 144 (70%) had completed the month 12 visit, and 68 patients (33.2%) had completed the 24 months visit. In addition, subjects in the so called "former Oleogel-S10 group" have received an additional 3 months of exposure to Oleogel-S10 during the previous DBP. Thus, the 82 patients in the "former Oleogel-S10-group" that completed the month 9 visit, have been exposed to Oleogel-S10 for 12 months in total, i.e., 156 patients have been exposed to Oleogel-S10 for 12 months. In comparison with the safety data submitted with the initial submission, it was agreed that there were no new safety issues detected from the 90-Day Safety Update Report with data lock point 21 April 2021.

As all subgroups were small in the BEB-13 study dataset, the interpretation of subgroup data was limited, in particular in the subgroups race and geographic regions. While EB occurs in all races and ethnic groups, Black and Asian patients were underrepresented in the safety analysis. This is reflected in the SmPC section 5.1.

While there did not appear to be a difference in safety profile by age group category from the data presented, there was uncertainty around this assumption due to the small subgroups. The applicant argued that considering that Oleogel-S10 is a topical treatment and minimally systemically absorbed, the use in children under 6 months is not expected to have any different safety profile to those already seen in the rest of the population. This was not agreed by the CHMP. Since the immune system of newborns and infants is not fully developed, they are considered to be more susceptible to infections. Therefore, due to lack of data, it is not known if children under the age of 6 months may have a higher risk of for example wound infections when treated with Oleogel-S10. Therefore, at present, the available safety database for Oleogel-S10 in the long-term treatment of JEB and DEB patients under the age of 6 months was considered insufficient. Consequently, the applicant agreed to restrict the therapeutic indication to patients 6 months and older.

In SmPC section 4.8, the most frequently observed adverse reactions in epidermolysis bullosa (EB) patients, were wound complication (in 11.6% of patients), application site reaction (5.8%), wound infections (4.0%), pruritus (3.1%) and hypersensitivity reactions (1.3%). In patients with grade 2a burn wounds or split thickness skin grafts, the most frequently observed adverse reactions were wound complication (in 2.9% of patients), pain of skin (2.5%) and pruritus (1.3%).

Hypersensitivity symptoms have been reported in both BEB-13 subjects and in subjects from the supportive clinical studies for the Episalvan indication of partial-thickness wounds. The same extract from birch bark and the same vehicle are included in Episalvan and hypersensitivity to the active substance or to the excipient contained in the product is a contraindication for the use of Episalvan. In addition, hypersensitivity and dermatitis are listed in SmPC section 4.8 for Episalvan. It is agreed that the same risk of hypersensitivity reactions is anticipated during the use of Filsuvez in EB patients. Therefore, the proposed contraindication and warning in the SmPC for Filsuvez is agreed. It is also agreed that hypersensitivity should be listed in SmPC section 4.8.

Wound infections were reported also at baseline in the EB patients including wound infection (5.8%), skin infection (4.5%), staphylococcal skin infection (1.8%) sepsis (1.3%), pseudomonal skin infection (0.9%), skin bacterial infection (0.4%), staphylococcal bacteraemia (0.4%), staphylococcal infection (0.4%), and pseudomonal infection (0.4%). Nevertheless, in case of wound infection the treatment with Filsuvez should be discontinued as recommended in SmPC section 4.4.

Five patients had AEs leading to study withdrawal during the DBP of BEB-13, three patients in the Oleogel-S10 group and two in the control gel group. The AEs leading to study withdrawal in the Oleogel-S10 group were wound haemorrhage in one patient, procedural pain in one patient and SCC of the skin in one patient. Wound haemorrhage and SCC were considered SAEs. Cumulatively (up to 21 April 2021), a total of 60 patients have discontinued the OLP. A total of 14 patients have been withdrawn from the OLP because of AEs.

Since the intended action of Filsuvez gel is to promote wound healing, the CHMP considered that there was a potential proliferative and/or carcinogenic effect of the product, even if there was no evidence of such effects from the currently available data. In order to address this safety concern, the applicant planned to further characterise this important potential risk (clinical) and has included additional pharmacovigilance activities in the RMP which will include both a specific skin malignancies questionnaire and a registry-based study (see RMP section 2.7). It is agreed, considering the chronic nature of the underlying disease and the recommended long-term treatment with Filsuvez, that monitoring of SCC and other skin malignancy events is clinically important. The direct effect of Oleogel-S10 on cell differentiation and/or proliferation, i.e., an underlying potential, local carcinogenic action was also discussed from a non-clinical perspective. Furthermore, in terms of non-clinical characterisation of carcinogenicity, carcinogenicity studies have been performed so far (see Non-clinical sections). Further, a warning regarding the need to discontinue treatment with Filsuvez in the case of diagnosis of squamous cell carcinoma or other skin malignancies, has been agreed upon in SmPC section 4.4.

Taking into account that Filsuvez gel is a local treatment and the systemic exposure is limited it is agreed that no dose adjustment or special considerations are anticipated for elderly patients or patients with renal or hepatic impairment. Furthermore, no effects on human fertility are anticipated since the systemic exposure is low. No studies of Oleogel-S10 in pregnant women have been conducted, and it is unknown whether birch bark extract/metabolites are excreted in human milk after the administration of Oleogel-S10. Animal studies with respect to reproductive toxicity have been assessed in the non-clinical sections. Since there are no data on pregnant women, it is considered appropriate to state in SmPC section 4.6 that there are no data in pregnant women. The additional standard phrase 'limited amount of data (less than 300 pregnancy outcomes)' was deleted as it was considered misleading, in particular since that the total safety database in EB patients is less than 300 patients.

In the pivotal BEB-13 study, 201 (90.1%) subjects took at least one concomitant product during the DBP, including medicinal products and food supplements. Concomitant products were taken for conditions of the alimentary tract and metabolism (57.8%; mostly laxatives, vitamins and minerals), blood and blood forming organs (49.3%; mostly iron supplements), respiratory system (48.0%; mostly piperazine derivatives and antihistamines), nervous system (42.6%; mostly analgesics), and dermatologicals (39.9%). Filsuvez is a locally applied, locally acting product with limited systemic absorption. Hence, no systemic drug-drug interactions are expected and it is accepted that no drug-drug interaction studies were included in the development program. In SmPC section 4.5 of Episalvan, the recommendation is that other topical products should not be concomitantly used together with Episalvan but rather sequentially or alternatively depending on the clinical need. Due to the lack of additional data or other justification for Filsuvez, the text in SmPC section 4.5 was harmonised with the SmPC of Episalvan.

In SmPC section 4.4 the applicant has proposed a warning that the product should be removed by eye irrigation in the case of exposure to eyes. This warning is considered relevant.

Considering that Filsuvez is a locally applied, locally acting product with limited systemic absorption and taking into account the reported AEs up to now, the statement that Filsuvez has no or negligible influence on the ability to drive and use machines in SmPC section 4.7 is agreed.

Overdosing with Filsuvez is unlikely. No case of overdose has been reported when a maximum amount of 69 g was used on a daily basis for more than 90 days. No data have been generated to establish the effect of accidental ingestion. This is included in SmPC section 4.9.

2.6.10. Conclusions on the clinical safety

The safety data base of Oleogel-S10 in JEB and DEB patients must be regarded as limited, even if the study was fairly large considering the orphan status of EB. Moreover, very limited long-term data are currently available for this chronic treatment. Data from the authorised Episalvan are considered supportive only, taking into account uncertainties concerning long-term treatment, larger wound size area and a different target population in EB.

The 24-month open-label follow up phase (OLP) with 205 EB patients is still ongoing and at present, the applicant has provided interim safety data with data lock point of 21 April 2021. The final CSR will be submitted once available (i.e., by Q1 2023). On 21 April 2021, out of 205 patients who entered the ongoing BEB-13 OLP 144 (70%) had completed the month 12 visit, and 68 patients (33.2%) had completed the 24 months visit. EB is a rare, designated orphan disease and the constraints in recruitment due to the rare condition is acknowledge.

As all subgroups are small in the BEB-13 study dataset, it is agreed that the interpretation of subgroup data is limited, in particular in the subgroups race and geographic regions. While there does not appear to be a difference in safety profile by age group category from the data presented, there is uncertainty around this assumption. In the pivotal BEB-13 study, the majority of the included patients were <18 years of age, of which 16 patients (8%) under 4 years of age entered the OLP. There are no safety data for children under the age of 6 months. The Applicant initially applied for an indication covering all ages. However, considering the very limited data in the youngest age group, an indication from birth onwards was not supported and a lower age limit of 6 months has been introduced.

Since the intended action of Filsuvez 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. The applicant plans to further characterise the important potential risk (clinical) and has included additional pharmacovigilance activities in the RMP which will include both a specific skin malignancies questionnaire and a registry-based study (see RMP section 2.7). A warning that in the case of diagnosis of squamous cell carcinoma or other skin malignancies, treatment to the affected area should be discontinued has been agreed upon in SmPC section 4.4. The warning also highlights to prescribers that while there has been no increase of skin malignancies associated with Filsuvez to date, a theoretical increased risk of skin malignancies associated with use of Filsuvez cannot be ruled out.

In SmPC section 4.8, the most frequently observed adverse reactions in epidermolysis bullosa (EB) patients, were wound complication (in 11.6% of patients), application site reaction (5.8%), wound infections (4.0%), pruritus (3.1%) and hypersensitivity reactions (1.3%). In conclusion, the overall safety profile of Oleogel-S10 in JEB and DEB patients over the age of 6 months is considered acceptable.

2.7. Risk Management Plan

2.7.1. Safety concerns

Important identified risks	• Allergic reaction / Hypersensitivity (*in patients with Partial thickness wounds*)
Important potential risks	• Wound infection Prolonged healing of burn wounds and risk of hypertrophic scarring if surgery is delayed (*in patients with Partial thickness wounds*) • Squamous cell carcinoma and other skin malignancies *(in patients with Epidermolysis Bullosa)*
Missing information	• Use in patients with different skin types regarding ethic origin/Fitzpatrick skin types

2.7.2. Pharmacovigilance plan

Study name/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Filsuvez Observational Safety and Effectiveness Evaluation Registry-	To collect pre-specified safety data in patients with EB irrespective of their treatment regimen to evaluate the	• Evaluate the long-term safety of Filsuvez amongst patients treated for EB in relation to the incidence, severity and	Submission study protocol (along with feasibility assessment)	Within 6 months of EC decision

Study name/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
based study in EB (FOStER-EB) [(AEB-21)] Planned	incidence of skin malignancies including SCC in EB patients treated with Filsuvez and provide data in a control population receiving treatment with standard of care therapy.	relatedness of skin malignancies (including SCC, BCC and MM), and use in patients with different skin types regarding ethnic origin		
			Estimated start date of data collection (patient recruitment)	Q3 2023
			Estimated end date of data collection	When the Registry Steering committee determines that scientific question has been answered
			Submission of Study Annual reports	Annually during the life of the registry-based study

2.7.3. Risk minimisation measures

Safety concern	Indication	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk Allergic reaction / hypersensitivity	Partial thickness wounds (Episalvan)	**Routine risk communication:** *SmPC section 4.3, 4.4 and 4.8.* *PL section 2 and 4* **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None

Safety concern	Indication	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risk 1 Wound infection	Partial thickness wounds (Episalvan)	**Routine risk communication:** *SmPC section 4.4 and section 4.8* *PL section 2 and 4* **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Important potential risk 2 Prolonged healing of burn wounds and risk of hypertrophic scarring if surgery is delayed	Partial thickness wounds (Episalvan)	**Routine risk communication:** *SmPC section 4.4* *PL section 2* **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Indication	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risk 3 Squamous cell carcinoma and other skin malignancies	Epidermolysis bullosa	**Routine risk communication:** *SmPC section 4.4* *PL section 2* **Other routine risk minimisation measures beyond the Product Information:** Not Applicable Legal status: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Follow-Up Questionnaire for Skin Malignancies Monitoring the risk using 'Skin neoplasms, malignant and unspecified (SMQ)' and 'Skin malignant tumours (SMQ)' during monthly Signal management activities **Additional pharmacovigilance activities**: Filsuvez Observational Safety and Effectiveness Evaluation Registry-based study in EB (FOStER-EB) [(AEB-21)]
Missing information 1 Interaction with other topically applied medicinal products	Partial thickness wounds (Episalvan)	**Routine risk communication:** *SmPC section 4.5* *PL section 2* **Other routine risk minimisation measures beyond the Product Information:** Legal status: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities**: None

Safety concern	Indication	Risk minimisation measures	Pharmacovigilance activities
Missing information 2 Use in patients with different skin types regarding ethnic origin / Fitzpatrick skin types	Partial thickness wounds (Episalvan) Epidermolysis bullosa	**Routine risk communication:** *None* **Other routine risk minimisation measures beyond the Product Information:** Not Applicable Legal status: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Filsuvez Observational Safety and Effectiveness Evaluation Registry-based study in EB (FOStER-EB) [(AEB-21)]

2.7.4. Conclusion

The CHMP considers that the risk management plan version 2.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. 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.

2.8.2. Periodic Safety Update Reports submission requirements

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.

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.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

EB is a rare ('orphan') heterogeneous group of genetic skin fragility disorders characterised by blistering and erosions of epithelial surfaces in response to minor trauma or friction. EB is divided into 4 major subtypes, based on the level of skin cleavage:

- Epidermolysis bullosa simplex (EBS, intra-epidermal skin separation).
- Junctional epidermolysis bullosa (JEB, skin separation within the lamina lucida or central basement membrane zone).
- Dystrophic epidermolysis bullosa (DEB, sublamina densa or dermal separation). Based on the mode of inheritance, this is subdivided into dominant (DDEB) and recessive (RDEB) forms.
- Kindler syndrome (variable level of separation in the skin within basal keratinocytes, at the level of the lamina lucida or below the lamina densa).

One of the most significant problems in EB is the lifelong presence of skin blistering and partial-thickness wounds that result in pruritus, pain, scarring, deformity, loss of function, and immobility as well as a high risk of complications, such as infection. In addition, there is an increased incidence of aggressive cutaneous SCC at a younger age than in the general population. In patients with generalised severe RDEB, SCC occurs in approximately 80% of patients by their mid-40s and can occur as early as adolescence.

The applicant has sought a marketing authorisation for Filsuvez for the following indication:

Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.

3.1.2. Available therapies and unmet medical need

No approved therapy exists for EB in the EU. There are no medical treatments that have demonstrated efficacy in the treatment or prevention of the recognised clinical manifestations of this rare genetic disorder, which include debilitating symptoms and substantial morbidity; those with moderate to severe disease may have life-threatening manifestations and in a proportion of patients, the disease reduces life expectancy.

The current treatment of EB wounds is symptomatic, including early judicious treatment of wounds to prevent or minimise infection and wound protection with non-adhesive dressings to enable wound healing. Patients with EB take care to minimise new wounds; however, this is particularly difficult for young children as minor trauma or friction results in partial-thickness wounds.

The efficacy of topical agents aimed at improving wound healing may have direct implications on outcomes and quality of life for patients with EB. With regular application of such a product, the total wound burden and associated symptoms and complications of unhealed wounds such as infections, itching, and pain could be expected to decrease.

Hence, an unmet need to achieve faster and improved wound healing exists in EB, to decrease complication (e.g., infections) and to improve quality of life (e.g. by reduced pain and itch). Most

experts agree that "any acceleration" and "each day gained" in time to wound healing would be important and clinically significant for EB patients with partial-thickness wounds.

3.1.3. Main clinical studies

The clinical efficacy data to support an EB indication for Filsuvez come primarily from a single phase 3 study, BEB-13, with some support also from a small phase 2 study in EB patients, BEB-10. Two phase 2 healthy subject studies with the control gel (AHV-18-A and AHV-18-B) are also referred to. In addition, the studies included in the submission for Episalvan are included as supportive data.

Study BEB-13 was a randomised, controlled, 90-day double-blind phase 3 study, with a 24-month open-label follow-up of Oleogel-S10 in subjects with inherited EB. The study included subjects with dystrophic or junctional EB. Patients should have a target wound of 10 to 50 cm^2 in surface, aged ≥21 days but less than 9 months. The study had broad age inclusion criteria; subjects from the age of 21 days could be included.

A total of 223 subjects were randomized 1:1 to Oleogel-S10 (N=109) or control gel (N=114), both on top of standard of care (non-adhesive wound dressing). The control gel was specifically developed for use in this study, since the pure 'vehicle' (sunflower oil) could not be used. Oleogel-S10 or the control gel were to be applied on the EB target wound and also to all areas on the subject's body that were affected by EB partial-thickness wounds. No maximum body surface area to be covered was specified in the protocol.

The primary efficacy endpoint was the proportion of subjects with first complete closure of the EB target wound within 45 days of treatment with Oleogel-S10 compared with control gel based on clinical assessment by the investigator (the wound was to be rated as "closed" at first appearance of complete re-epithelialisation without drainage).

Several secondary endpoints were also evaluated, reflecting other aspects of wound healing, incidence and severity of wound infections, change from baseline in total body wound burden and change from baseline in itching and pain.

3.2. Favourable effects

The primary efficacy endpoint was met as the proportion of subjects with first complete closure of the EB target wound within 45 days of initiating treatment was higher in the Oleogel-S10 group (41.3%) compared to the control gel group (28.9%). The relative risk was 1.44 (1.01, 2.05) with an odds ratio (95% CI) of 1.84 (1.02, 3.30). This resulted in a p-value of 0.041 (CHM method) or a p-value of 0.013 (CHW method).

For the presentation based on stratification factors, the DEB strata showed higher rates of wound closure for Oleogel-S10 vs. control gel across wound size. For the overall RDEB group (n=175), 44.0% in the Oleogel-S10 group and 26.2% in the control group met the primary endpoints (p=0.008).

When the Complete analysis set (CAS) and per protocol set (PPS) were evaluated, results of the primary efficacy analysis were numerically similar to those of the FAS. The proportion of subjects with first complete closure of the EB target wound within 45 days of treatment was higher for both populations in the Oleogel-S10 group compared to the control gel group (CAS: 44.0% vs. 30.3%; PPS: 42.4% vs. 33.3%, respectively). Results for the CAS were statistically significant in favour of Oleogel-S10 based on the CMH test stratified by EB subtype and target wound size class (p=0.034).

In a sensitivity analysis, result for the primary endpoint was assessed based on confirmed, sustained healing of the target wound, at 7 days after the first healing was observed. Fewer subjects were rated as 'success' for both groups, with 17.4% achieving confirmed closure in the Oleogel-S10 group vs. 8.8% in the control group. This difference was borderline significant (p=0.048).

For the first key secondary endpoint (time to first complete closure of the EB target wound as evidenced by clinical assessment within 90 days) the difference between the treatment groups was not statistically significant (p=0.302). The median time to closure within 90 days was similar between treatment groups (92 days Oleogel-S10 and 94 days control gel). Hence, the results for the additional key secondary endpoints are not confirmatory.

Apart from EB subtype, other subgroups were also analysed. With respect to *age*, the largest part of the study population were aged below 18 years with the largest sub-group being those aged 4 to <12 years, comprising 38% overall. In this age subgroup, the most pronounced difference between treatments in favour of Oleogel-S10 was observed. Results for the two other age groups below 18 years were also numerically in favour of Oleogel-S10.

3.3. Uncertainties and limitations about favourable effects

Primary efficacy endpoint

The primary analysis used a non-responder imputation for missing data. Even if the amount and reasons of missing data was similar in the two treatment groups, this is no guarantee that data are Missing at Random (MAR). Hence, a tipping point analysis evaluating robustness to any such bias was considered important. In the pre-planned tipping point analysis, the MI analysis on original data gave borderline significant results and switching the result for only one control patient resulted in a non-significant p-value. While the applicant could explain that the missing data at the primary analysis time point were indeed comparably distributed over both treatments, concern was raised that in fact one patient in the control group that had a wound closure at D52 was treated as non-responder in the primary analysis. Handling of this patient as such was not agreed to and was considered anti-conservative. This patient should have been considered as responder, and in light of a borderline statistical analysis, a concern was raised that treating this patient as a responder could tip the result when using the predefined primary analysis method and render this as insignificant. Nevertheless, the applicant provided an analysis demonstrating that when treating this patient as responder in the primary analysis, the primary analysis remained statistically significant (p=0.021). Further sensitivity analyses were discussed, which supported the conclusion of the primary analysis timepoint.

Secondary efficacy endpoints

The results for the first key secondary endpoint were not statistically significant, hence, the results for the key secondary endpoints are not confirmatory. Thus, no formally demonstrated positive effects on wound infections, total body wound burden, itch, pain or sleep can be claimed for Filsuvez.

Other aspects

For the JEB/Kindler EB sub-types, the patient numbers were small (n=26 in total) and Oleogel-S10 showed a lower rate of wound closure up to 45 days vs. the control gel (18.2% vs. 26.7%; p=0.522). For the DDEB sub-type, the patient numbers were also small (n=20 in total) and Oleogel-S10 showed a similar rate of wound closure up to 45 days vs the control gel (50% vs 50%; p=0.844). Given that a clinical effect is considered to be established in the study population, an indication covering both subtypes (DEB and JEB) was ultimately considered acceptable by the CHMP. Effectiveness of Filsuvez is planned to be assessed as part of the planned PASS (AEB-21), see RMP section 2.7.

In subgroup analyses with respect to *age*, the youngest age group in study BEB-13 (0-<4 years) was very small (n=17 in total, 7 in the Oleogel-S10 group and none <12 months), which make interpretations uncertain. For the oldest age group (≥18 years, i.e., adults, comprising 30% of the study population), the results were not in favour of Oleogel-S10 (odds ratio and 95% CI: 0.86, 0.31; 2.43). A restriction for adults and elderly is not necessary and for the youngest children, an age limit of 6 months has been introduced in the indication.

Results with respect to *race* are difficult to make since 83.4% of subjects were White. Section 5.1 of the SmPC includes a statement on limited data available for Black and Asian patients.

Limited additional data from the OLE study (BEB-13) have been submitted; however, the study is still ongoing. Thus, limited long-term efficacy data for Filsuvez are available. The BEB-13 final CSR will be submitted for assessment once available i.e., by Q1 2023. In the Phase 2 study, no data beyond Day 28 were collected. If symptoms persist or worsen after use, or if wound complications occur, the patient's condition should be fully clinically assessed prior to continuation of treatment, and regularly re-evaluated thereafter (SmPC section 4.2).

3.4. Unfavourable effects

The most frequently observed adverse reactions in EB patients are wound complication (in 11.6% of patients), application site reaction (5.8%), wound infections (4.0%), pruritus (3.1%) and hypersensitivity reactions (1.3%).

Hypersensitivity symptoms have been reported in both BEB-13 patients and in patients from the supportive clinical studies for the Episalvan indication of partial-thickness wounds. The same extract from birch bark and the same vehicle are included in Episalvan and hypersensitivity to the active substance or to the excipient contained in the product is a contraindication for the use of Episalvan. In addition, hypersensitivity and dermatitis are listed in SmPC section 4.8 of Episalvan. It is agreed that the same risk of hypersensitivity reactions is anticipated during the use of Filsuvez in EB patients.

3.5. Uncertainties and limitations about unfavourable effects

The safety data base of Oleogel-S10 in JEB and DEB patients is limited, with 109 patients treated for 90-days in the finalised part of the pivotal BEB-13 study. The 24-month open-label follow up phase (OLP) with 205 EB patients is still ongoing and at present, the applicant has provided safety data with data lock point of 21 April 2021. On 21 April 2021, out of 205 patients who entered the ongoing BEB-13 open label phase (OLP) 144 (70%) had completed the month 12 visit, and 68 patients (33.2%) had completed the 24 months visit. While there does not appear to be a difference in safety profile depending on age, race or gender from the data presented, there is uncertainty around this assumption. The meaningfulness of any sub-analyses of safety profile in BEB-13 by age is limited by the low numbers, with n=17 children less than 4 years of age and none less than 6 months. The median daily and cumulative extent of exposure for all patients and by age category are displayed in the SmPC section 5.1. Similarly, Asian and Black patients are poorly represented in this safety set. Section 5.1 of the SmPC includes a statement on limited data available for Black and Asian patients. The missing information 'Use in patients with different skin types regarding ethnic origin/Fitzpatrick skin types' will be followed-up in the post-marketing setting as part of a PASS (AEB-21), see RMP section 2.7. Further, the final BEB-13 CSR will be submitted for assessment once available (i.e., by Q1 2023).

Adverse events recorded during clinical development program, including during the pivotal safety and efficacy study, are in general, those typically associated with the underlying disease. With a small safety set it is difficult to definitively identify a causal relationship for adverse reactions which overlap with complications of EB. In relation to squamous cell carcinomas (SCC), it is acknowledged that the clinical cases presented here are not uncharacteristic for the patient population. Patients with severe RDEB in particular have an extremely high risk of developing aggressive SCC, which is the leading cause of death in this group. Nonetheless, given the concerns regarding the potential risk for local site carcinogenicity with a compound whose action is to accelerate re-epithelialisation, this issue is communicated in the product information (SmPC section 4.4). This important potential risk will also be followed-up in the post-marketing setting as part of a PASS (AEB-21), see RMP section 2.7.

The gel is sterile. However, wound infection is an important and serious complication that can occur during wound healing. In the case of infection, it is recommended to interrupt treatment. Additional standard treatment may be required. This is adequately reflected in SmPC section 4.4.

3.6. Effects Table

Table 32. Effects Table for Filsuvez in Epidermolysis Bullosa (data cut-off: 21 April 2021)

Effect	Short Description	Unit	Treatment: Oleogel-S10	Control: Control gel	Uncertainties/ Strength of evidence	References
Favourable Effects						
PEP: Target wound closure in 45 days	Proportion of Subjects with First Complete Closure of Target Wound within 45 Days Based on Clinical Assessment (FAS)	%	41.3%	28.9%	p=0.013 (CHW adjustment) Uncertainties related to the robustness of the results (however, a CHW tipping point analysis was statistically significant; p=0.021)	Study BEB-13
Sensi-tivity analysis, confirmed closure after 7 days	Proportion of Patients with First Complete Closure of EB Target Wound within D45±7 days, Clinical Assessment Confirmed by a Second Observation after 7+2 Days (stratified CMH test, FAS)	%	17.4%	8.8%	p= 0.048	Study BEB-13
First key SEP: Time to target wound closure in 90 days	Time to first complete closure of the EB target wound as evidenced by clinical assessment within 90 days	Days	92 days	94 days	p=0.302 No significant difference	Study BEB-13
Unfavourable Effects						

Effect	Short Description	Unit	Treatment: Oleogel-S10	Control: Control gel	Uncertainties/ Strength of evidence	References
Wound complication	Includes different kinds of local complications such as increase in wound size, wound re-opening and wound pain.	%	11.6	NA	AEs assessed as having a reasonable causal relationship and qualified as ADRs in SmPC section 4.8.	(1)
Application site reaction	Includes application site pain and application site pruritis.	%	5.8	NA	AEs assessed as having a reasonable causal relationship and qualified as ADRs in SmPC section 4.8.	(1)
Wound infections		%	4.0	NA	AEs assessed as having a reasonable causal relationship and qualified as ADRs in SmPC section 4.8.	(1)
Pruritus		%	3.1	NA	AEs assessed as having a reasonable causal relationship and qualified as ADRs in SmPC section 4.8.	(1)
Hypersensitivity	Includes rash, urticaria and eczema.	%	1.3	NA	AEs assessed as having a reasonable causal relationship and qualified as ADRs in SmPC section 4.8.	(1)

Notes: (1) Data from the ongoing 24-month OLP of the pivotal BEB-13. The frequencies have been updated with the OLP interim safety data as of 21 April 2021 and contains all treatment-emergent AEs assessed as having a causal relationship.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

EB is a chronic condition. There are no medicinal products currently authorised for the treatment of any EB subtypes in the EU and therefore there is a high unmet medical need in this condition. Currently used treatments for EB target symptoms, with professional wound care being the mainstay of therapeutic intervention. The changing of dressings is painful, time consuming and stressful for patients. The aim of the current product, Filsuvez, is to accelerate wound healing in patients with EB.

The more severe EB subtypes represent a large disease burden and experts/treating physicians generally state that 'any improvement' in wound healing can be of importance for the patient. This was strongly emphasised by experts and patient representatives at the AHEG meeting.

The pivotal study BEB-13 met its primary efficacy endpoint as the proportion of subjects with first complete closure of the EB target wound within 45 days of initiating treatment was higher in the

Oleogel-S10 group compared to the control gel group. Given the results of study BEB-13, an effect of Filsuvez has thus been established in the studied population (i.e., JEB and DEB).

The result for the first key secondary endpoint (time to first complete closure of the target wound within 90 days) was not statistically significant, hence, in line with the prespecified hierarchical testing strategy, the results for additional key secondary endpoints are not confirmatory. Although the results were mostly numerically in favour of Oleogel-S10, the absolute differences were small for important outcomes such as total wound burden, itch or pain.

During the consultation of the Ad-Hoc Expert Group (AHEG), the majority of the clinical experts and all patient representatives considered that, based on the data presented, an effect, although modest, has been established with Filsuvez. Moreover, the reduction of time for dressing, frequency of the dressing and pain reduction were also discussed during and the results presented, although limited, were considered to be of clinical relevance for the EB patients and carers.

In early phases of the procedures, there was some uncertainty related to a potential, detrimental effect of the comparator used in the pivotal study. Collectively, however, the information from the literature review, the results of study AHV-18-A (clinical score and planimetry), the planimetry results in study AHV-18-B and the comparison with the external study suggest that the control gel did not have a detrimental effect on wound healing. Hence, the uncertainty related to the control gel has to the extent possible been alleviated.

The observed safety profile indicates no major cause for concern apart from local, mainly wound-related AEs and no systemic AEs. Nevertheless, the safety data base of Oleogel-S10 in JEB and DEB patients must be regarded as limited, even if the study was fairly large considering the orphan status of EB. Moreover, very limited long-term data are currently available for this chronic treatment. Further safety data are expected to be submitted by Q1 2023 (BEB-13 final CSR). A potential proliferative and/or carcinogenic effect of the product is listed as an important potential risk and will be followed as part of a PASS in the post-marketing setting (study AEB-21, see RMP section 2.7).

3.7.2. Balance of benefits and risks

The conduct of a randomised controlled study in the rare and severe condition EB is acknowledged and appreciated. The overall study design is endorsed, and the study was fairly large considering the orphan condition, with 223 patients randomised. The study met its primary endpoint; complete closure of the EB target wound within 45 days of initiating treatment. The support from secondary endpoints was very limited, but demonstration of statistical significance for secondary endpoints is not a strict regulatory requirement. Even if the statistical robustness of the analysis of the primary endpoint has been questioned during the procedure, the CHMP concluded, in line with the recommendation of the AHEG, that an effect of Filsuvez has been established in the overall study population considering that some of the sensitivity analyses supported the primary analysis of the primary endpoint. Moreover, the effect size, albeit modest, is considered clinically meaningful. Considering the acceptable safety profile, it is concluded that the benefit risk balance is positive in the following indication:

Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.

3.7.3. Additional considerations on the benefit-risk balance

The applicant initially applied for an indication covering all ages. However, considering the very limited data in the youngest age group, an indication from birth onwards was not supported and the applicant agreed to introduce a lower age limit of 6 months.

In addition, the applicant proposed to include both the DEB and the JEB sub-types, even though, data in patients with DDEB and JEB is very limited. EB experts in the AHEG considered that one cannot infer that a drug that works in DEB would work in JEB as well, while the patients' representatives considered that any drug that overall works in EB would be considered as important for the EB patients. It was finally considered acceptable by the CHMP to include also the JEB subtype in the indication, given the established effect in the overall study population and taking into account that the mechanism of action does not target specific EB sub-types; however, with a cautionary statement in SmPC section 4.4 clarifying the limited data available in the JEB and DDEB subtypes.

Concerning the duration of treatment and when to stop treatment if an effect is not shown, the SmPC section 4.2 states that "If symptoms persist or worsen after use, or if wound complications occur, the patient's condition should be fully clinically assessed prior to continuation of treatment, and regularly re-evaluated thereafter". This wording is agreed by the CHMP.

In the context of an orphan condition, the data submitted are considered as comprehensive considering that a controlled study has been performed and safety data is available for approx. 140 patients exposed for one year. The applicant proposal for a full marketing authorisation is therefore accepted by the CHMP.

Third party intervention during the evaluation of Filsuvez

The CHMP received, during the assessment of this application, a correspondence from the EB patient community (hereinafter referred to as "third party") expressing the third party' views about the perspective and experience of people affected by EB, and the unmet medical need of EB patients. The CHMP considered this intervention in the context of its assessment and concluded that the observations put forward by the EB patient community were already known by CHMP, and as such had no impact on the CHMP assessment or its conclusions.

3.8. Conclusions

The overall benefit/risk balance of Filsuvez is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Filsuvez is favourable in the following indication:

'Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.'

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other 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 marketing authorisation holder (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.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0425/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.