Australian Government
Department of Health, Disability and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Filsuvez

Active ingredient: Birch bark dry extract (84 - 95% triterpenes)

Sponsor: Chiesi Australia Pty Ltd

June 2026

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, Disability and Ageing and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety, and efficacy.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
AHEG	Ad-Hoc Expert Group
ARTG	Australian Register of Therapeutic Goods
ASA	Australia-specific annex
BCCs	Basal cell carcinomas
BMI	Body Mass Index
CAS	Completer Analysis Set
CHMP	Committee for Medicinal Products for Human Use (EMA)
CMI	Consumer Medicines Information
CSR	Clinical Study Report
DBP	Double-blind phase
DBS	Dried blood spot
DEB	Dystrophic epidermolysis bullosa
DIBD	Development international birth date
DLP	Data lock point
EB	Epidermolysis bullosa
EBDASI	EB Disease Activity and Scarring Index
EBS	Epidermolysis bullosa simplex
EDTA	Ethylenediaminetetraacetic Acid
EMA	European Medicines Agency
FAS	Full analysis set
fu,p	Unbound fractions in plasma
IDMC	Independent drug monitoring committee
INV	Involucrin
JEB	Junctional epidermolysis bullosa
KRT 10	Keratin, type I cytoskeletal 10
KS	Kindler syndrome
LLOQ	Lower limit of quantification
mRNA	Messenger ribonucleic acid
NDIS	National Disability Insurance Scheme
NEBDS	National Epidermolysis Bullosa Dressing Scheme

Abbreviation	Meaning
OLP	Open-label phase
PD	Pharmacodynamics
PI	Product Information
PK	Pharmacokinetics
PPS	Per-protocol Set
PSUR	Periodic safety update report
RDEB	Recessive (r) inheritance dystrophic epidermolysis bullosa
RMP	Risk management plan
SAE	Serious adverse event
SAS	Safety Analysis Set
SCC	Squamous cell carcinoma
SD	Standard deviation
TEAE	Treatment emergent adverse events
TGA	Therapeutic Goods Administration

Product submission

Submission details

Type of submission:	New chemical entity
Product name:	Filsuvez
Active ingredient:	Birch bark dry extract (84% - 95% triterpenes)
Decision:	Approved
Date of decision:	28 April 2026
Date of entry onto ARTG:	5 May 2026
ARTG number:	483785
▼*Black Triangle Scheme*	Yes
for the current submission:	
Sponsor's name and address:	Chiesi Australia Pty Ltd Level 7, Suite 1, 500 Bourke Street, Melbourne, Victoria, 3000.
Dose form:	Gel - colourless to slightly yellowish, opalescent, non-aqueous gel.
Strength:	Each 1 g of gel contains 100 mg birch bark dry extract (10% w/w).
Container:	Tube
Pack sizes:	1 x 23.4 g tube, 10 x 23.4 g tubes, 30 x 23.4 g tubes.
Approved therapeutic use for the current submission:	*Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.*
Route of administration:	For topical application only.
Dosage:	The gel should be applied at a thickness of approximately 1 mm to a sterile non-adhesive wound dressing that is placed directly over the wound or applied to the wound surface and covered by the dressing. The gel should be applied liberally. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	**Category B1** There are no data from the use of Filsuvez in pregnant women. No effects during pregnancy are anticipated, since systemic exposure to Filsuvez is negligible. Filsuvez can be used during pregnancy. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health

professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by Chiesi Australia Pty Ltd (the Sponsor) to register Filsuvez (birch bark dry extract - 84-95% triterpenes) 100 mg/g gel tube for the following proposed indication:[1]

> *Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.*

This is a Type A (new chemical entity) COR-B application to register a new medicine. The primary evaluation was provided by the European Medicines Agency (EMA) Centralised procedure.

Condition

According to Laimer and Murrell (2025),

> Epidermolysis bullosa (EB) is a clinically and genetically heterogeneous inherited skin fragility disorder characterized by disruption of the skin's structure at the dermoepidermal junction or in the basal layer of the epidermis, resulting in increased cutaneous vulnerability to mechanical stress. Depending on the specific genetic defect and its molecular sequelae, clinical hallmarks include blisters, wounds, and scars following minor trauma. Wounds may present as acute, chronic, open (i.e. not healing within six weeks), or recurrent (with repetitive blistering, healing, and subsequent reopening). EB, and particularly its more severe variants, carries a considerable societal burden that affects patients, caregivers, and health care providers. [2]

Furthermore,

> EB is caused by variants in several genes encoding structural proteins within keratin intermediate filaments, focal adhesions, desmosome cell junctions, and hemidesmosome attachment complexes. These structures form the intraepidermal adhesion and dermoepidermal anchoring complexes within the basement membrane zone of the skin and mucosae. The molecular aberrations interfere with the functional and structural integrity of the basement membrane that is crucial for cell adhesion, proliferation, and differentiation, tissue repair and barrier function.[2]

Disruption of the basement membrane results in cell and tissue dehiscence, skin fragility and the tendency of the skin to blister and break down with minor trauma. This epithelial fragility may not be restricted to the skin and adnexa. Depending on the nature of the underlying pathology, EB may also directly affect the gastrointestinal system, the genitourinary tract and the

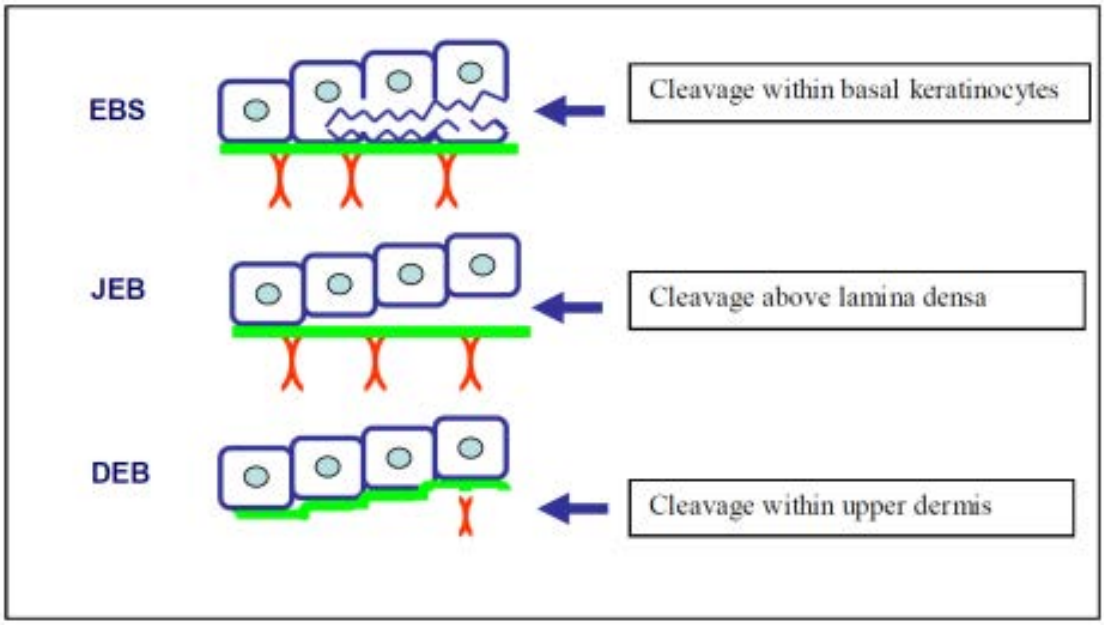
[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

[2] Laimer M & Merrell D. Epidermolysis bullosa: Epidemiology, pathogenesis, classification, and clinical features, *UptoDate,* updated Oct 28, 2024. Accessed Jan 31, 2025.

respiratory system, while the consequences of EB may affect the heart, endocrine and haematopoietic systems.[2,3]

Traditional classification systems differentiate between four major types of EB: EB simplex (EBS), dystrophic EB (DEB) (including forms with dominant (d) and recessive (r) inheritance), junctional EB (JEB) and Kindler syndrome (KS), which all differ in their severity and clinical presentation. Recently, molecular typing technologies have allowed for more detailed categorization between and within the major types. In the simplest categorisation of EB, the distinction relies on the layer of the skin in which disruption occurs (Figure 1).[4]

Figure 1: Different cleavage levels within the skin of EB patients.[4]



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

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 squamous cell carcinoma (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.[5]

Current treatment options

In the absence of a cure, management of EB is based on preventive measures, together with symptomatic treatment of cutaneous and extracutaneous manifestations and complications.[6] In Australia and elsewhere, treatment by multidisciplinary teams is considered best practice

[3] El Hachem M, et al. (2014) Multicentre consensus recommendations for skin care in inherited epidermolysis bullosa. *Orphanet Journal of Rare Diseases*, 9:76. http://www.ojrd.com/content/9/1/76

[4] C. Has, J.W. Bauer, C. Bodemer, M.C. Bolling, L. Bruckner-Tuderman, et al. (2020) Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility, *British Journal of Dermatology*, 183(4): 614–627. https://doi.org/10.1111/bjd.18921

[5] Fine JD, Johnson LB, Weiner M, Li KP, Suchindran C. (2009) Epidermolysis bullosa and the risk of life-threatening cancers: the National EB Registry experience, 1986-2006. J Am Acad Dermatol, 60(2):203-211. https://www.jaad.org/article/S0190-9622(08)01216-4/abstract

[6] The Australasian College of Dermatologists. Epidermolysis bullosa, updated April 2023, accessed 31 Jan 2025

management of EB.[3,7] Overall, the management of EB involves skin and wound care, itch management, acute and chronic pain management, nutritional management, psychological care and consideration of physical therapy and rehabilitation to delay and avoid contractures and deformities, and routine screening for macro- and micro-nutritional deficiencies. Patients with some types of EB also require regular screening for skin malignancies.

At the time of this assessment, there were no registered therapeutic goods (medicines or devices) with specific indications in EB in Australia.

However, the Australian government subsides the costs of specialised dressings, bandages, and ancillary products for people with EB through the National Epidermolysis Bullosa Dressing Scheme (NEBDS),[8] currently administered by Independence Australia, a registered NDIS supplier. Products provided under the NEBDS include non-stick soft silicone dressings, hydrocolloid impregnated polyester mesh dressings for wounds at risk of infection, foam dressings for exudative wounds and soft tubular bandages to hold dressings in place.[9] In the absence of these specialised products, patients with EB would be reliant on the wide range of ARTG registered or listed wound dressings (eg paraffin-impregnated or medicated gauzes) and bandages as well as other skin care approaches including emollients, mild steroids, or antiseptics if indicated. There is a paucity of scientific data on the effectiveness of emollients.

The Australasian College of Dermatologists makes the following general recommendation regarding wound care:

> *Wound care - using non-stick dressings to open wounds with secondary absorbent dressings and bandages to aid healing, regular bathing to keep skin clean, soaking dressings to facilitate removal.*

There are a range of topical antiseptic preparations for prevention and treatment of bacterial infections in minor cuts, wounds, abrasions and burns, but not specifically to aid in wound healing.

Some of the specialised dressings provided under the NEBDS are not included in the ARTG (e.g. Adaptic non-adherent dressing, Atrauman silicone dressing, Cuticell Contact, Mepitel dressings, Spycra dressings, Mepilex Transfer dressings, Biatain Foam dressings, Polymem dressings).

However, examples of silver-impregnated dressings regulated as Class III medical devices, which are included in the NEBDS as prescription items for patients with EB, include:

- Atrauman Ag – wound-nonadherent dressing, absorbent, antimicrobial.[10]
- Urgotul Ag/Silver – dressing, highly-absorbent, hydrophilic gel-forming, antimicrobial.[11]
- Tegaderm CHG chlorhexidine gluconate dressing or gel pad.[12,13]
- Mepilex Transfer Ag – Dressing, wound-nonadherent, permeable, antimicrobial.[14]

[7] Harris AG, et al. (2016) The distribution of epidermolysis bullosa in Australia with a focus on rural and remote areas. *Australasian Journal of Dermatology doi: 10.1111/ajd.12431*

[8] National Epidermolysis Bullosa (EB) Dressing Scheme

[9] National EB Dressing Scheme: List of Approved Dressings - Product List

[10] Paul Hartmann Pty Ltd - Atrauman Ag - Wound-nonadherent dressing, absorbent, antimicrobial. (432293)

[11] Urgo Medical Australia Pty Ltd - Urgotul Ag - Dressing, highly-absorbent, hydrophilic gel-forming, antimicrobial. (394054)

[12] KCI Medical Australia Pty Ltd - 3M Tegaderm CHG Chlorhexidine Gluconate Dressing - Antimicrobial synthetic polymer semi-permeable film dressing, adhesive. (431070)

[13] KCI Medical Australia Pty Ltd – Tegaderm CHG Chlorhexidine Gluconate gel pad - Antimicrobial synthetic polymer semi-permeable film dressing, adhesive. (422430)

[14] Molnlycke Health Care Pty Ltd - Mepilex Transfer Ag - Dressing, wound-nonadherent, permeable, antimicrobial. (226604)

- Biatain Silicone Ag, - exudate-absorbent dressing, non-hydrophilic-gel-forming, antimicrobial.[15]

An international consensus statement on the appropriate use of silver dressings in wounds, based on limited studies of silver dressings in children including those with EB, recommends:

> S*ilver dressings should be used in the treatment of children with caution, and the dressings should not be used for more than two weeks without good clinical reasons.*[16]

Three amniotic membrane products are included in the ARTG as Class II biologicals, for the intended uses –

- as a wound covering, or barrier membrane over chronic and acute wounds, including dermal ulcers or defects,
- for treatment of acute and chronic wounds to enhance healing,
- for treatment of ophthalmic disorder/disease/trauma, or as a wound dressing,

While not specifically referring to wounds associated with EB, each of the registered products may be effective in their treatment. Notably, none of the available products claim cicatrizant properties.

Clinical rationale

The exact mechanism of action of Filsuvez in the treatment of wounds associated with EB is unknown.

In vitro cell culture assays with human primary keratinocytes and fibroblasts and ex vivo studies with porcine skin show that the birch bark dry extract, which includes the main component betulin, modulates inflammatory mediators and is associated with activation of intracellular pathways known to be involved in keratinocyte differentiation and migration, wound healing and closure.[17,18]

Regulatory status

Australian regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

Birch bark dry extract was designated as an orphan drug for the *'treatment of epidermolysis bullosa'* on 18 February 2025. While there is no evidence that birch bark extract may be effective in treating aspects of EB other than skin wounds, the orphan indication had been accepted in major international jurisdictions other than Australia.

[15] Coloplast Pty Ltd - Biatain Silicone Ag - Exudate-absorbent dressing, non-hydrophilic-gel-forming, antimicrobial. (311822)
[16] International consensus. *Appropriate use of silver dressings in wounds. An expert working group consensus*. London: Wounds International, 2012. 26953778fdfb53b9c87f7c6f05dd07eb.pdf
[17] Wölfle U, Laszczyk MN, Kraus M, et al. (2010) Triterpenes promote keratinocyte differentiation in vitro, ex vivo and in vivo: a role for the transient receptor potential canonical (subtype) 6. J Invest Dermatol, 130(1):113-123. https://www.jidonline.org/article/S0022-202X(15)34531-0/fulltext
[18] Ebeling S, Naumann K, Pollok S, Wardecki T, Vidal-y-Sy S, et al. (2014) From a Traditional Medicinal Plant to a Rational Drug: Understanding the Clinically Proven Wound Healing Efficacy of Birch Bark Extract. PLOS ONE 9(1): e86147. https://doi.org/10.1371/journal.pone.0086147

International regulatory status

This submission was submitted through the TGA's Comparable Overseas Regulator (COR–B - COR approach B) process, using evaluation reports from the Europeans Medicines Agency (EMA). The full dossier was submitted to the TGA. At the time the TGA considered this submission, similar submissions had been approved by comparable regulators (Table 1).

Table 1. International regulatory status at the time of approval.

Region	Submission date	Status	Approved indications
European Union	08-Mar-2021	Approved on 21 June 2022	*Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.*
United Kingdom	03-May 2022	Approved on 11 August 2022	*Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.*
USA	29-Jun-2020	Approved on 18 December 2023	*Treatment of wounds associated with dystrophic and junctional epidermolysis bullosa in adult and paediatric patients 6 months of age and older.*
Switzerland	14-Dec-2024	Approved on 25 July 2025	*Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older*

Registration timeline

The following table captures the key steps and dates for this submission.

The active ingredient with its proposed indication was given orphan drug designation.

Table 2. Timeline for Submission PM-2025-01059-1-1.

Description	Date
Designation (Orphan)	18 February 2025
Submission dossier accepted and first round evaluation commenced	30 April 2025
Evaluation completed (End of round 2)	28 April 2026
Registration decision (Outcome)	28 April 2026
Registration in the ARTG completed	5 May 2026
Number of working days from submission dossier acceptance to registration decision*	134

* The COR-B process has a 175 working day evaluation and decision timeframe.

Assessment overview

A summary of the TGA's assessment for this submission is provided below.

Quality evaluation summary

The application and the supporting data relating to the composition, development, manufacture, quality control, stability and bioavailability of the product were assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopeial standards and the technical guidelines adopted by the TGA. The evaluator reviewed the EMA assessment reports to identify where there are any Australian-specific considerations, or new issues, or where the TGA does not agree with the EMA assessment. There are no objections to registration of this product.

Filsuvez (birch bark dry extract 84-95% triterpenes) contains a plant-derived birch bark dry extract from the *Betula pendula* Roth, *Betula pubescens* Ehrh species, as well as hybrids of both species. The active component of the birch bark extract consists of naturally occurring substances known as triterpenes, including betulin, betulinic acid, erythrodiol, lupeol and oleanolic acid.

Filsuvez is formulated as a sterile, colourless to slightly yellowish, opalescent, non-aqueous gel. The only excipient in the product is sunflower oil. The proposed pack size is a 23.4 g tube that is provided in packs of 1, 10 and 30 tubes. Each tube is for single use only and should be stored below 30°C. It is recommended for immediate use after opening.

Filsuvez is a γ-irradiated sterile viscous, thixotropic, water-free preparation with a consistency resembling petrolatum jelly. In contrast to petrolatum jelly, Filsuvez gel does not soften at body temperature. The fact that the topical gel remains firm at body temperature is considered an advantage for the treatment of wounds.

The proposed maximum total wound area per application is 5,300 cm^2 with a medium total wound area of 735 cm^2. The approximate thickness to be applied to a wound dressing is 1 mm either to a wound dressing prior to application or directly to the wound surface itself. There is no suggested maximum treatment duration.

Nonclinical evaluation summary

There were no nonclinical objections to the registration of Filsuvez. The evaluator provided the following summary of findings:

- The overall quality of the Module 4 dossier is high, with no major deficiencies identified.
- The primary pharmacology studies lend some support for the drug's use in the proposed indication, but the exact mechanism of action could not be defined.
- No clinically relevant hazards were identified.
- The Sponsor proposes a Pregnancy Category B1, which is acceptable.
- There remains an outstanding local carcinogenicity concern associated with the long-term use of the product in EB patients. To support the risk assessment, a long-term carcinogenicity study in rodents is required. The Sponsor has proposed to conduct a two-

year dermal local carcinogenicity study in mice as a post-authorisation commitment,[19] considering the orphan nature of the disease and the unmet medical need. This approach is considered acceptable. This study should be submitted to the TGA for evaluation once available.

Recommendations for amendments to the product information were accepted by the sponsor.

Clinical evaluation summary

Summary of clinical studies

A Phase 3 clinical trial is the pivotal study for the proposed indication in EB, and a Phase 2 study provides supportive data in the target patient population. This is acceptable for an orphan disease.

BEB-13 (EASE)

A Phase 3 double-blind, randomised, vehicle-controlled study to evaluate efficacy, safety and betulin pharmacokinetics in adults and children ≥21 days of age with inherited EB (n=223) treated with the active gel versus control gel plus non-adhesive wound dressing, applied at dressing changes over 90 days.

BEB-13 OLP

An open label follow-on study to evaluate long-term efficacy and safety over 24 months in children and adults who previously participated in the EASE study (n=205). Several versions of the Clinical Study Report (CSR) for BEB-13 were included in the dossier. The sponsor stated that these were provided at the request from EMA for updates to the OLP study during the evaluation.

BEB-10

A Phase 2 prospective, open-label, intra-individually controlled, blindly evaluated study to evaluate efficacy and safety in children and adults aged 1-95 years (n=10) with inherited EB treated with active gel plus non-adhesive wound dressing versus non-adhesive wound dressing alone at dressing changes for 14 or 28 days.

Three additional Phase 3 studies (BSH-12, BSG-12 and BBW-11) in other non-EB partial-thickness wounds were presented as proof-of-concept studies. The applicant stated that these studies informed the pivotal study design and provide secondary supportive data for the studies in patients with EB. These three studies had previously been reviewed by the EMA for marketing authorisation of the same product, known as Episalvan, for treatment of partial thickness wounds.

[19] In response to an FDA requirement the European MAH Chiesi Farmaceutici initiated a 2-year dermal carcinogenicity study of Oleogel-S10 in CD-1 mice. The first dosing was initiated on the 15 October 2024. The in-life portion of the study is due for completion on the 13-27 October 2026 with the final approved report delivered in the second half (H2) of 2027. The study is being conducted by Charles River Laboratories (Spencerville, Ohio, USA) in accordance with the protocol provided under Special Protocol Assistance, SN0038 and reviewed on 7 December 2021 by the FDA.

BSH-12, BSG-12

Two multicentre Phase 3 prospective, randomised, open-label, intra-individually controlled, blindly evaluated studies to evaluate the pharmacokinetics (PK), efficacy and safety of Oleogel-10 over 28 days in adults ≥18 years with split-thickness skin graft (STSG) donor site wounds (BSH-12, n=107 and BSG-12, n=112)

BBW-11

A multicentre Phase 3 prospective, randomised, open-label, intra-individually controlled, blindly evaluated study to evaluate PK, efficacy and safety over 21 days in adults ≥18 years (n=66) with Grade 2a burn wounds.

A further two Phase 2 studies conducted in patients with STSG donor site wounds (BSH-10) and actinic keratoses lesions (BAK-08) were submitted to provide additional safety data.

Reports of post-marketing experience were included in module 5.3.6 as PSURs numbered 1 - 6, spanning the period from June 2022 to 14 Jan 2025.

Pharmacology

Clinical pharmacology studies as outlined above were supported by several *in vitro* pharmacology studies with betulin, the main component of the birch bark extract. These studies included a protein binding study, Caco-2 transporter study, an examination of the metabolic profile of betulin in hepatocytes, cytochrome P450 phenotyping of betulin using recombinant human CYP enzymes and by chemical enzyme inhibition in human hepatocytes, and as an inhibitor or as an inducer of a range of enzymes in human hepatocytes.

The Committee for Medicinal Products for Human Use (CHMP- EMA) assessment report[20] outlines the following:

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* [BSH-12, BSG-12 BBW-11]*, 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 (pre-dose) 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 (fu,p) could not be determined as betulin concentrations in buffer compartments were below LLOQ* [lower limit of quantification]*.*

[20] Committee for Medicinal Products for Human Use (CHMP) (2022) Filsuvez, common name-birch bark extract, Assessment Report - EMA/260035/2022. Pg 36-37, 45, 71.

This indicates that the fu,p of betulin is below 0.1% and fraction bound (fb,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 [of the product] *with hepatocytes... 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.*

Based on the CL_{int} values determined for the individual CYP [cytochrome P450] *isoforms using recombinant [rh] 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.

Additional information was provided in the discussion on clinical pharmacology, where the evaluator noted that evaluators of a marketing application for Episalvan had concluded that systemic absorption of betulin was minimal and no further studies on elimination, special populations or drug-drug interactions were required. This was acceptable to the primary evaluators of Filsuvez.

Pharmacokinetics

Pharmacokinetic (PK) samples were taken to measure betulin concentrations in the BEB-13 study in patients with EB. Owing to the fragile skin of the EB population, as well as the difficulty in taking venous blood draws from children and infants, a dried blood spot (DBS) analytical technique using capillary blood samples (finger or heel prick) was developed to measure whole blood concentrations of betulin. The bioanalysis method with dried blood spots was used both for capillary and venous blood samples.

Capillary samples were obtained by finger or heel stick, if consent was obtained, on Day 0, 7, 14, 30, 45, 60, 90 and at confirmation of complete closure of the target wound. The protocol was amended in Version 4.0 to also allow venous bloods collected on days 0 and 90 and at month 24 for analysis of safety haematology and biochemistry to be used for betulin assays on DBS. 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.

Betulin concentrations in baseline samples were in the range 0-122 ng/ml. The applicant stated that measurable levels could be the result of intake of food or natural substances containing betulin. A similar range of concentrations was reported in capillary and venous samples from control gel treated patients.

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 comparing venous and capillary blood betulin concentrations collected from the same patient/s suggest that capillary betulin concentrations may have been falsely elevated by contamination by topical betulin during collection, and that venous concentrations may be a more accurate representation of systemic exposure to betulin. The highest measured post-dose venous blood concentration of betulin was 207 ng/mL. The primary evaluation accepted this explanation.

No studies have been conducted with Oleogel-S10 in patients with renal or hepatic impairment. Betulin concentration did not correlate with BMI or age. 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.

Pharmacodynamics

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 that supported beneficial effects of triterpenes on wound healing in general were included in the dossier. Based predominantly on three of these, the applicant argued that birch bark extract supports 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.[21,22,23] KRT 10 expression induced by birch bark extract depends on up-regulation and indirect activation of TRPC6 by high extracellular Ca^{2+} concentrations. Birch bark extract is also proposed to influence the cytoskeleton possibly by induction of filopodia and lamellipodia, mediated by activation of the Rho GTPase RhoA (Ras homolog gene family, member A).

With respect to pharmacodynamic interactions, the product is locally applied and locally acting. Systemic drug-drug interactions are not expected.

The Committee for Medicinal Products for Human Use (CHMP- EMA) states:

> *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.* [20]

Efficacy

Study BEB-13 (EASE)

The single pivotal study for efficacy was Study BEB-13 (EASE), a double-blind, randomised, vehicle-controlled, phase III, efficacy and safety study with 24-month open-label follow-up of

[21] Wölfle U, Laszczyk MN, Kraus M, et al. Triterpenes promote keratinocyte differentiation in vitro, ex vivo and in vivo: a role for the transient receptor potential canonical (subtype) 6. *J Invest Dermatol*. 2010;130(1):113-123 https://doi.org/10.1038/jid.2009.248

[22] Ebeling S, Naumann K, Pollok S, et al. From a traditional medicinal plant to a rational drug: understanding the clinically proven wound healing efficacy of birch bark extract. *PLoS One*. 2014;9(1):e86147 https://doi.org/10.1371/journal.pone.0086147

[23] Wardecki T, Werner P, Thomas M, et al. Influence of Birch Bark Triterpenes on Keratinocytes and Fibroblasts from Diabetic and Nondiabetic Donors. *J Nat Prod*. 2016; 79(4):1112-1123. https://doi.org/10.1021/acs.jnatprod.6b00027

Oleogel-S10 (birch triterpenes, also known as birch bark extract)[24] in subjects with inherited Epidermolysis Bullosa (EB).

This was a multicentre study in two parts with 49 study sites in Australia and internationally.[24,25] The first part was a randomised, controlled, 90-day double-blind phase (DBP) 3 study, and the second part a 24-month open-label follow-up of Oleogel-S10 in children and adults with inherited EB. Each participant was randomly allocated to 90 days treatment with Oleogel-S10 or comparator in the DBP. First patient, first visit was 19 April 2017, last patient last visit in the DBP was 3 June 2020.

At the end of the DBP (Day 90), participants 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 protocol was subject to five changes before completion of the study. Version 6.0 was released 18 April 2019.

Inclusion criteria

- Males and females aged ≥4 years with DEB, JEB, and Kindler syndrome subtypes of EB.
- The presence outside of the anogenital region of an EB partial-thickness wound of 10 cm^2 to 50 cm^2 in size, having persisted for ≥21 days and <9 months (the EB target wound). The specification for the target wound to have persisted <9 months was introduced in Protocol Version 4.0. The specification for the target wound to be outside the anogenital region was clarified in Protocol Version 6.0.
- Children ≥21 days old and <4 years could be included, but only after confirmation by an independent drug monitoring committee (IDMC) after review of the safety and bioanalytical (betulin) data at an interim safety review.

Exclusion criteria

- EB subtype EBS: Two patients with the EBS subtype were removed from the analysis following a change in the eligibility criteria 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 seven days prior to enrolment.
- Administration of systemic or topical steroids for skin wounds within 30 days before enrolment (topical applications for oesophageal strictures, such as budesonide suspension, and inhaled or ophthalmic preparations were permitted).
- Immunosuppressive therapy or cytotoxic chemotherapy within 60 days prior to enrolment.
- Stem cell transplant or gene therapy for the treatment of inherited EB.

[24] Kern, J.S., Sprecher, E., Fernandez, M.F., Schauer, F., Bodemer, C., Cunningham, T., Löwe, S., Davis, C., Sumeray, M., Bruckner, A.L., Murrell, F.F. for the EASE investigators. (2023) Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: results from the phase III randomized double-blind phase of the EASE study, *British Journal of Dermatology*, Volume 188, Issue 1, Pages 12–21, https://doi.org/10.1093/bjd/ljac001

[25] EASE Study BEB-13 CLINICAL STUDY REPORT (Double-Blind Phase and Interim Open-Label Data) VERSION 1.0, Date of report 9 Feb 2021

- Current and/or former malignancy including basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs).
- Enrolment in another investigational clinical study or treatment with any investigational drug for any disease within four weeks prior to study entry.
- Factors present in the patient and/or his/her legal representative that could interfere with study compliance such as inability to attend scheduled study visits or to comply with home dressing changes.
- Pregnant or nursing women.
- Women of childbearing potential including post-menarchal female adolescents, and men 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 (reference to men added in Protocol Version 4.0).
- Member of the investigational team or his/her immediate family.

Procedure and outcomes

On Day 0, the investigator selected the EB target wound and up to four additional wounds that met target wound criteria. The EB partial-thickness target wound and all areas on a person'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 (matching Oleogel-S10 in texture and visual appearance, the control gel consisted of 85 g sunflower oil, 5 g Cera flava/yellow wax, and 10 g Carnauba wax per 100 g of product) 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 the DBP. The participants were 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. If a wound was closed, it was not necessary to continue to apply study medication. The participant could use a wound dressing on the closed wound to protect the area, if desired. Areas on the 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.

The primary endpoint of the DBP was the proportion of study participants with first complete closure of the EB target wound within 45±7 days of treatment.[20] 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.

The key secondary endpoints included time to first complete closure of the EB target wound (within 90±7 days of treatment); proportion of participants 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 and Day 90±7; the change from baseline in total body wound burden as evidenced by clinical assessment (using Section I of the 'EB Disease Activity and Scarring Index', EBDASI[26]) at Day 90±7; the change from baseline in itching before wound dressing changes at Day 90±7 using the 'Itch Man Scale' in participants ≥4 years and up to 13 years of age and the 'Leuven Itch Scale' in participants ≥14 years of age. Safety endpoints included adverse event (AE) and serious adverse event (SAE)

[26] EBDASI Section 1 (Skin Activity) scores evidence of blistering, erosions and crusting in 10 anatomical locations, excluding anogenital regions and buttocks for the purposes of this study. The maximum possible score of the partial EBDASI based on skin activity is 100 (10 points in each of the ten locations).

reporting; assessment of tolerance and betulin exposure levels. Several additional endpoints are not discussed in this overview.

A total of 192 participants were planned to be enrolled into the study and treated to account for an estimated dropout rate of 5%. Following the unblinded interim analysis of efficacy for 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 enrolees. Enrolment ceased 06 March 2020, at which time 223 participants were enrolled.

The primary efficacy endpoint, defined as the proportion of participants with first complete closure of the EB target wound within 45 days based on clinical assessment by the investigator, was first compared between treatment groups using the Cochran-Mantel-Haenszel (CMH) test, stratified by EB subtype and target wound size. 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. The overall level of significance for the primary endpoint analysis was 0.05 (2-sided). If the primary analysis of the primary efficacy endpoint demonstrated superiority at the 5% significance level, hierarchical confirmatory testing of the six key secondary endpoints was to be performed.

Results

A total of 223 study participants (109, Oleogel-S10; 114, control gel) were randomized and received at least one dose of study medication (Safety Analysis Set, SAS); 223 were also included in the Full Analysis Set (FAS), 185 were in the Per-protocol Set (PPS) (92, Oleogel-S10; 93, control gel), and 199 who completed the DBP were included in a Completer Analysis Set (CAS) (100, Oleogel-S10; 99, control gel). A total of 205 (91.9%) study participants continued into the OLP.

The most common protocol violations were non-compliance with the recommended treatment regime, including use of prohibited concomitant treatments or dressings, dressing changes >4 days apart, not applying the medication to all wounds or incorrect administration. While common, these violations are likely to reflect real world use and occurred at comparable frequency in both treatment groups.

The overall median age of study participants was 12 years (range: 6 months to 81 years); 134 (60.1%) were male and 89 (39.9%) were female. Most (83.4%) were white. A total of 195 (87.4%) participants had the EB subtype DEB: of these, 175 (78.5%) had RDEB and 20 (9.0%) had DDEB. Twenty-six (11.7%) had JEB, and two (0.9%) subjects had EBS. Following implementation of Version 4.0 of the protocol, the two patients with EBS were excluded from the analysis. No participant had Kindler syndrome. The demographics and baseline characteristics of study participants were generally well balanced between the two treatment groups. However, within the DEB subtype, the Oleogel-S10 group had a higher proportion of participants with RDEB (83.5%) compared to the control gel group (73.7%) and a lower proportion of subjects with DDEB (5.5%, Oleogel-S10 vs. 12.3%, control gel). Further, the median wound age was slightly greater in the Oleogel-S10 group (39 days) vs. 32 days in the control gel group.

Table 3 summarises the EB target wounds in the safety analysis set.

Table 3. BEB-13 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 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 participants (n=8, Oleogel-S10 vs. n=6, control gel) with wounds persisting longer than 9 months (range: 11.5 to 156 months) were enrolled prior to the implementation of Version 4.0. In the subset of participants 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%). A total of 63 participants had at least one additional wound that met target wound criteria. Most of these had no more than two additional wounds that met the criteria. A higher proportion of participants in the control gel group had two or more additional wounds (13/30, 43.3%) compared to the Oleogel-S10 group (8/33, 24.2%). Most participants changed their dressings daily (44.4%) or every 2 days (37.7%). Most participants (91%) used the same type of dressing for all wounds (*i.e.*, target, additional, and other).

Over 90% of participants in both treatment groups were considered to have a mild total wound burden based on EBDASI skin activity scores, with no reported severe burden, owing to the use of the partial EBDASI scale rather than the complete scale.

The primary efficacy endpoint in the DBP was met. The proportion of study participants reporting 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). Participants

in the Oleogel-S10 group were 44% more likely to achieve the first complete closure of the EB target wound within 45 days of treatment compared to those in the control gel group.

Similar results for the primary efficacy analysis were seen when the CAS or PPS were evaluated, with statistically significant results for the CAS (p= 0.034) but not the PPS.

Most sensitivity analyses did not achieve statistical significance although the results directionally supported the results of the primary efficacy analysis.

The Committee for Medicinal Products for Human Use (CHMP- EMA) evaluators made the following comments:

> *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 … 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.*[20]

This major objection was resolved with a *verbal explanation* and CHMP review of several alternative sensitivity analyses to support the primary conclusion.[27]

The results for the first key secondary endpoint were not statistically significant. 50.5% of participants in the Oleogel-S10 group achieved first EB target wound closure by 90±7 days compared to 43.9% of participants in the control gel group (p= 0.296). Under hierarchical testing strategies, results for the other secondary endpoints were subsequently not tested for statistical significance and are only presented here using descriptive statistics.

The median time to closure within 90 days was similar between the two treatment groups (92 days Oleogel-S10 and 94 days control gel). Participants with the RDEB subtype who were treated with Oleogel-S10 had a faster median time to closure of the EB target wound than subjects with RDEB who were treated with control gel (64 days vs 94 days, respectively).

Regarding wound infection adverse events (AEs) and/or use of topical and/or systemic antibiotics two participants (1.8%) treated with Oleogel-S10 and five participants (4.4%) in the control group were reported to have experienced a target wound infection between baseline and Day 90. It was later identified that in one participant in the Oleogel-S10 group the infection occurred in a non-target wound. Wound infections in the treatment group were reported to be less severe than in the control group.

The mean EBDASI skin activity score at baseline was 19.6 (SD: 11.91). Small mean decreases (reflecting improvement) were reported in the Oleogel-S10 treatment group at Day 30, 60, or 90 (Day 30: -0.64, Day 60: -1.08, Day 90: -0.44); there were arguably comparable improvements in the control group at Day 30 and Day 90, but not at Day 60 (Day 30: -0.59, Day 60: +0.09, Day 90: -0.56).

Using the Itch Man Scale, children aged 4 to 13 years in both treatment groups recorded small mean improvements in itching from baseline at 90 days (-0.44 Oleogel-S10 group vs -1.0 control gel group). Using multiple domains of the Leuven Itch Scale, older participants in the Oleogel-S10 group reported 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

[27] Committee for Medicinal Products for Human Use (CHMP) (2022) Filsuvez, common name-birch bark extract, Assessment Report - EMA/260035/2022. Pg 115, 117 - 118.

control gel), and surface areas affected by itch (-1.54 Oleogel-S10 vs +0.68 control gel) at Day 90, while participants in the control gel group recorded greater mean reductions from baseline in the frequency (-8.13 Oleogel-S10 vs. -10.14 control gel) and severity of itch (-4.95 Oleogel-S10 vs. -10.76 control gel) at Day 90.
Post hoc analysis demonstrating a significant reduction in size of the target EB wound from a mean of 16.68 cm^2 at baseline to 7.72 cm^2 by Day 45 (-8.96 cm^2) for Oleogel-S10, compared to a reduction from 17.44 cm^2 at baseline to 10.51 cm^2 by Day 45 (-6.93 cm^2) for the control gel arm was not considered meaningful by the evaluators.

Supportive studies

Study BEB-10

Study BEB-10 was a Phase 2 open-label, prospective, blindly evaluated controlled case series in 10 children and adults that compared the efficacy and tolerance of Oleogel-S10 (named Sericare in this study) versus non-adhesive wound dressing alone in accelerating the epithelialisation of skin lesions in patients with inherited EB. Male or female with at least one skin lesion between 10 cm^2 and 200 cm^2 or two comparable skin lesions of at least 5 cm^2 each were enrolled in the study.

The study was conducted at a single centre in Germany, between 3 November 2010 and 14 June 2011. Nine patients diagnosed with RDEB and one patient with DDEB were included. Study participants ranged from six years to 48 years of age, seven were male, three were female, and five participants were younger than 18 years old.

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

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, or progress of re-epithelialisation from baseline to D14 or D28 of two comparable lesions of at least 5 cm^2 (one treated with Oleogel-S10 and dressing, the other just dressing). 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 recorded.

Wound dressings were to be changed 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'[28]. The participant or carer for the participant took photographs of the respective wounds before the start of the treatment and at each wound dressing change. Two independent experts conducted blinded assessment of efficacy based on the chronological series of photographs. Where expert assessments agreed, these were noted as 'decided cases' in favour of Oleogel-S10 or no treatment or equal effect, where the assessments disagreed these were noted as 'undecided cases'.

The assessments agreed that Oleogel-S10 + non-adhesive wound dressing significantly accelerated the re-epithelialisation (8 of 8 decided cases; p=0.0078, binomial test) of wounds in

[28] These descriptions were not defined in the study report or the evaluation and given the nature of the study are unlikely to be of significance. No further clarification requested.

inherited EB compared to non-adhesive wound dressing only (0 of 8 decided cases). Both efficacy assessment experts were in full agreement in seven cases, of which five cases were scored in favour of Oleogel-S10 + non-adhesive wound dressing, two cases were scored as equal, and none was scored in favour of non-adhesive wound dressing only.

Studies in partial thickness wounds other than those associated with EB

Three studies in adult patients with partial thickness wounds at split-thickness skin graft (STSG) donor sites (BSH-12 and BSG-12) or with Grade 2A burns (BBW-11) which had previously been reviewed by the EMA for marketing authorisation of the same product, known as Episalvan, were provided as supportive evidence of efficacy in partial thickness wounds. In these studies, investigators and study participants completed a questionnaire at the end of the treatment phase to provide a global assessment of efficacy.

Oleogel-S10 was assessed as more effective or much more effective than control for most participants by both investigator and patient assessments. An overview of efficacy results in the 'intention to treat' populations of each study is provided in Table 4.

Table 4. BSH-12, BSG-12, BBW-11 Overview of efficacy results (ITT populations).

		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)				
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
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

The applicant also provided reports of two additional small studies that were intended to confirm that the control gel in study BEB-13 was not likely to have a detrimental effect on healing. This was required as a control gel consisting only of the vehicle for the triterpenes (sunflower oil) would appear and feel different from the active containing product. The EMA evaluators acknowledged that these two studies and a literature review did not suggest an obvious harmful effect of the control gel but concluded that some degree of uncertainly exists.

After evaluating the submitted data, and accepting additional arguments from the applicant and additional testimonies from the EB patient community and experts in the field (an *ad hoc* expert group, AHEG), the CHMP concluded that,

> *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.*[27]

Furthermore, with reference to the Ad-hoc Expert Advice Group (AHEG) and patient representatives, CHMP also stated

> *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.*[27]

Safety

Overall exposure

At the time of submission of the application to the primary evaluator, a total of 754 children or adults had been treated with Oleogel-10 birch bark triterpenes in clinical trials for skin damage

including EB, STSG donor sites, Grade 2a burns, atopic dermatitis, actinic keratosis and psoriasis (Table 5).

Table 5. Cumulative exposure to birch bark dry extract during clinical development.

	Grade 2a Burns	STSG Donor Sites			AD	Psoriasis	Actinic Keratosis			Epidermolysis Bullosa		Total
	BBW-11	BSH-12	BSG-12	BSH-10 BfArM 4035991	BfArM 4017557	BfArM 4017785	Pilot study	BfArM 4030185	BfArM 4034406	BEB-10 BfArM 4036466	BEB-13	
Oleogel-S10/TE	61	107	112	24	33	24	28	30	111	10	214[d]	754
Control gel/ placebo	-	-	-	-	33	24	-	-	54	-	9	120
Comparator	61	107	112	24	-	24	14	30	-	10	-	382
Total[e]	61[a]	107[a]	112[a]	24[a]	33[a]	24[a]	28[b]	45[c]	165	10[a]	223	832[a]

Abbreviations: AD, Atopic dermatitis; BfArM, Bundesinstitut für Arzneimittel und Medizinprodukte (German Federal Institute for Drugs and Medical Devices); DLP, data lock point; TE, triterpene dry extract from birch bark; STSG, Split-thickness skin graft.

a. The total accounts for the intra-individual studies in which subjects served as their own controls; subjects are not counted twice.

b. Patients received Oleogel-S10/TE either with or without comparator

c. Three treatment groups: Oleogel-S10, cryotherapy, and Oleogel-S10 and cryotherapy. Fifteen patients received either Oleogel-S10 or cryotherapy and 15 patients received both Oleogel-S10 and cryotherapy.

d. Patients were randomized to Oleogel-S10 or control gel for the double-blind phase (109 received Oleogel-S10 and 114 received control gel). 205 of these patients (100 former Oleogel-S10, 105 former control gel) entered the open-label phase after the 90-day double-blind phase and all received Oleogel-S10 treatment.

e. Of the patients included in all clinical studies of Oleogel-S10/TE, 78 subjects received only control gel, placebo, or comparator (15 patients in study 4030185, 54 patients in study 4034406, and 9 patients in BEB-13)

A summary of overall exposure in the pivotal study BEB-13 DBP is provided in Table 6 and in the OLP in Table 7.

Table 6. BEB-13 Extent of exposure (DBP, SAS).

		Oleogel-S10 N=109 n (%)	Control Gel N=114 n (%)	All Subjects N=223 n (%)
Treatment duration [days][a]	n	109	114	223
	Mean (SD)	89.0 (18.34)	86.8 (23.64)	87.9 (21.20)
	Min	2	2	2
	Median	91.0	91.0	91.0
	Max	140	161	161
Total duration of interruptions overall [days][b]	n	109	114	223
	Mean (SD)	0.0 (0.19)	0.4 (2.97)	0.2 (2.13)
	Min	0	0	0
	Median	0.0	0.0	0.0
	Max	2	23	23
Total duration of interruptions due to AEs [days] [b,c]	n	109	114	223
	Mean (SD)	0.0 (0.0)	0.4 (2.97)	0.2 (2.13)
	Min	0	0	0
	Median	0.0	0.0	0.0
	Max	0	23	23
Actual treatment duration overall [days] [b,d]	n	109	114	223
	Mean (SD)	89.0 (18.43)	86.4 (23.88)	87.7 (21.38)
	Min	0	0	0
	Median	91.0	91.0	91.0
	Max	140	161	161

[a] Treatment duration [days] = Treatment end date - Treatment start date +1. Treatment duration >90 days was caused by prolonged treatment due to late visits or other external factors.

[b] Only the interruptions on the target wound were considered in the calculations. If the reason for dose interruption is recorded as "wound closure" in the eCRF, this was not considered for the calculation of interruption duration.

[c] Duration of interruptions due to AEs, treatment duration in relation to AEs, and treatment compliance in relation to AEs were derived considering only "reasons for dose interruption" due to AEs as recorded in the eCRF.

[d] Actual treatment duration overall [days] = Treatment duration [days] - Total duration of interruptions overall [days].

Table 7. BEB-13 Extent of exposure (OLP, SAS).

		Former OleogelS10 N=100 n (%)	Former Control Gel N=105 n (%)	All Subjects N=205 n (%)
Treatment duration [days][a]	n	100	105	205
	Mean (SD)	594.4 (235.34)	575.4 (256.76)	584.7 (246.13)
	Min	14	7	7
	Median	725.0	727.0	727.0
	Max	841	840	841
Total duration of interruptions overall [days][b]	n	100	105	205
	Mean (SD)	1.4 (6.84)	3.9 (16.26)	2.7 (12.61)
	Min	0	0	0
	Median	0.0	0.0	0.0
	Max	41	122	122
Total duration of interruptions due to AEs [days][b,c]	n	100	105	205
	Mean (SD)	0.4 (3.70)	1.4 (7.67)	0.9 (6.07)
	Min	0	0	0
	Median	0.0	0.0	0.0
	Max	37	57	57
Actual treatment duration overall [days][b,d]	n	100	105	205
	Mean (SD)	593.0 (236.32)	571.5 (258.31)	582.0 (247.45)
	Min	14	7	7
	Median	723.0	726.0	725.0
	Max	841	840	841

a Treatment duration [days] = Treatment end date - Treatment start date +1. Treatment duration >90 days was caused by prolonged treatment due to late visits or other external factors.

b Only the interruptions on the target wound were considered in the calculations. If the reason for dose interruption is recorded as "wound closure" in the eCRF, this was not considered for the calculation of interruption duration.

c Duration of interruptions due to AEs, treatment duration in relation to AEs, and treatment compliance in relation to AEs were derived considering only "reasons for dose interruption" due to AEs as recorded in the eCRF.

d Actual treatment duration overall [days] = Treatment duration [days] - Total duration of interruptions overall [days].

Detailed descriptions and analyses of adverse events associated with birch bark triterpenes included in this overview are restricted to the EB studies, particularly BEB-13. Pooled analyses were not considered appropriate owing to the distinctly different study designs of BEB-13 and BEB-10. The primary evaluator considered the safety reports from BEB-10 in EB patients and additional studies with Episalvan gel in BSG-12, BSH-12 and BBW-11 supportive only, noting that the approval of Episalvan gel was based on short-term treatment.

BEB-13 Double-Blind Phase

In the BEB-13 DBP the overall frequency of adverse events (AE) was similar in the Oleogel-S10 group (89/109 participants, 81.7%, 282 reports) and in the control gel group (92/114 participants, 80.7%, 277 reports, Table 8). There were no deaths during the DBP.

Table 8. BEB-13 Overall summary of adverse events (DBP, SAS).

	Oleogel-S10 N=109 n (%) E	Control Gel N=114 n (%) E	All Subjects N=223 n (%) E
Any AEs	89 (81.7) 282	92 (80.7) 277	181 (81.2) 559
Any serious AEs	7 (6.4) 10	5 (4.4) 7	12 (5.4) 17
Any severe AEs	13 (11.9) 19	6 (5.3) 7	19 (8.5) 26
Any related AEs	27 (24.8) 50	26 (22.8) 49	53 (23.8) 99
Any serious related AEs	1 (0.9) 1	0	1 (0.4) 1
Any AEs leading to study withdrawal	3 (2.8) 4	2 (1.8) 2	5 (2.2) 6
Any serious AEs leading to study withdrawal	2 (1.8) 3	0	2 (0.9) 3
Any related AEs leading to study withdrawal	2 (1.8) 2	0	2 (0.9) 2
Any serious related AEs leading to study withdrawal	1 (0.9) 1	0	1 (0.4) 1
Any serious AEs leading to death	0	0	0
Any AEs due to wound complications[a]	67 (61.5) 100	61 (53.5) 88	128 (57.4) 188
Any AEs leading to drug withdrawal	3 (2.8) 4	4 (3.5) 4	7 (3.1) 8

Abbreviations: AE=adverse event; E=number of events; LLT=lower-level term; N=number of subjects in specific group; n=number of subjects; PT=preferred term.

[a] Refers to any AEs with PT or LLT of "wound complication." Note there are other AEs involving wounds (e.g., wound hemorrhage, wound secretion) but with a different PT/LLT and are thus not included in this table. Wound

Note: Calculation of percentages is based on N.

While there was some variability in reports of AEs between age groups, these were not substantially different between treatment arms in each age group (Table 9).

Table 9. BEB-13 Treatment-emergent adverse events by age group (DBP, SAS).

Study Phase = Double-blind
Age group = 0 - <4 years

System Organ Class Preferred Term	Oleogel-S10 (N=7) n (%) E	Control Gel (N=10) n (%) E	All Patients (N=17) n (%) E
Any treatment emergent adverse event	6 (85.7) 18	7 (70.0) 11	13 (76.5) 29

Age group = 4 - <12 years

System Organ Class Preferred Term	Oleogel-S10 (N=42) n (%) E	Control Gel (N=43) n (%) E	All Patients (N=85) n (%) E
Any treatment emergent adverse event	34 (81.0) 113	35 (81.4) 136	69 (81.2) 249

Age group = 12 - <18 years

System Organ Class Preferred Term	Oleogel-S10 (N=25) n (%) E	Control Gel (N=29) n (%) E	All Patients (N=54) n (%) E
Any treatment emergent adverse event	22 (88.0) 76	25 (86.2) 76	47 (87.0) 152

Age group = >= 18 years

System Organ Class Preferred Term	Oleogel-S10 (N=35) n (%) E	Control Gel (N=32) n (%) E	All Patients (N=67) n (%) E
Any treatment emergent adverse event	27 (77.1) 75	25 (78.1) 54	52 (77.6) 129

Seven participants (6.4%, 10 reports) in the Oleogel-S10 group, including five children or adolescents (aged 4 to <18), and five participants (4.4%, seven reports) in the control gel group, including three children or adolescents, had serious AEs (SAEs). The serious treatment emergent (TE)AEs in the Oleogel-10 group included three reports of anaemia in children/adolescents, not considered treatment-related. In addition, one report each of wound haemorrhage (adolescent participant), squamous cell carcinoma (SCC) of the skin (adult participant), sepsis and bacterial wound infection (in adolescents), device-related infection (adult), pneumonia and haematuria (in children 4 to <12 years) were recorded in this group. The SAE of wound haemorrhage in the adolescent treated with Oleogel-10 was considered related to the study medication and resulted in withdrawal from the study. The serious TEAE reported in the control gel group included two reports of sepsis (one adult, one adolescent) and one report each of bacterial wound infection (one adult), erysipelas (adult), upper respiratory tract infection (adolescent), wound infection and increased GGT (in children 4 - <12 years). Adverse events leading to study withdrawal included procedural pain, wound haemorrhage and SCC in the Oleogel-S10 group (one each) and pregnancy and allergic dermatitis in the control gel group (one each).

The most frequently reported AEs in the Oleogel-S10 group and in the control gel group, 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%). The most frequently reported treatment-related AE was wound complication, which was similar in incidence between the two treatment groups (13.8% in the Oleogel-S10 group and 14.9% in the control gel group).

Most AEs (around 70%) in both treatment groups were of mild or moderate severity. Severe AEs were reported for 13 participants (11.9%, 19 reports including one life-threatening) in the Oleogel-S10 group. These included seven reports of anaemia in five participants, two reports of pruritus in two participants and single reports of bacterial wound infection, sepsis, eye infection, pneumonia, procedural pain, wound haemorrhage, dysphagia, ulcerative keratitis, administration site dysaesthesia and SCC. In the control gel group seven reports of severe TEAE in six participants (5.3%) included two reports of bacterial wound infection in two participants, and single reports of sepsis, erysipelas, upper respiratory tract infection, wound infection and oesophageal spasm. Six reports in five study participants overall were considered certainly treatment related, whereas 93 reports in 48 participants had treatment-emergent AE that were considered probably or possibly treatment-related.

BEB-13 Open-Label Phase

In the OLP of BEB-13, Oleogel-S10 was administered to all study participants. All areas on the body affected by EB partial-thickness wounds were treated. 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. The safety objectives were to evaluate the safety of Filsuvez based on the incidence, severity and relatedness of adverse events (AEs) and laboratory assessments. An evaluation of the clinical safety aspects of the BEB-13 OLP up to 1 July 2022 (database lock) was provided in an EMA Type II variation assessment report.[29]

At database lock, the median duration of Filsuvez treatment for all patients in the DBP and OLP was 733 days and the maximum duration of treatment was 931 days. In total, 141 study participants (68.8%) had completed the OLP, and 64 participants (31.2%) had discontinued the OLP prior to Month 24. Among the discontinuations, 33 were reported as 'withdrawal of consent', 16 were reported for adverse events (including nine deaths), and 11 were for 'other

[29] EMA/4657/2024, dated 14 December 2023 https://www.ema.europa.eu/en/documents/variation-report/filsuvez-h-c-005035-ii-0006-epar-assessment-report-variation_en.pdf

reasons' including lack of efficacy, desire to participate in another study, or loss to follow-up. The nine deaths were considered consistent with the course of the disease and none of the deaths were considered related to study treatment.

During the OLP 158 (77.1%) participants reported at least one AE. The most frequently reported AEs (≥5% of all participants) were wound complication (41.0%, wound complications considered treatment-related 6.8%), anaemia (18.0%), wound infection (10.2%), wound infection staphylococcal (10.2%), pyrexia (9.8%), oesophageal stenosis (9.3%), wound infection bacterial (7.8%), pruritus (6.8%), and dysphagia (6.3%). These conditions were all considered consistent with the course of the disease. Adverse events leading to study withdrawal reported for more than one participant each were SCC (2), pneumonia (2 deaths), and staphylococcal wound infection (2 deaths). The other patient deaths were separately associated with disease progression, heart failure, intestinal ischaemia, sepsis (not related to wound treatment) and acute kidney injury. Administration site pain, staphylococcal infection and rash SAE were considered associated with treatment.

Adverse events of special interest

Adverse events of interest were identified based on a review of the DBP and OLP safety data in addition to a Standardized MedDRA Query (SMQ) analysis. AEs selected for further evaluation were hypersensitivity (primarily rash), squamous cell carcinoma of the skin (SCC), haemorrhage and anaemia.

Twelve subjects exposed to Oleogel-S10 in the DBP or OLP reported 16 AEs that coded to the Hypersensitivity SMQ. Two separate events of rash and anaphylactic reaction were considered grade 3 severity, the remaining were considered grade 1 or grade 2. One event of rash was considered serious and resulted in discontinuation.

Four subjects with RDEB were diagnosed with SCC while on study; all were adult subjects (20-49 years) with generalized severe (3) or generalized intermediate (1) RDEB. Two SCC lesions had not been treated with Oleogel-S10 and were not considered related to study medication. The other 2 cases of SCC, which occurred in adults 46 and 49 years of age, had Oleogel-S10 applied to the area prior to the SCC diagnosis. Three of the four participants who developed SCC discontinued the study.

Twenty-three AEs in 15 participants exposed to Oleogel-S10 were coded to terms included in the haemorrhage terms SMQ. These events included five events of epistaxis (in 3 participants); three events of rectal haemorrhage (3); three events of haematuria (2); three events of wound haemorrhage (2); two events of hematemesis (2); two events of haematochezia (2); and one event respectively of blood urine present, gastrointestinal haemorrhage, blood loss anaemia, hemoperitoneum and heavy menstrual bleeding. All but four of these events were grade 1 or grade 2 in severity; one event of wound haemorrhage and the hemoperitoneum were classified grade 3, and the events of blood loss anaemia and gastrointestinal haemorrhage were classified grade 4.

Analysis of anaemia-related AEs recorded 70 reports with anaemia-related preferred terms (PTs: including anaemia, iron deficiency anaemia, Coombs positive haemolytic anaemia) in 45 participants exposed to Oleogel- S10 during the DBP or the OLP. These included 64 events of anaemia in 42 participants, four events of iron deficiency anaemia in three participants, and one report each of blood loss anaemia and of Coombs positive haemolytic anaemia (this participant also experienced several separate recorded events of anaemia). All anaemia related AEs were considered unlikely related to the study medication. This is accepted in view of the known association of EB with anaemia.

In the OLP, target wound infections occurred in very few study participants, with only seven reports of infection of the target wound. The maximum severity of target wound infections

occurring in the OLP (between OLP Day 0 and Month 24) was mild (n= 2) and severe (n= 2) in the former Oleogel-S10 subjects, and moderate in former control gel subjects (n=3). The incidence and severity of additional and other wound infections were very similar between the DBP and OLP through Month 24.

The primary evaluators concluded:

> *The additional data provided from the finalised OLP does not change* [the conclusion that Filsuvez is a locally applied and locally acting with limited systemic absorption]. *Betulin systemic exposure was low, similar to concentrations observed following ingestion of betulin-containing foods, the majority of samples were below the lower limit of quantification, and thus, are unlikely to result in systemic AEs.*

Further,

> *The number of patients that discontinued from the OLP and the reasons for discontinuations were similar at the end of the OLP compared to interim data up to 21 April 2021. In total 64 patients discontinued the OLP (31%), which is considered reasonable in a 24-months follow-up study in a severe disease.*
>
> *In comparison to the safety data from the OLP at the time of approval of Filsuvez (up to 21 April 2021), it is agreed that there was no apparent change in the patterns of reported AEs as of the final database lock of 01 July 2022.*

Post-market experience

The applicant provided the following cumulative information in its 6th periodic safety update report (PSUR) for birch bark extract, dated 18 March 2025.

> *From the development international birth date (DIBD) of 22 March 2001 up to the end of the reporting period there was an estimated cumulative exposure of 754 clinical trial subjects to the treatment with Oleogel-S10. In addition, 78 patients were exposed to control gel, placebo, or a comparator only.*
>
> *As of the* [data lock point] *DLP for this PSUR, cumulative commercial patient exposure is estimated to be 225.8 patient years for the cumulative period (14 January 2016 to 14 January 2025). Additionally, patient exposure for patients who are supplied product through an expanded access program (e.g., free of charge supply) is based on absolute patient numbers. Cumulatively there have been 180 patients exposed to birch bark extract through Compassionate use/Expanded access programs in the EMEA, UK, USA and ROW* (rest of world).

There have been few reports of adverse events, which align with the safety information identified in the clinical studies. New safety signals have not been identified.

Other (e.g. companion diagnostic considerations, drug delivery device)

Real world evidence/real world data arising from post-approval safety reports were provided in the submission and did not affect the benefit-risk safety profile.

Risk management plan

Chiesi Australia Pty Ltd has submitted EU-RMP version 2.1 (date 14 June 2023; DLP 14 January 2023) and ASA version 1.0 (date 21 March 2025) in support of this application. With the s31 responses the sponsor provided EU RMP version 2.3 (date 14 June 2023; DLP 14 January 2023) and ASA version 1.1 (date 27 October 2025).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 10. The TGA may request an updated RMP at any stage of a product's life cycle, during both the pre-approval and post-approval phases.

Table 10. Summary of safety concerns.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–
Important potential risks	Squamous cell carcinoma and other skin malignancies	✓*	✓†	✓	–
Missing information	Use in patients of different race/ethnicity	✓	✓†	–	–

*Follow-up questionnaire
†Observational Safety Registry-based study (FOSteR)– in Europe

Subject to the evaluation of the nonclinical and clinical aspects of the safety specifications, the summary of safety concerns is acceptable from an RMP perspective.

The pharmacovigilance plan is acceptable from an RMP perspective. Although Australian patients are not included in the patient registry, the outcomes of this activity will be applicable in the Australian context.

Only routine risk minimisation activities are proposed. This approach is the same as that implemented in the EU. Routine risk minimisation measures are considered acceptable to manage the risks associated with this product.

RMP evaluator recommendations regarding conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The RMP evaluation recommended conditions of registration relating to the versions of the risk management plan, requirement for periodic safety update reports, and inclusion of the medicine in the Black Triangle Scheme.

Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia-specific annex (ASA) can be found on the TGA website.

Risk-benefit analysis

Delegate's considerations

The claim for efficacy of Filsuvez is supported by a clinical study comparing wound healing time in patients with dystrophic EB or junctional EB and with a target partial-thickness wound lasting ≥21 days and <9 months that was 10–50 cm^2 in size, allocated to treatment with birch triterpenes (Oleogel-S10) or control gel (85% sunflower oil, 5% cera flava/yellow wax, and 10% carnauba wax) – both with standard-of-care non-adhesive dressings.[16] The types of standard-of-

care dressings were not described. Wounds other than the nominated 'target' wound were allowed treatment with topical antiseptics at wound dressing changes, steroid medications, silver dressings and topical antibiotics as required. Skin products including creams (including barrier creams), ointments (and dressings containing topical emollients, e.g., vaselinised gauze), gels, or emollients, were not permitted to be used on any areas affected by EB wounds during the double-blind period, and systemic steroids (other than those inhaled for oesophageal strictures, or ophthalmic preparations), immunosuppressive or cytotoxic chemotherapy and systemic antibiotics were not allowed for 3 months into the open-label extension study.

The median age of the participants was 12 years (range 6 months to 81 years). By age categories, 8% of study participants were 6 months 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 adults (≥18 years of age) three were 65 years of age or older. This reflects a population with severe EB.

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.

One weakness in this application is that by focusing on wounds associated with EB, the investigators chose comparison with a 'control' gel and did not consider other topical preparations as comparators. While the mechanism of action of birch triterpenes has not been clearly elucidated, the applicant and investigators have considered literature promoting antibacterial, antimycotic, antiviral, anti-inflammatory, antitumoral and wound-healing properties. This suggests that birch triterpenes may also be effective in wounds associated with conditions other than EB. Indeed, the published report referenced three small phase III studies of Oleogel-S10 which demonstrated accelerated wound-healing effects in split-thickness skin graft donor sites and grade 2a burn wounds.

Accepting that birch bark extract is at least moderately efficacious in the treatment of wounds related to EB further supports the plausibility of positively influencing healing of other partial thickness wounds, irrespective of the underlying cause of the lesions. The mechanism of action, while yet undefined, may simply be as a general support to achieve faster wound healing rather than a specific mechanism of action targeting specific EB sub-types.

Regarding safety, the clinical studies have not identified any significant adverse effects of topical application of birch triterpenes. Similar rates of adverse events were reported in both active and placebo-treated populations, and many of these could be considered a result of the underlying condition. One concern that is being monitored is that the potentially long-term use, either chronic or intermittent, of a product proposed to have effects on cell proliferation could also contribute to an increased risk of skin cancers. This is already a risk in the population with EB. Safety update reviews to date have not identified any change in the rate of development of skin cancers in patients with EB using Filsuvez.

Proposed action

Filsuvez is considered a locally applied, locally acting gel with limited systemic absorption. The gel should be applied to the surface of a partial thickness wound 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 be reapplied at each wound dressing change.

While there were several weaknesses with the submission, none of them either in isolation or in combination indicate major concerns with the safety of Filsuvez (birch bark dry extract). The product has been approved in major comparable jurisdictions for the proposed indication, and historically in the European Union for a separate wound-healing indication.

I propose to approve the application subject to conditions of registration proposed by the RMP evaluation and a commitment from the sponsor to provide to TGA results of the FDA requested long-term carcinogenicity study in rodents when they become available.

Assessment outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Filsuvez birch bark dry extract (84 - 95% triterpenes) 100 mg/g gel tube, indicated for:

> *Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.*

Specific conditions of registration

- Filsuvez (birch bark dry extract, 84 - 95% triterpenes) is to be included in the Black Triangle Scheme. The PI and CMI for Filsuvez must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date of first supply of the product.
- The Filsuvez EU-Risk Management Plan (RMP) version 2.3 (dated 8 May 2025; DLP 14 January 2023), with Australia-Specific Annex (ASA) version 1.1 (dated 27 October 2025), included with submission PM-2025-01059-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter. Each report must be submitted within ninety calendar days of the data lock point for that report.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Product Information and Consumer Medicine Information

For the most recent Product Information (PI) and Consumer Medicine Information (CMI), please refer to the TGA PI/CMI search facility.

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Reference/Publication #