14 December 2023
EMA/4657/2024
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Filsuvez

International non-proprietary name: Birch bark extract

Procedure No. EMEA/H/C/005035/II/0006

## Note

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

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| Status of this report and steps taken for the assessment | | | | |
|---|---|---|---|---|
| **Current step[1]** | **Description** | **Planned date** | **Actual Date** | **Need for discussion[2]** |
| ☐ | Start of procedure | 14 Aug 2023 | 14 Aug 2023 | ☐ |
| ☐ | CHMP Rapporteur Assessment Report | 18 Sep 2023 | 17 Sep 2023 | ☐ |
| ☐ | CHMP members comments | 02 Oct 2023 | 28 Sep 2023 | ☐ |
| ☐ | Updated CHMP Rapporteur Assessment Report | 05 Oct 2023 | 05 Oct 2023 | ☐ |
| ☐ | Request for supplementary information | 12 Oct 2023 | 12 Oct 2023 | ☐ |
| ☐ | Submission of MAH responses | 14 Nov 2023 | 14 Nov 2023 | ☐ |
| ☐ | Re-start of procedure | 15 Nov 2023 | 15 Nov 2023 | ☐ |
| ☐ | CHMP Rapporteur Assessment Report | 29 Nov 2023 | 28 Nov 2023 | ☐ |
| ☐ | CHMP members comments | 04 Dec 2023 | 28 Nov 2023 | ☐ |
| ☐ | Updated CHMP Rapporteur Assessment Report | 07 Dec 2023 | 06 Dec 2023 | ☐ |
| ☒ | Opinion | 14 Dec 2023 | 14 Dec 2023 | ☐ |

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

| Procedure resources | |
|---|---|
| Rapporteur: | Kristina Dunder |

## Declarations

☒The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report, including in the Product Information, if any.

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# 1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Amryt Pharmaceuticals DAC submitted to the European Medicines Agency on 30 June 2023 an application for a variation.

The following changes were proposed:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.4 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | Type II | I and II |

Update of sections 4.8 and 5.1 of the SmPC in order to update clinical information based on final results from study EASE (BEB-13); this is a double-blind, randomised, placebo (vehicle) controlled trial to evaluate efficacy and safety of birch bark extract on top of standard of care in paediatric and adult patients with epidermolysis bullosa. In addition, the MAH took the opportunity to introduce minor changes to the PI.

The requested variation proposed amendments to the Summary of Product Characteristics and Annex II.

### *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0541/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0541/2023 was completed.

The PDCO issued an opinion on compliance for the PIP P/0541/2023.

# 2. Overall conclusion and impact on the benefit/risk balance

Filsuvez, gel, is indicated for treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.

1 g of gel contains 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.

Filsuvez, known as Oleogel-S10 throughout its clinical development program, was approved in the EU/EEA on 21 June 2022. The efficacy and safety of Filsuvez in the treatment of partial thickness wounds associated with inherited EB were evaluated in a pivotal global Phase 3, randomised, double blind, controlled study in adults and children (Study BEB-13; EASE). Patients with DEB and JEB were randomised 1:1 to receive Filsuvez (n = 109) or a blinded control gel (consisting of sunflower oil, refined; beeswax, yellow and carnauba wax) (n = 114). The primary endpoint was the proportion of patients with first complete closure of the target wound by day 45 of the 90 day double blind phase (DBP) of the study. Following completion of the DBP, patients entered a 24-month single arm open label phase (OLP) of the study during which all wounds were treated with Filsuvez. Final safety data for the 205 subjects who have participated in the OLP of BEB-13 (final database lock date of 01 July 2022) has been presented in this variation application.

Beside safety data, the finalised OLP of the BEB-13 study also includes efficacy data and the results have been included in the Clinical Overview and Summary of Clinical Efficacy (SCE). Improvements seen with

Oleogel-S10 treatment during the DBP were generally maintained during the OLP (mostly assessed at Month 3). Importantly, the OLP efficacy analyses were not powered for statistical significance and there was no control gel and no blinding applied during the OLP. In addition, in the MAA evaluation of Filsuvez it was concluded that 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. This conclusion remains the same from the efficacy results from the finalised OLP of BEB-13.

Secondary efficacy endpoints were nearly identical between the DBP and OLP. Two new efficacy endpoints were included in the OLP evaluating changes from OLP baseline in disease severity (Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa [iscorEB]) and subject quality of life (EuroQol 5 Dimensions ([EQ-5D]) between the DBP and OLP. However, these two endpoints were added during the conduct of the study and only a few subjects in the OLP had baseline assessments and some subjects were not able to complete the instruments.

In conclusion, it is agreed that there are no new data on efficacy from the OLP of the BEB-13 study that alters previous assessments or the approved product information. There are no new safety issues arising from the presented efficacy results.

The safety objectives of the 24-month OLP were to evaluate the safety of Filsuvez based on the incidence, severity and relatedness of adverse events (AEs) and laboratory assessments. Exposure to betulin was also assessed, with final venous blood samples collected at Month 24.

At the time of approval of Filsuvez, the BEB-13 24-months single arm OLP was still ongoing and the applicant provided interim safety data with data lock point of 21 April 2021. Thus, the final study report of BEB-13 submitted for this variation fills the gap from 21 April 2021 to 1 July 2022. Based on the safety results from the finalised OLP, the MAH has updated the safety sections of the Clinical Overview and Summary of Clinical Safety (SCS) and proposed updates to the SmPC (PI Annex I) with changes introduced in sections 4.8 and 5.1. These changes are discussed below.

In addition, the MAH took the opportunity to introduce a minor change in Annex II section C on the requirements for submission of PSURs. This change is agreed.

Filsuvez is considered a locally applied, locally acting gel with limited systemic absorption. The additional data provided from the finalised OLP does not change this conclusion. Betulin systemic exposure was very low, the majority of samples were below the lower limit of quantification, and thus are unlikely to result in systemic AEs.

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. However, the reason for changing the frequency of wound complication from 11.6% to 11.2% in EB patients in SmPC section 4.8 was not clearly presented. Therefore, the MAH was requested to provide further information on the data and calculations supporting this change. In addition, two reports of wound haemorrhage were reported (in the same subject), one of which was a serious reaction. Both were assessed as related to study medication. The SAE resulted in discontinuation from the study. The MAH was requested to consider if wound haemorrhage should be included in the description of selected events paragraph detailing wound complications in SmPC section 4.8. In their response, the MAH agreed to include wound haemorrhage under the description of wound complications, as requested by CHMP. Since the number of subjects who have experienced a related wound complication event is 25 subjects (with wound complication PT) plus 1 subject (with wound haemorrhage PT) making it 26 subjects out of 224 subjects which brings the frequency percentage back to 11.6%, the frequency of wound complication in SmPC section 4.8 will not be changed. This is agreed.

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 out of 205 patients discontinued the OLP (31%) that is considered reasonable in a 24-month follow-up study in a severe disease.

In the SCS, the MAH has presented that the extent of exposure for patients in the OLP was in median duration 727 days and maximum duration 841 days. In the DBP, the Oleogel-S10 exposure was in median duration 91 days and maximum duration 140 days. In the updated SmPC section 5.1, the median durations of Filsuvez treatment for all patients in the DBP and OLP have been combined and updated from 695 to 733 days and the maximum duration of treatment from of 924 days to 931 days. The MAH was requested to present the data and the calculations in support of this change. In addition, the median number of tubes introduced in the SmPC section 5.1 was not clearly presented in the SCS. The MAH was requested to present the data from the DBP and the OLP combined (preferably in one table) and the calculations for the data to be included in SmPC section 5.1. This was also requested for the median daily extent of exposure and median cumulative extent of exposure (grams). In their response, the MAH has presented the data for median and maximum duration of Filsuvez treatment for all patients in the DBP and OLP, median daily extent of exposure, median cumulative extent of exposure and median number of tubes used per month. In conclusion, all data in support of changes to SmPC section 5.1 have been provided and the changes are considered acceptable by the CHMP.

Overall, the safety database of Filsuvez in JEB and DEB patients is small, however, EB is a rare, designated orphan disease and the constraints in recruitment due to the rare condition is acknowledged. The demographics and baseline characteristics of the OLP population were similar to those of the overall study population that participated in the DBP. As all subgroups were small in the BEB-13 study dataset, it was agreed that the interpretation of subgroup data was limited.

In conclusion, the benefit-risk balance of Filsuvez remains positive in the approved indication.

# 3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.4 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | Type II | I and II |

Update of sections 4.8 and 5.1 of the SmPC in order to update clinical information based on final results from study EASE (BEB-13); this is a double-blind, randomised, placebo (vehicle) controlled trial to evaluate efficacy and safety of birch bark extract on top of standard of care in paediatric and adult patients with epidermolysis bullosa. In addition, the MAH took the opportunity to introduce minor changes to the PI.

☒is recommended for approval.

## *Paediatric data*

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0541/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

# 4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

## *Scope*

Please refer to the Recommendations section above

## *Summary*

Please refer to Scientific Discussion ‘Filsuvez/H/C/005035/II/0006’

# Annex: CHMP Rapporteur assessment comments on the type II variation

# 5. Introduction

Filsuvez, gel, is indicated for treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.

1 g of gel contains 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.

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 be reapplied at each wound dressing change.

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.

Filsuvez, known as Oleogel-S10 throughout its clinical development program, was approved in the EU/EEA on 21 June 2022. The efficacy and safety of Filsuvez in the treatment of partial thickness wounds associated with inherited EB were evaluated in a pivotal global Phase 3, randomised, double blind, controlled study in adults and children (Study BEB-13; EASE). Patients with DEB and JEB were randomised 1:1 to receive Filsuvez (n = 109) or a blinded control gel (consisting of sunflower oil, refined; beeswax, yellow and carnauba wax) (n = 114). The primary endpoint was the proportion of patients with first complete closure of the target wound by day 45 of the 90 day double blind phase (DBP) of the study. Following completion of the DBP, patients entered a 24-month single arm open label phase (OLP) of the study during which all wounds were treated with Filsuvez.

In the BEB-13 study double-blind phase (DBP), patients with EB subtypes JEB (11.7%) and DEB (87.5%), with a median age of 12 years (range 6 months to 81 years) were enrolled. 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%). 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. Comorbidities reported in included EB patients were e.g., anaemia, malnutrition, oesophageal stenosis, susceptibility to infections.

**Table 1 Overview of BEB-13 (EASE) study**

| Study Number & Phase<br>Country<br>Study Status | Study Population/ Indication | Study Design | Study Treatment(s) and Duration of Treatment<br>Duration of Follow-Up | Number of Study Subjects<br>Demographics |
|---|---|---|---|---|
| **BEB-13 (EASE Study)**<br>Phase 3<br>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)<br><br>Double-blind phase (DBP) completed<br>Open-label phase (OLP) ongoing | Subjects ≥21 days of age with inherited EB (subtypes JEB, DEB, or Kindler syndrome) 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.<br>Oleogel-S10 was applied in the same manner to all EB partial-thickness wounds for up to **24 months** during OLP.<br>Subjects were followed during the 24-month OLP (Follow-up period). | 223 subjects enrolled:<br>109 Oleogel-S10<br>114 Control gel<br>(At the time of data cut-off, 11 Jun 2020, 134 subjects remained in the OLP).<br>60% Male<br>Median age 12 years (range 6 months to 81 years)<br>Race:<br>83% White<br>5% Not reported<br>5% Asian<br>1% Black<br><br>Fitzpatrick skin type:<br>6% Type I,<br>49% Type II,<br>34% Type III,<br>9% Type IV,<br>2% Type V,<br><1% Type VI |

At the time of approval, the BEB-13 24-months single arm open-label phase (OLP) was still ongoing. The applicant had provided interim safety data with data lock point of 21 April 2021. On 21 April 2021, out of 205 patients who entered the OLP, 144 (70%) had completed the month 12 visit, and 68 patients (33%) completed the month 24 visit. In addition, subjects in the so called "former Oleogel-S10 group" had 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, had been exposed to Oleogel-S10 for 12 months in total, i.e., 156 patients had been exposed to Oleogel-S10 for 12 months on 21 April 2021. 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.

The demographics and baseline characteristics of the OLP population were similar to those of the overall study population that participated in the DBP. At baseline of the OLP, the overall median age of subjects was 12 years (range: 6 months to 81 years), and the highest number of subjects were in the 4 to <12-year-old range (39.5%). A total of 126 (61.5%) subjects were male and 79 (38.5%) were female. Most (82.4%) subjects were White. A total of 178 (86.8%) subjects had the EB subtype of DEB; of these,

160 (78.0%) subjects had RDEB and 18 (8.8%) subjects had DDEB. Twenty-five (12.2%) subjects had JEB, and 2 (1.0%) subjects had EBS and were enrolled before subjects with EBS were excluded from study participation (protocol Version 4.0).

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

It has been agreed that the Filsuvez is a locally applied, locally acting gel with limited systemic absorption. The most frequently observed adverse reactions in epidermolysis bullosa (EB) patients were related to the application site i.e., wound complication (in 11.6% of patients), application site reaction (5.8%), wound infections (4.0%), pruritus (3.1%) and hypersensitivity reactions (1.3%).

**Table 2 Adverse reactions listed in SmPC section 4.8**

| 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 and application site pruritis) | Pain[a] |
| 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 last subject last visit in the OLP was 27 May 2022 and the database lock was 01 July 2022. Thus, the final study report of BEB-13 submitted for this variation fills the gap from 21 April 2021 to 1 July 2022.

Recently, the 2nd Periodic Safety Update Report (PSUR) for birch bark extract (EMEA/H/C/PSUSA/00010446/202301) summarised the results of the benefit-risk analysis of the data received by Amryt Pharmaceuticals DAC from 15 July 2022 to 14 January 2023. Importantly, the MAH concluded that there is no need to update the PI at this time based on the analysis of the finalised BEB-13 OLP.

In the current variation procedure (procedure II/0006), the MAH has submitted the final results from BEB-13 study (EASE study). The Clinical Study Report (CSR) Addendum Version 3 includes the Double-Blind Phase and Open-Label Data Through the End of Study. CSR addendum was prepared at the end of the open-label phase (EOLP) to report the final efficacy and safety data from the OLP.

The updated Clinical Overview, Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS) submitted for this variation includes data from the completed BEB-13 study. Based on the results, the MAH has enclosed the updated SmPC (PI Annex I) with changes introduced in sections 4.8 and 5.1.

In SmPC section 4.8, the frequency of wound complication has been changed from 11.6% to 11.2% in EB patients.

In SmPC section 5.1, the median duration of Filsuvez treatment for all patients in the DBP and OLP have been updated from 695 to 733 days and the maximum duration of treatment from of 924 days to 931 days. In addition, Table 3 in this section has been updated as presented below.

**Table 3 Median daily and cumulative extent of exposure and number of tubes used monthly 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 | 15 | 10 | 10 | 9 |
| **Median cumulative extent of exposure (grams)** | 6117 | 8240 | 7660 | 5769 | 3467 |
| **Median number of tubes used per month** | 19 | 24 | 17 | 20 | 19 |

In addition, the MAH took the opportunity to introduce minor change in Annex II section C on the requirements for submission of PSURs.

Some linguistic corrections were identified for Dutch, Danish and Finnish product information. These are detailed in the present and proposed annex with justifications.

No changes have been introduced in PI Annex III i.e., the Labelling and Package Leaflet.

As no new identified or potential risks have been observed, the MAH has not included a revised risk management plan (RMP) in this variation.

Detailed information on the BEB-13 study and assessment of the data for the approval of Filsuvez is referred to the EPAR https://www.ema.europa.eu/en/documents/assessment-report/filsuvez-epar-public-assessment-report_en.pdf.

## *5.1. GCP*

The BEB-13 study was conducted in accordance with the International Council on Harmonization tripartite guideline on the ethical principles of Good Clinical Practice (ICH E6), and applicable regulatory requirements including the archiving of essential documents. Patients 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). According to the MAH, the clinical trials conducted outside the European Union (EU) meet the ethical requirements of Directive 2001/20/EC.

### *5.2. Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0541/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0541/2023 was completed.

The PDCO issued an opinion on compliance for the PIP P/0541/2023.

# 6. Clinical Efficacy aspects

In the DBP of BEB-13 study, 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).

In the MA of Filsuvez it was concluded that 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. Limited additional data from the OLP of BEB-13 was submitted, thus, limited long-term efficacy data for Filsuvez was available at that time.

The consistent direction of improvement observed in reduction of total wound burden during the 90-day DBP with Oleogel-S10 treatment was sustained as shown in the interim OLP efficacy analysis which was performed at the request of CHMP in the Day 120 responses.

In particular, BEB-13 OLP Month 12 efficacy results for the following secondary endpoints were included already in the MA of Filsuvez:

- Body surface area percentage (BSAP) of total body surface area (TBSA) affected by EB Partial Thickness Wounds based on "Lund and Browder"
- Total Body Wound Burden (TBWB) based on Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI)

The results of the completed BEB-13 OLP are presented in the update to the Clinical Overview and in the Summary of Clinical Efficacy (SCE) submitted in this variation application.

In the SCE, the MAH states that efficacy endpoints were similar between the DBP and OLP with one main difference: in the OLP, clinical assessment of the target wound was only performed at one follow-up visit (the Month 3 visit) and was not an efficacy endpoint. Therefore, duration of target wound closure could not be assessed for the OLP. The remaining secondary efficacy endpoints were nearly identical between the DBP and OLP and many endpoints evaluated a similar time frame (e.g., approximately 90 days from DBP or OLP baseline). OLP baseline was defined as the first day of the OLP (OLP Day 0) which occurred at Day 90 of the DBP; however, OLP baseline only includes subjects that entered the OLP.

Two new efficacy endpoints were incorporated in the OLP including comparisons of results between the DBP and OLP and changes from OLP baseline in disease severity and subject quality of life. Of note, the disease severity (Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa [iscorEB]) and quality of life (EuroQol 5 Dimensions ([EQ-5D]) patient-reported outcome (PRO) assessments/endpoints were added in Protocol Version 6.0, approximately 2.5 years after the study was initiated. As a result, site implementation and incorporation of these new PROs occurred slowly, and few subjects in the OLP had baseline assessments (Day 90 of the DBP) which made interpretation of change

from baseline assessments unmeaningful. In addition, since the iscorEB and EQ-5D instruments were added during the conduct of the study, some subjects were not able to complete the instrument.

The BEB-13 SAP OLP has been updated accordingly. Of note, results for Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) and Body Surface Area Percentage (BSAP) assessments at the Month 24 visit excluded a high number of subjects (n=36 [28%]) as the study visits were performed outside of the visit window largely due to the COVID-19 pandemic. Post hoc analyses of these assessments were performed to include all subjects' scores by removing visit windows from the analyses (see SAP [Section 12]). The only other efficacy assessments performed at Month 24 were disease severity (iscorEB) and quality of life (EQ-5D); however, post hoc analyses were not performed for these assessments due to the already small sample sizes.

The MAH concludes that there are no new data on efficacy from the OLP of the BEB-13 study that alters previous assessments, and which are described in the approved product information.

***CHMP comment:***

Since the primary efficacy endpoint was the proportion of subjects with first complete closure of the EB target wound within 45 days of initiating treatment, the primary efficacy endpoint is not included in the OLP.

The efficacy endpoints for the OLP were included already in the DBP except for two new endpoints i.e.:

• Changes from OLP baseline (OLP Day 0) in disease severity from both clinician and subject/family perspective as quantified with the Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa (iscorEB) [Schwieger-Briel 2015] at Months 12 and 24

• Changes from OLP baseline (OLP Day 0) in subjects' quality of life as assessed by the 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with the EuroQol 5 Dimensions (EQ-5D) instrument at Months 12 and 24

However, according to the MAH, these PROs were added in Protocol Version 6.0, approximately 2.5 years after the study was initiated. As a result, site implementation and incorporation of these new PROs occurred slowly, and few subjects in the OLP had baseline assessments (Day 90 of the DBP) which made interpretation of change from baseline assessments unmeaningful. In addition, some subjects were not able to complete the instrument.

According to the MAH, overall improvements seen with Oleogel-S10 treatment during the DBP were generally maintained during the OLP (mostly assessed at Month 3). However, in the MA of Filsuvez it was concluded that 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. This conclusion remains the same from the presented efficacy results from the finalised BEB-13 OLP.

The Statistical Analysis Plan version 6.0 (dated 9 September 2022) has been included in this variation application. The MAH highlights that the OLP efficacy analyses were not powered for statistical significance. Importantly, 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.

In conclusion, it is agreed that there are no new data on efficacy from the OLP of the BEB-13 study that alters previous assessments or the approved product information.

## *6.1. Methods – analysis of data submitted*

The methods used in the OLP of BEB-13 are presented and assessed in the initial MA of Filsuvez. Only minor changes have been introduced in the Statistical Analysis Plan version 6.0 (dated 9 September 2022) included in this variation application.

### 6.1.1. Efficacy endpoints in the OLP of the BEB-13 study

Thee following efficacy endpoints were included in the OLP of BEB-13:

1. The maximum severity of wound infection between OLP baseline (OLP Day 0) and Month 24 as evidenced by AEs and/or use of topical and/or systemic antibiotics that are related to wound infection
2. Changes from OLP baseline (OLP 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 Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) [Loh 2014] at Months 3, 12, and 24
3. Changes from OLP baseline (OLP 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 Months 3, 12, and 24
4. Changes from OLP baseline (OLP Day 0) in "background" pain using the Face, Legs, Activity, Cry, Consolability (FLACC) [Merkel 1997] scale 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 Month 3
5. Changes from OLP baseline (OLP 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 Month 3
6. Changes from OLP baseline (OLP 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 Month 3
7. Changes from OLP baseline (OLP Day 0) in impact of wounds on sleep (in the prior 7 days, in subjects ≥14 years of age) as measured by differences in 11-point Likert scales [Blome 2014] at Month 3
8. The number of days missed from school or from work due to EB as reported by subjects at Month 3 for the last 14 days
9. Evaluation of the treatment satisfaction (in subjects ≥14 years of age) using the Treatment Satisfaction Questionnaire for Medication (TSQM) [Bharmal 2009], Version 9, before wound dressing changes at Month 3
10. Changes from OLP baseline (OLP Day 0) in disease severity from both clinician and subject/family perspective as quantified with the Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa (iscorEB) [Schwieger-Briel 2015] at Months 12 and 24
11. Changes from OLP baseline (OLP Day 0) in subjects' quality of life as assessed by the 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with the EuroQol 5 Dimensions (EQ-5D) instrument at Months 12 and 24

12. Proportion of subjects with complete closure of the EB target wound at Month 3 based on clinical assessment by the investigator and blinded evaluation of photographs, and at Months 12 and 24 based on clinical assessment only

***CHMP comment:***

The efficacy endpoints for the OLP were included already in the DBP except for two new endpoints i.e.:

10. Changes from OLP baseline (OLP Day 0) in disease severity from both clinician and subject/family perspective as quantified with the Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa (iscorEB) [Schwieger-Briel 2015] at Months 12 and 24

11. Changes from OLP baseline (OLP Day 0) in subjects' quality of life as assessed by the 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with the EuroQol 5 Dimensions (EQ-5D) instrument at Months 12 and 24

## *6.2. Results*

### 6.2.1. Participant flow

First subject in: 24 July 2017

Last subject last visit: 27 May 2022

Database lock: 01 July 2022

The OLP of BEB-13 had a 68.8% completion rate.

**Table 4 Disposition of Study Treatment Periods of the BEB-13 OLP (Safety Analysis Set)**

| | Number Enrolled | Number Treated | Number of Subjects Who Completed Study | Number of Subjects who Terminated Early |
|---|---|---|---|---|
| Former Oleogel-S10 | 100 | 100 | 66 (66.0%)[1] | 34 (34.0%) |
| Former Control | 105 | 105 | 75 (71.4%)[1] | 30 (28.6%) |
| Total | 205 | 205 | 141 (68.8%) | 64 (31.2%) |

Abbreviations: DBP=double-blind phase; OLP=open-label phase
[1]In BEB-13, completion refers to completion of the respective phase of the study (i.e., the 90-day DBP or the 2-year OLP).

Six subjects in study BEB-13, 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 (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 completers plus 6 subjects who discontinued the DBP prematurely) continued to the OLP.

As of the study completion database lock (01 July 2022), a total of 141 subjects (68.8%) completed the OLP and 64 subjects (31.2%) discontinued the OLP prior to Month 24. Five subjects completed the study but did not have an End of OLP (EOLP) visit. The percentage of subjects discontinuing the study at each 3-month visit interval tended to decrease over time during the OLP with the exception of small increases in discontinuations around planned study visits at Months 12 and 24.

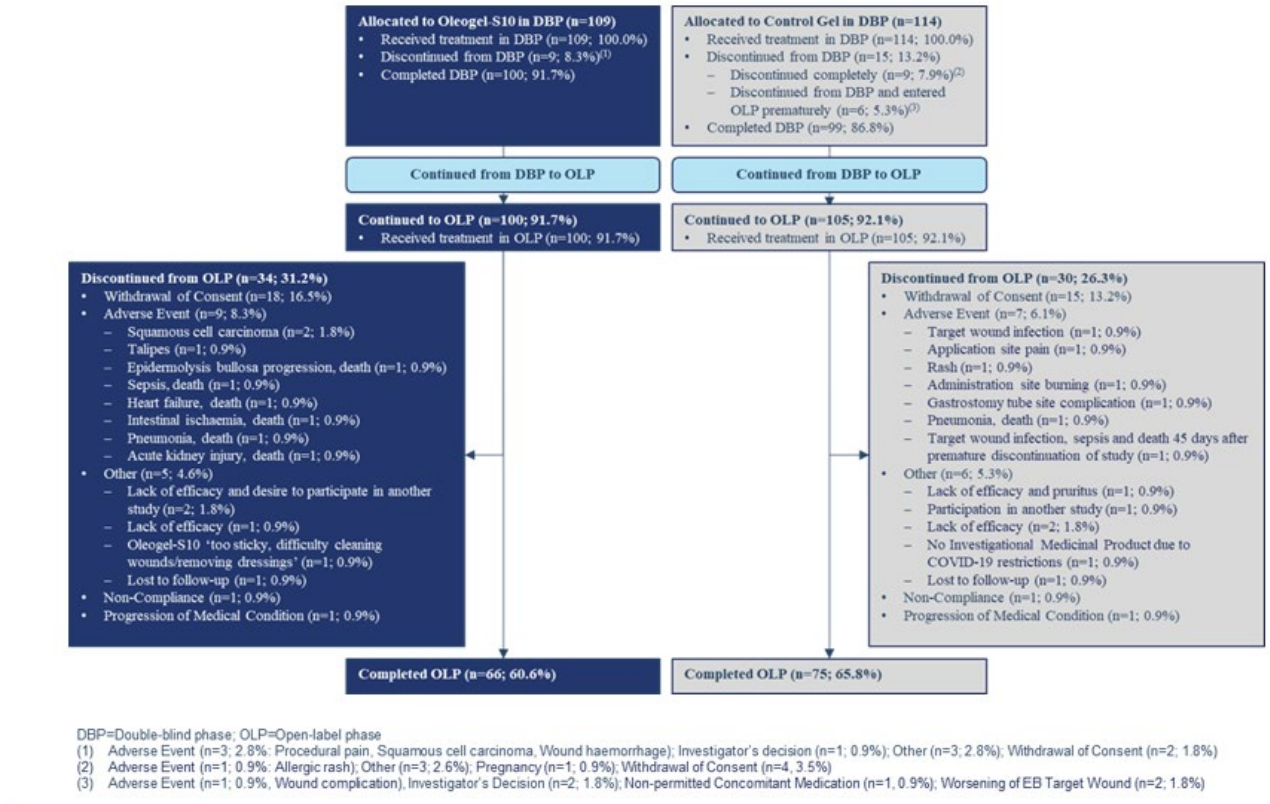


**Figure 1 Subject disposition BEB-13**

## 6.2.2. Outcomes

**Wound infection**

***Endpoint 1.*** The maximum severity of wound infection between OLP baseline (OLP Day 0) and Month 24 as evidenced by AEs and/or use of topical and/or systemic antibiotics that are related to wound infection

***Outcome endpoint 1:*** In the OLP, target wound infections occurred in very few subjects, with only 7 subjects experiencing an 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 all target wound infections in former control gel subjects were moderate (n=3). The incidence and severity of additional and other wound infections were very similar between the DBP and OLP through Month 24.

**Wound burden**

***Endpoint 2:*** Changes from OLP baseline (OLP 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 Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) [Loh 2014] at Months 3, 12, and 24

***Endpoint 3:*** Changes from OLP baseline (OLP Day 0) in Body Surface Area Percentage (BSAP) of Total Body Surface Area (TBSA) affected by EB partial-thickness wounds as evidenced by clinical assessment based on the Lund and Browder chart [Miminas 2007] at Months 3, 12, and 24

***Outcome endpoints 2 and 3:*** The number of subjects with EBDASI and BSAP scores recorded within visit windows in the OLP was lower than expected due to the impact of COVID-19. Therefore, post hoc analyses of the summary statistics outputs were produced without visit windows in the OLP which according to the MAH reflects a "real-world" situation. When OLP visit windows were excluded from the

analyses due to the high number of subjects (n=36 [28%]) who had EBDASI and BSAP assessments performed out of window due to COVID-19, both treatment groups showed further improvement from OLP baseline at Month 24 in the TBWB based on mean EBDASI skin activity and BSAP scores.

When OLP visit windows are included, at Month 24, mean EBDASI skin activity scores were generally comparable to OLP baseline scores in both treatment groups, which reflects reductions in TBWB from DBP baseline over a 2-year period.

When OLP visit windows are included, at Month 24, mean total BSAP scores were comparable to OLP baseline scores in the former Oleogel-S10 group, while the former control gel group had a reduction in BSAP from OLP baseline (OLP baseline: 8.3%; Month 24: 4.4%); results for both treatment groups reflect reductions in BSAP from DBP baseline over a 2-year period.

**Pain**

***Endpoint 4:*** Changes from OLP baseline (OLP Day 0) in "background" pain using the Face, Legs, Activity, Cry, Consolability (FLACC) [Merkel 1997] scale 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 Month 3

***Endpoint 5:*** Changes from OLP baseline (OLP 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 Month 3

***Outcome endpoints 4 and 5:*** In BEB-13, 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) were evaluated using the Wong-Baker FACES scale for subjects ≥4 years of age or the FLACC scale for subjects <4 years of age. Using the Wong-Baker FACES scale for subjects ≥4 years of age or the FLACC scale for subjects <4 years of age, the effects on procedural and background pain achieved in the DBP were generally maintained at Month 3 of the OLP for the former Oleogel-S10 group.

Results for younger subjects (<4 years) are not discussed by the MAH due to small sample size (N=16).

**Itch**

***Endpoint 6:*** Changes from OLP baseline (OLP 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 Month 3

***Outcome endpoint 6:*** Results using the Itch Man Scale for subjects 4 to 13 years of age showed that overall, both treatment groups maintained reductions in itching below the DBP baseline value at Month 3 of the OLP. Results using the Leuven Itch Scale for subjects ≥14 years showed that, in the former control gel group, mean scores decreased from OLP baseline to Month 3 for the duration, distress, and surface area domain scores and increased from OLP baseline for frequency, severity, and consequences. In the former Oleogel-S10 group, mean scores for duration and surface area decreased at Month 3, whereas mean scores for frequency, severity, distress, and consequences increased at Month 3. Overall, both treatment groups maintained reductions in itching below the DBP baseline value at Month 3.

**Sleep**

***Endpoint 7:*** Changes from OLP baseline (OLP Day 0) in impact of wounds on sleep (in the prior 7 days, in subjects ≥14 years of age) as measured by differences in 11-point Likert scales [Blome 2014] at Month 3

***Outcome endpoint 7:*** At OLP Month 3, a slight decrease from OLP baseline (Day 90 of DBP) in the mean sleep assessment score was observed in the former Oleogel-S10 group whereas a slight increase from OLP baseline was observed in the former control gel group. When the change from baseline in the DBP

(Day 0 to Day 90) was compared to the change from baseline in the OLP, decreases in mean sleep assessment scores were observed in both treatment groups.

**Days missed from school or from work**

***Endpoint 8:*** The number of days missed from school or from work due to EB as reported by subjects at Month 3 for the last 14 days

***Outcome endpoint 8:*** A decrease in the number of days of school or work missed because of problems with EB was observed in both treatment groups when compared between the DBP and the OLP (to Month 3).

**Treatment satisfaction and QoL**

***Endpoint 9:*** Evaluation of the treatment satisfaction (in subjects ≥14 years of age) using the Treatment Satisfaction Questionnaire for Medication (TSQM) [Bharmal 2009], Version 9, before wound dressing changes at Month 3

***Outcome endpoint 9:*** When overall treatment satisfaction scores reflecting a subject feeling satisfied (results for somewhat satisfied, satisfied, very satisfied, or extremely satisfied were grouped), treatment satisfaction decreased in both treatment groups from OLP baseline to Month 3. However, when the overall treatment satisfaction score was evaluated using an ANCOVA model, subjects who were treated with Oleogel-S10 in both the DBP and OLP remained satisfied throughout the study to Month 3, whereas subjects who were treated with control gel in the DBP experienced an increase in their overall satisfaction score after switching to Oleogel-S10 treatment in the OLP.

***Endpoint 10:*** Changes from OLP baseline (OLP Day 0) in disease severity from both clinician and subject/family perspective as quantified with the Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa (iscorEB) [Schwieger-Briel 2015] at Months 12 and 24

***Endpoint 11:*** Changes from OLP baseline (OLP Day 0) in subjects' quality of life as assessed by the 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with the EuroQol 5 Dimensions (EQ-5D) instrument at Months 12 and 24

***Outcome endpoints 10 and 11:*** Both the iscorEB and EQ-5D instruments were added during the conduct of the study, resulting in small numbers of subjects who completed these assessments, particularly at OLP baseline. No clear trends were observed in either treatment group for disease severity (iscorEB) or quality of life (EQ-5D).

**Wound closure**

***Endpoint 12:*** Proportion of subjects with complete closure of the EB target wound at Month 3 based on clinical assessment by the investigator and blinded evaluation of photographs, and at Months 12 and 24 based on clinical assessment only.

***Outcome endpoint 12:*** During the DBP, approximately half (47%) of subjects experienced the first complete closure of the EB target wound within 90 days; therefore, these subjects could not have had the first complete closure of the target wound during the subsequent OLP period. Those target wounds identified at OLP baseline that remained open throughout the 90-day DBP were obviously in situ for a longer period of time. Furthermore, assessment of closure of the target wound was only performed at Month 3 in the OLP, which limited interpretation of wound closure to a single time point. Closure of the target wound based on blinded evaluation of photographs taken with the ARANZ Silhouette system supported the efficacy results obtained by the investigator's clinical assessment.

**Ancillary analyses**

*Percentage Change from Baseline in Wound Size Based on Photographic Assessment by Visit*

The analysis of target wound size based on the blinded evaluation of photographs demonstrated that the mean improvement (i.e., reduction in target wound size) continued in the OLP from the DBP in the former Oleogel-S10 group; however, the mean target wound size increased at Month 3 in the former control gel group. Improvements in target wound size seen with Oleogel-S10 treatment during the DBP were generally maintained in the OLP as determined by clinical assessment.

*Status of target wounds by visit*

The status of target wounds as evidenced by clinical assessment by the investigator was not included as an OLP efficacy endpoint in the SAP; however, a clinical assessment of the target wound was performed at 1 follow-up visit (the Month 3 visit). The denominator was the total number of subjects in each treatment group. The target wound closure categories included closed, not closed, not assessed, and missing. The category of not closed was further divided into 3 subcategories: improved from baseline; unchanged from baseline; and worsened from baseline. At Month 3, 143 subjects had a clinical assessment of the target wound (73 former Oleogel-S10 and 70 former control gel) with 119 subjects improving (48 subjects with target wound closed and 71 improved) compared to DBP baseline. Only a small number of subjects (n=18) had a worsening of the target wound based on clinical assessment at Month 3 compared to DBP baseline.

*Post hoc review of the frequency of dressing changes*

The results of a post hoc review of the frequency of dressing changes showed a clear reduction in dressing changes over the 90-day DBP period for Oleogel-S10, but not for the control gel. At Day 90, the change with Oleogel-S10 equated to one dressing change every 2 weeks. These reductions in the frequency of dressing changes were maintained in the OLP.

***CHMP comment:***

The presented efficacy results from the finalised BEB-13 OLP are acknowledged.

According to the MAH, overall improvements seen with Oleogel-S10 treatment during the DBP were generally maintained during the OLP (mostly assessed at Month 3). However, in the MA of Filsuvez it was concluded that 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. This conclusion remains the same from the presented efficacy results from the finalised BEB-13 OLP.

Importantly, 7 subjects experiencing an infection of the target wound during the OLP. The incidence and severity of additional and other wound infections were very similar between the DBP and OLP through Month 24.

In conclusion, it is agreed that there are no new data on efficacy from the OLP of the BEB-13 study that alters previous assessments or the approved product information.

There are no new safety issues arising from the presented efficacy results.

## *6.3. Discussion*

Secondary efficacy endpoints were nearly identical between the DBP and OLP. Two new efficacy endpoints were included in the OLP evaluating changes from OLP baseline in disease severity (Instrument for

Scoring Clinical Outcome of Research for Epidermolysis Bullosa [iscorEB]) and subject quality of life (EuroQol 5 Dimensions ([EQ-5D]) between the DBP and OLP. However, these two endpoints were added during the conduct of the study and only a few subjects in the OLP had baseline assessments and some subjects were not able to complete the instruments.

In general, improvements seen with Oleogel-S10 treatment during the DBP were generally maintained during the OLP (mostly assessed at Month 3). Importantly, the OLP efficacy analyses were not powered for statistical significance and there was no control gel and no blinding applied during the OLP.

In the MA of Filsuvez it was concluded that 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. This conclusion remains the same from the presented efficacy results from the finalised BEB-13 OLP.

In conclusion, it is agreed that there are no new data on efficacy from the OLP of the BEB-13 study that alters previous assessments or the approved product information. There are no new safety issues arising from the presented efficacy results.

# 7. Clinical Safety aspects

Following the DBP of the BEB-13 study, 205 of the initial 223 randomized subjects (91.9%) continued into the subsequent OLP (of whom 105 subjects had been treated with control gel in the DBP) and were administered Oleogel-S10 to all their partial-thickness wounds for up to an additional 24 months. Final safety data from the OLP of the BEB-13 study are presented in the Clinical Overview update and in the Summary of Clinical Safety (SCS) submitted for this variation as of a study completion database lock date of 01 July 2022.

## *7.1. Methods – analysis of data submitted*

The methods used in the OLP of BEB-13 are presented and assessed in the initial MA of Filsuvez. Only minor changes have been introduced in the Statistical Analysis Plan version 6.0 (dated 9 September 2022) included in this variation application.

The safety analyses are based on the Safety Analysis Set, defined as all subjects treated at least once with Oleogel-S10.

Since all subjects received Oleogel-S10 in the OLP, data for the OLP are presented for all Oleogel-S10-treated subjects combined and by their DBP treatment assignment; thus, the subject groups in the OLP are referred to as "former Oleogel-S10 group" or "former control gel group". For the OLP dataset, subjects in the "former Oleogel S10 group" had received an additional 3 months' exposure to Oleogel-S10 during the DBP.

### 7.1.1. Safety endpoints in the OLP of the BEB-13 study

The safety endpoints for both the DBP and OLP of BEB-13 were:

- Incidence, severity, and relatedness of adverse events (AEs)
- Local tolerability as judged by the investigator
- Laboratory assessments

• Vital signs

• Electrocardiograms (ECGs)

Exposure to betulin was also assessed, with final venous blood samples to be collected at Month 24/end of the open-label phase.

## *7.2. Results*

At the time of approval, the BEB-13 24-months single arm open-label phase (OLP) was still ongoing. The applicant had provided interim safety data with data lock point of 21 April 2021. On 21 April 2021, out of 205 patients who entered the OLP, 144 (70%) had completed the month 12 visit, and 68 patients (33%) completed the month 24 visit. The last subject last visit in the OLP was 27 May 2022 and the database lock was 01 July 2022. Thus, the final study report of BEB-13 submitted for this variation fills the gap from 21 April 2021 to 1 July 2022.

### 7.2.1. Patient exposure

As of the study completion database lock (01 July 2022), a total of 141 subjects (68.8%) completed the OLP and 64 subjects (31.2%) discontinued the OLP prior to Month 24 (Table 5). Five subjects completed the study but did not have an End of OLP (EOLP) visit. The percentage of subjects discontinuing the study at each 3-month visit interval tended to decrease over time during the OLP with the exception of small increases in discontinuations around planned study visits at Months 12 and 24.

**Table 5 Subject Disposition, Phase 3 Study BEB-13 in EB; Open-Label Phase (All Subjects)**

| | Former Oleogel-S10 (N=100) n (%) | Former Control Gel (N=105) n (%) | All Subjects (N=205) n (%) | *All Subjects (N=205) 21 April 2021 n (%) E* |
|---|---|---|---|---|
| | 100 (100.0) | 105 (100.0) | 205 (100.0) | *205 (91.9)* |
| Subjects who entered the OLP and received Oleogel-S10[a] | 100 (100.0) | 105 (100.0) | 205 (100.0) | *205 (91.9)* |
| Subjects who completed the OLP | 66 (66.0) | 75 (71.4) | 141 (68.8) | *68 (33.2)* |
| Subjects who discontinued from the OLP | 34 (34.0) | 30 (28.6) | 64 (31.2) | *60 (26.9)* |
| Reason for discontinuation | | | | |
| Withdrawal of consent | 18 (18.0) | 15 (14.3) | 33 (16.1) | *33 (14.8)* |
| AE | 9 (9.0) | 7 (6.7) | 16 (7.8) | *14 (6.8)* |
| Other | 5 (5.0) | 6 (5.7) | 11 (5.4) | *11 (4.9)* |
| Noncompliance | 1 (1.0) | 1 (1.0) | 2 (1.0) | - |
| Progression of medical condition | 1 (1.0) | 1 (1.0) | 2 (1.0) | *1 (0.4)* |
| Death | 7 (7.0) | 2 (1.9) | 9 (4.4) | *6 (2.9)* |

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 subjects who entered the OLP.

The primary reason for discontinuation was withdrawal of consent (33 of 205 subjects; 16.1%), followed by AEs (16 subjects; 7.8%) and other reasons (11 subjects; 5.4%). Other reasons included lack of efficacy (6 subjects), lost to follow-up (2 subjects), participation in another clinical trial (1 subject), difficulty with wound cleaning and removing dressings (1 subject), and medication delivery problems due to pandemic (1 subject).

Data on the extent of exposure and treatment compliance from the DBP and through the final database lock date (01 July 2022) are summarized in Table 6 and Table 7. The mean (standard deviation [SD]) duration of treatment in the OLP was 584.7 (246.13) days. Overall treatment compliance (specifically in relation to the target wound) was approximately 99% in both former treatment groups.

The calculation of study medication interruption data only considered interruptions of treatment of the target wound (Table 6 and Table 7). In the finalised OLP, the mean (±SD) total duration of study medication interruptions in treating the target wound was low (2.7±12.61 days), as was the mean (±SD) number of days of duration of treatment interruption due to AEs (0.9±6.07 days). There was negligible effect of AEs in relation to compliance with treating the target wound.

**Table 6 Extent of Exposure, Phase 3 Study BEB-13 in EB; DBP (Safety Analysis Set)**

| | | **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 |

| | | **Oleogel-S10 N=109 n (%)** | **Control Gel N=114 n (%)** | **All Subjects N=223 n (%)** |
|---|---|---|---|---|
| Actual treatment duration in relation to AEs [days] [b, c,e] | n | 109 | 114 | 223 |
| | Mean (SD) | 89.0 (18.34) | 86.4 (23.82) | 87.7 (21.31) |
| | Min | 2 | 2 | 2 |
| | Median | 91.0 | 91.0 | 91.0 |
| | Max | 140 | 161 | 161 |
| Treatment compliance overall [%][b,f] | n | 109 | 114 | 223 |
| | Mean (SD) | 99.08 (9.578) | 98.67 (9.926) | 98.87 (9.738) |
| | Min | 0.0 | 0.0 | 0.0 |
| | Median | 100.00 | 100.00 | 100.00 |
| | Max | 100.0 | 100.0 | 100.0 |

Abbreviations: AE=adverse event; eCRF=electronic case report form; Max=maximum; Min=minimum; N=number of subjects in specific group, n=number of subjects in the analysis; SD=standard deviation.
[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].
[e]Actual treatment duration in relation to AEs [days]=Treatment duration [days] - Total duration of Interruptions due to AEs [days].
[f]Treatment compliance overall [%]=Actual treatment duration overall / Treatment duration * 100.

**Table 7 Extent of Exposure for Subjects in the OLP of BEB-13 (Safety Analysis Set)**

| | | Former Oleogel-S10 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) |

| | | Former Oleogel-S10 N=100 n (%) | Former Control Gel N=105 n (%) | All Subjects N=205 n (%) |
|---|---|---|---|---|
| | 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 |
| Actual treatment duration in relation to AEs [days][b,e] | n | 100 | 105 | 205 |
| | Mean (SD) | 594.0 (235.68) | 574.0 (257.98) | 583.8 (246.95) |
| | Min | 14 | 7 | 7 |
| | Median | 725.0 | 727.0 | 726.0 |
| | Max | 841 | 840 | 841 |
| Treatment compliance overall [%][b,f] | n | 100 | 105 | 205 |
| | Mean (SD) | 99.51 (2.573) | 98.86 (4.966) | 99.18 (3.986) |
| | Min | 82.9 | 59.9 | 59.9 |
| | Median | 100.00 | 100.00 | 100.00 |
| | Max | 100.0 | 100.0 | 100.0 |

Abbreviations: AE=adverse event; eCRF=electronic case report form; Max=maximum; Min=minimum; N=number of subjects in specific group, n=number of subjects in the analysis; OLP=open-label phase; SD=standard deviation.

a Treatment duration [days]=Treatment end date - Treatment start date +1.

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].

e Actual treatment duration in relation to AEs [days]=Treatment duration [days] - Total duration of interruptions due to AEs [days].

f Treatment compliance overall [%]=Actual treatment duration overall / Treatment duration * 100.

A post hoc analysis of study medication usage (number of tubes used) showed that over the course of the study (both DBP and OLP, for subjects with available data [n=214]), the median number of tubes used was 381.0, and the median number of tubes used per month was 18.59. (Note that the overall study phase data only considered exposure to Oleogel-S10, that is, the Oleogel-S10 group in the DBP and OLP and the former control gel group in the OLP. In addition, the dressing change frequency of at least every 4 days as per the protocol). Study medication usage (number of tubes used) is summarized by age group in BEB-13 CSR Addendum [Post hoc Table 14.1.5.24].

During the OLP, the median total number of tubes used was 419.5 in the age group 0 - <4 years (n=16, with 14 subjects having available data); the median number of tubes used per month during the OLP was 20.43. In the age group 4 - <12 years, the median total number of tubes used during the OLP was 358.0 (n=81, with 68 subjects having available data); the median number of tubes per month in this age group during the OLP was 16.29. In the age group 12 - <18 years, the median total number of tubes used during the OLP was 407.5 (n=50, with 40 subjects having available data); the median number of tubes per month in this age group during the OLP was 21.14. In the age group ≥18 years, the median total number of tubes used during the OLP was 360.0 (n=58, with 51 subjects having available data); the median number of tubes per month in this age group during the OLP was 17.11.

**Concomitant treatments**

In the Safety Analysis Set of BEB-13 DBP, 201 (90.1%) subjects took at least one concomitant medication during the DBP, including over-the-counter medications and dietary supplements. The most common medications in the Anatomical Therapeutic Chemical (ATC 1) classification level 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%).

Concomitant medication use in the OLP was similar to that in the DBP. The most common medications in the ATC 1 classification level were taken for conditions of the alimentary tract and metabolism (62.9%), blood and blood-forming organs (57.6%), respiratory system (54.1%), nervous system (53.2%), the skin (i.e., dermatologicals) (47.3%), and anti-infectives for systemic use (47.3%).

**Betulin exposure**

In the OLP, there were low betulin concentrations observed at Month 24, but as reported for the DBP, the majority of samples were below the lower limit of quantification (i.e., 10 ng/mL). Data from the venous blood samples indicate that betulin can be absorbed systemically following topical administration of Oleogel-S10. However, betulin systemic exposure was very low, similar to concentrations observed following ingestion of betulin-containing foods, and thus are unlikely to result in systemic AEs. Based on the final OLP betulin concentration data, there is no impact on these earlier conclusions.

AEs with a temporal relationship to betulin levels above 70 ng/ml (the maximum value seen in previous clinical studies) within 4 weeks, did not retrieve any new potential signal. The type and frequency of reported AEs in these subjects (n=13) was consistent with the overall safety profile of the study drug

**Frequency of Dressing Change**

A post hoc review of all subjects showed that a higher proportion of Oleogel-S10 subjects (21.1%) had a reduction in the frequency of dressing changes at the end of the DBP in comparison to control gel subjects (10.5%). The reduction in dressing changes noted in the post hoc analyses of the DBP data continued into the OLP. During the OLP, results between former treatment groups in dressing change frequency or the use of different dressings on non-target wounds were generally similar; however, more subjects in the former Oleogel-S10 group changed dressings every 2 days (range: 34-46%) than subjects in the former control gel group (29-35%), whereas more subjects in the former control gel group changed daily (37-47%) as compared with subjects in the former Oleogel-S10 group (24-34%).

***CHMP comment***

The demographics and baseline characteristics of the OLP population were similar to those of the overall study population that participated in the DBP. At baseline of the OLP, the overall median age of subjects was 12 years (range: 6 months to 81 years), and the highest number of subjects were in the 4 to <12-year-old range (39.5%). A total of 126 (61.5%) subjects were male and 79 (38.5%) were female. Most (82.4%) subjects were White. A total of 178 (86.8%) subjects had the EB subtype of DEB; of these, 160 (78.0%) subjects had RDEB and 18 (8.8%) subjects had DDEB. Twenty-five (12.2%) subjects had JEB, and 2 (1.0%) subjects had EBS and were enrolled before subjects with EBS were excluded from study participation (protocol Version 4.0).

It is agreed that betulin systemic exposure was low, similar to concentrations observed following ingestion of betulin-containing foods, the majority of samples below the lower limit of quantification, and thus are unlikely to result in systemic AEs.

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 month follow-up study in a severe disease.

In the SCS, the MAH has presented that the extent of exposure for patients in the OLP was in median duration 727 days and maximum duration 841 days. In the DPB, the Oleogel-S10 exposure was in median duration 91 days and maximum duration 140 days. In the updated SmPC section 5.1, the median duration of Filsuvez treatment for all patients in the DBP and OLP have been combined and updated from 695 to 733 days and the maximum duration of treatment from of 924 days to 931 days. The MAH is requested to present the data and calculations supporting this change. **(OC)**

In addition, the median number of tubes used per month introduced in the SmPC section 5.1 has not been clearly presented in the SCS. The applicant refers to BEB-13 CSR Addendum Post hoc Table 14.1.5.24. The MAH is requested to present the data from the DBP and the OLP combined (preferably in one table) and the calculations for the data to be included in SmPC section 5.1. **(OC)** This is also requested for the median daily extent of exposure and median cumulative extent of exposure (grams). **(OC)**

Concomitant treatments are common in EB patients. Since Filsuvez is considered a locally applied, locally acting product with limited systemic absorption, no systemic drug-drug interactions are expected. In SmPC section 4.5 the recommendation is that other topical products should not be concomitantly used together but rather sequentially or alternatively depending on the clinical need.

## 7.2.2. Adverse events

The safety analyses are based on the Safety Analysis Set, defined as all subjects treated at least once with study medication.

Treatment-emergent AEs were defined by the MAH as AEs that occurred from the first study treatment to 4 weeks after the last study treatment and did not necessarily have a causal relationship to the use of the study medication. Treatment-emergent AEs are simply referred to as AEs.

Of the 205 subjects who have participated in the OLP (all of whom received Oleogel-S10), a total of 158 (77.1%) subjects have reported at least 1 AE as of the final database lock (01 July 2022). The most frequently reported AEs (≥5% of all subjects) were wound complication, anemia, wound infection, wound infection staphylococcal, pyrexia, esophageal stenosis, wound infection bacterial, pruritus, and dysphagia. These conditions are all consistent with the course of the disease. Wound complication was the most frequently reported treatment-related AE (6.8%).

A total of 9 subjects (4.4%) died during the OLP. The deaths were considered consistent with the course of the disease and none of the deaths were considered related to study treatment.

Fifty of the 205 subjects (24.4%) have reported a total of 116 serious AEs (SAEs) in the OLP. Two subjects had SAEs considered by the investigator to be related to the study medication.

A total of 16 subjects (7.8%) were withdrawn from the OLP because of AEs. These include 3 subjects who had treatment-related AEs leading to study withdrawal (administration site pain, staphylococcal wound infection, and the SAE of rash). A total of 16 (7.8%) subjects had AEs leading to study withdrawal during the OLP: 9/100 subjects (9.0%) in the former Oleogel-S10 group and 7/105 subjects (6.7%) in the former control gel group. Of these events, 3 were considered by the investigator to be related to the study medication: wound infection staphylococcal, rash, and administration site pain.

Adverse events leading to study withdrawal reported for more than 1 subject each were Squamous cell carcinoma (SCC) of the skin (2 subjects), pneumonia (2 subjects), and staphylococcal wound infection (2 subjects); all others were reported for 1 subject each.

**Table 8 Overall Summary of Adverse Events, Phase 3 BEB-13 Study in EB; Open-Label Phase (Safety Analysis Set)**

| | **Former Oleogel-S10 (N=100) n (%) E** | **Former Control Gel (N=105) n (%) E** | **All Subjects (N=205) n (%) E** | ***All Subjects (N=205) 21 April 2021 n (%) E*** |
|---|---|---|---|---|
| Any AEs | 77 (77.0) 398 | 81 (77.1) 435 | 158 (77.1) 833 | *145 (70.7) 687* |
| Any serious AEs | 26 (26.0) 70 | 24 (22.9) 46 | 50 (24.4) 116 | *44 (21.5) 85* |
| Any severe AEs | 19 (19.0) 55 | 18 (17.1) 36 | 37 (18.0) 91 | *28 (13.7) 58* |
| Any related AEs | 8 (8.0) 21 | 17 (16.2) 41 | 25 (12.2) 62 | *26 (12.7) 63* |
| Any serious related AEs | 1 (1.0) 1 | 1 (1.0) 1 | 2 (1.0) 2 | *2 (1.0) 2* |
| Any AEs leading to study withdrawal | 9 (9.0) 9 | 7 (6.7) 7 | 16 (7.8) 16 | *14 (6.8) 14* |
| Any related AEs leading to study withdrawal | 0 | 3 (2.9) 3 | 3 (1.5) 3 | *3 (1.5) 3* |
| Any serious AEs leading to study withdrawal | 9 (9.0) 9 | 3 (2.9) 3 | 12 (5.9) 12 | *10 (4.9) 10* |
| Any serious related AEs leading to study withdrawal | 0 | 1 (1.0) 1 | 1 (0.5) 1 | *1 (0.5) 1* |
| Any serious AEs leading to death | 7 (7.0) 7 | 1 (1.0) 1 | 8 (3.9) 8 | *5 (2.4) 5* |
| Any AEs due to wound complications[a] | 38 (38.0) 43 | 46 (43.8) 64 | 84 (41.0) 107 | *81 (39.5) 103* |
| Any AEs leading to drug withdrawal | 9 (9.0) 9 | 7 (6.7) 7 | 16 (7.8) 16 | *13 (6.3) 13* |

Abbreviations: AE=adverse event; DBP=double-blind phase; 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.

[a] Refers to any AEs with PT or LLT "wound complication." Wound complication encompasses the following events: (1) increase in wound size compared to baseline (i.e., baseline of DBP), (2) wound reopening, (3) increase in wound size compared to the previous visit, (4) other (which included increase in wound burden, worsening of EB wound pain, and wound odor), (5) injury to the wound, and (6) wound worsening compared to baseline (i.e., baseline of DBP). 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.

The MAH concludes from the AEs reported during the OLP in subjects receiving Oleogel-S10 in the DBP and OLP of the study (i.e., representing longer-term exposure to Oleogel-S10), that no apparent increase in the type or severity of any treatment-related AE has been observed. In the OLP, 24.4% of subjects reported at least 1 SAE; however, only 2 subjects had an SAE (rash in 1 subject and wound infection in the other subject) considered by the investigator to be related to Oleogel-S10; the rash was the only treatment-related SAE that led to withdrawal from the OLP.

**AEs and dose-response information**

Adverse events by total quantity of product used show, as in the DBP, that the most frequently reported AE during the OLP for both former treatment groups and for all product quantity tertiles was wound complication. The incidence of wound complication was 38.3% (18/47 subjects) in the 1st tertile, 38.3% (18/47 subjects) in the 2nd tertile, and 39.1% (18/46 subjects) in the 3rd tertile. According to the MAH, final data from the longer-term use of Oleogel-S10 in the OLP showed no clinically meaningful change in the frequency of AEs with an increase in product quantity applied, including AEs of wound complication.

During the OLP, SAEs were reported for 9 of 47 subjects in the 1st tertile (19.1%), 14 of 47 subjects in the 2nd tertile (29.8%), and 10 of 46 subjects in the 3rd tertile (21.7%). The following SAEs were reported in more than 1 subject each in any tertile category:

- esophageal stenosis – 4 subjects in the 1st tertile; 2 subjects in the 2nd tertile; 2 subjects in the 3rd tertile
- malnutrition – 2 subjects in the 1st tertile
- septic shock – 2 subjects in the 2nd tertile
- anemia – 3 subjects in the 3rd tertile

Subjects in the 3rd tertile most likely had higher wound burden and therefore required more quantity of product. Anemia, malnutrition (including vitamin D deficiency), and susceptibility to infections (such as wound infections) are more pronounced in subjects with more severe disease, such as RDEB with a high wound burden [Reimer 2020].

Of note, subjects in the OLP who had used more Oleogel-S10 at the time of the final data cut off would likely be subjects who had been treated in the OLP for the longest duration and/or had more extensive skin involvement due to severity of their EB. With a longer period of time in the study, there is a greater chance of occurrence and reporting of any AE, and esophageal stenosis is known to occur in subjects with EB, particularly those with RDEB, due to repeated blistering and scarring of the esophagus, ultimately followed by stenosis [Pope 2020].

**Frequently Reported AEs**

The most frequently reported AEs (≥5% of all 205 subjects) were wound complication (41.0%), 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 are all consistent with the course of the disease.

With regard to treatment-related AEs during the OLP in subjects who had previously received Oleogel-S10 in the DBP of the study (i.e., representing longer-term exposure to the drug), in the final data there was no apparent increase in the type or severity of any treatment-related AEs.

**Table 9 Summary of Adverse Events by System Organ Class and Preferred Term with an Incidence ≥2% of Subjects Overall, Phase 3 BEB-13 Study in EB; Open-Label Phase (Safety Analysis Set)**

| | **Former Oleogel-S10 (N=100) n (%) E** | **Former Control Gel (N=105) n (%) E** | **All Subjects (N=205) n (%) E** | ***All Subjects (N=205) 21 April 2021 n (%) E*** |
|---|---|---|---|---|
| Any AEs | 77 (77.0) 398 | 81 (77.1) 435 | 158 (77.1) 833 | *145 (70.7) 687* |
| Injury, poisoning and procedural complications | 45 (45.0) 59 | 51 (48.6) 77 | 96 (46.8) 136 | *91 (44.4) 128* |
| Wound complication[a] | 38 (38.0) 43 | 46 (43.8) 64 | 84 (41.0) 107 | *81 (39.5) 103* |
| Wound secretion | 2 (2.0) 2 | 2 (1.9) 2 | 4 (2.0) 4 | *4 (2.0) 4* |
| Infections and infestations | 36 (36.0) 110 | 44 (41.9) 118 | 80 (39.0) 228 | *68 (33.2) 188* |
| Wound infection | 6 (6.0) 12 | 15 (14.3) 26 | 21 (10.2) 38 | *19 (9.3) 33* |
| Wound infection staphylococcal | 9 (9.0) 14 | 12 (11.4) 15 | 21 (10.2) 29 | *20 (9.8) 26* |
| Wound infection bacterial | 7 (7.0) 10 | 9 (8.6) 14 | 16 (7.8) 24 | *12 (5.9) 19* |
| Skin infection | 3 (3.0) 5 | 4 (3.8) 6 | 7 (3.4) 11 | *5 (2.4) 9* |
| Influenza | 1 (1.0) 4 | 4 (3.8) 4 | 5 (2.4) 8 | - |
| Upper respiratory tract infection | 2 (2.0) 2 | 3 (2.9) 3 | 5 (2.4) 5 | - |
| Conjunctivitis | 3 (3.0) 4 | 1 (1.0) 1 | 4 (2.0) 5 | - |
| Nasopharyngitis | 3 (3.0) 3 | 1 (1.0) 2 | 4 (2.0) 5 | *4 (2.0) 5* |
| Otitis externa | 2 (2.0) 3 | 2 (1.9) 2 | 4 (2.0) 5 | *4 (2.0) 5* |
| Pneumonia | 3 (3.0) 3 | 1 (1.0) 1 | 4 (2.0) 4 | - |
| Wound infection pseudomonas | 3 (3.0) 3 | 1 (1.0) 5 | 4 (2.0) 8 | - |
| Gastrointestinal disorders | 22 (22.0) 63 | 29 (27.6) 55 | 51 (24.9) 118 | *43 (21.0) 95* |
| Oesophageal stenosis | 8 (8.0) 16 | 11 (10.5) 14 | 19 (9.3) 30 | *18 (8.8) 26* |
| Dysphagia | 6 (6.0) 8 | 7 (6.7) 9 | 13 (6.3) 17 | *9 (4.4) 12* |
| Diarrhoea | 3 (3.0) 3 | 6 (5.7) 9 | 9 (4.4) 12 | *8 (3.9) 10* |
| Toothache | 4 (4.0) 5 | 1 (1.0) 1 | 5 (2.4) 6 | *5 (2.4) 6* |
| Vomiting | 3 (3.0) 4 | 2 (1.9) 2 | 5 (2.4) 6 | *5 (2.4) 6* |
| Blood and lymphatic system disorders | 16 (16.0) 27 | 24 (22.9) 37 | 40 (19.5) 64 | *30 (14.6) 45* |
| Anaemia | 16 (16.0) 24 | 21 (20.0) 30 | 37 (18.0) 54 | *29 (14.1) 39* |
| General disorders and administration site conditions | 17 (17.0) 25 | 16 (15.2) 26 | 33 (16.1) 51 | *30 (14.6) 45* |

| | Former Oleogel-S10 (N=100) n (%) E | Former Control Gel (N=105) n (%) E | All Subjects (N=205) n (%) E | *All Subjects (N=205) 21 April 2021 n (%) E* |
|---|---|---|---|---|
| Pyrexia | 10 (10.0) 13 | 10 (9.5) 15 | 20 (9.8) 28 | *17 (8.3) 24* |
| Asthenia | 2 (2.0) 3 | 2 (1.9) 3 | 4 (2.0) 6 | - |
| Skin and subcutaneous tissue disorders | 11 (11.0) 12 | 20 (19.0) 34 | 31 (15.1) 46 | *26 (12.7) 40* |
| Pruritus | 5 (5.0) 5 | 9 (8.6) 13 | 14 (6.8) 18 | *12 (5.9) 16* |
| Blister | 0 | 4 (3.8) 4 | 4 (2.0) 4 | - |
| Metabolism and nutrition disorders | 11 (11.0) 22 | 14 (13.3) 23 | 25 (12.2) 45 | *19 (9.3) 35* |
| Hypoalbuminaemia | 5 (5.0) 8 | 5 (4.8) 5 | 10 (4.9) 13 | *7 (3.4) 10* |
| Vitamin D deficiency | 4 (4.0) 4 | 6 (5.7) 6 | 10 (4.9) 10 | *7 (3.4) 7* |
| Malnutrition | 2 (2.0) 3 | 3 (2.9) 3 | 5 (2.4) 6 | *4 (2.0) 5* |
| Eye disorders | 10 (10.0) 13 | 7 (6.7) 17 | 17 (8.3) 30 | *14 (6.8) 25* |
| Ulcerative keratitis | 3 (3.0) 3 | 2 (1.9) 10 | 5 (2.4) 13 | *4 (2.0) 12* |
| Congenital, familial and genetic disorders | 4 (4.0) 4 | 4 (3.8) 4 | 8 (3.9) 8 | *7 (3.4) 7* |
| Syndactyly | 2 (2.0) 2 | 2 (1.9) 2 | 4 (2.0) 4 | *4 (2.0) 4* |
| Hepatobiliary disorders[b] | 4 (4.0) 4 | 2 (1.9) 2 | 6 (2.9) 6 | - |
| Hepatic function abnormal[b] | 3 (3.0) 3 | 2 (1.9) 2 | 5 (2.4) 5 | - |

Abbreviations: AE=adverse event; DBP=double-blind phase; E=number of events; EB=epidermolysis bullosa; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects in specific group; n=number of subjects.

[a] Refers to any AEs with Preferred Term (PT) or Lowest Level Term (LLT) "wound complication." Wound complication encompasses the following events: (1) increase in wound size compared to baseline (i.e., baseline of DBP), (2) wound reopening, (3) increase in wound size compared to the previous visit, (4) other (which included increase in wound burden, worsening of EB wound pain, and wound odor), (5) injury to the wound, and (6) wound worsening compared to baseline (i.e., baseline of DBP). Please note there are other AEs involving wounds (e.g., wound haemorrhage, wound secretion) but with a different PT/LLT.

[b] Note that this System Organ Class (SOC) and PT of "hepatic function abnormal" were newly added as a result of up-coding of AEs to MedDRA version 25.0. Previously, these events were under the Investigations SOC.

Note: Calculation of percentages is based on N.

**AEs related to Wound complications**

The overall incidence of wound complication-related AEs in the OLP was 41.0% (84/205 subjects, 107 events). Incidences of AEs related to wound complication were lower in the OLP compared with subjects who received Oleogel-S10 in the DBP (67 of 109 subjects, 61.5%).

In the finalised OLP of BEB-13, wound complication increased from 38% to 41% with a decrease from 7.3% to 6.8% considered as treatment-related.

**Table 10 Summary of Adverse Events Related to Wound Complications, Phase 3 BEB-13 Study in EB; Open-Label Phase (Safety Analysis Set)**

| | **Former Oleogel-S10 (N=100) n (%) E** | **Former Control Gel (N=105) n (%) E** | **All Subjects (N=205) n (%) E** | ***All Subjects N=205 n (%) E DLP 21 April 2021*** |
|---|---|---|---|---|
| Subjects with at least one AE with PT/LLT "wound complication" | 38 (38.0) 43 | 46 (43.8) 64 | 84 (41.0) 107 | *81 (39.5) 103* |
| Wound reopening | 19 (19.0) 20 | 21 (20.0) 25 | 40 (19.5) 45 | *40 (19.5) 45* |
| Increase in wound size compared to baseline | 12 (12.0) 12 | 17 (16.2) 17 | 29 (14.1) 29 | *30 (14.6) 30* |
| Other[a] | 5 (5.0) 6 | 8 (7.6) 10 | 13 (6.3) 16 | *9 (4.4) 11* |
| Increase in wound size compared to the previous visit | 3 (3.0) 3 | 9 (8.6) 9 | 12 (5.9) 12 | *12 (5.9) 12* |
| Wound worsening compared to baseline | 2 (2.0) 2 | 2 (1.9) 2 | 4 (2.0) 4 | *4 (2.0) 4* |
| Injury to the wound | 0 | 1 (1.0) 1 | 1 (0.5) 1 | *1 (0.5) 1* |

Abbreviations: 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; PT=Preferred Term.
Note: Refers to any AEs with PT or LLT of "wound complication." Please note there are other AEs involving wounds (e.g., wound haemorrhage, wound pain) but with a different PT/LLT.
Note: Calculation of percentages is based on N.
[a] "Other" events included increase in wound burden, worsening of EB wound pain, and wound odor.

**AEs related to Wound infections**

As wound infections contribute to morbidity, mortality, and the need for antibiotic therapy in EB patients, 2 of the key secondary efficacy endpoints in the DBP of BEB-13 assessed the incidence and severity of target wound infections. Collection of wound infection data for these efficacy endpoints was performed differently than for the safety analyses. For the efficacy analyses, both AEs of the MedDRA PT 'wound infection' and the use of topical and/or systemic antibiotics (related to wound infection) were collected.

In the OLP, a total of 4 former Oleogel-S10 subjects (4.0%) and 5 former control gel subjects (4.4%) experienced target wound infections. Of the infections evidenced by a PT of 'wound infection' in the former Oleogel-S10 subjects, 2 infections were mild and 2 were severe; in the former control gel subjects, all 3 of these infections were moderate. The remaining 2 former control gel subjects experienced wound infections as evidenced by the use of topical and/or systemic antibiotics which were not graded by severity.

In total during the OLP, 18 (18.0%) former Oleogel-S10 subjects and 29 (27.6%) former control gel subjects experienced infection of an 'other' wound as evidenced by either a PT of 'wound infection' (16 and 23, respectively) or by the use of topical and/or systemic antibiotics (2 and 6, respectively). Overall, results of the OLP were similar to those of the Oleogel-S10 group in the DBP; the overall proportion of infections was higher in other wounds than in target or additional wounds (22.9% in other wounds vs. 4.4% in target wounds and 2.4% in additional wounds). However, this is not unexpected as the probability of an infection in an 'other' wound was much higher than for target and additional wounds based on the larger BSAP affected by 'other' wounds.

From AE perspective, in the OLP, the incidences of wound infection AEs were 10.2% for the PT of wound infection, 10.2% for wound infection staphylococcal, and 7.8% for wound infection bacterial. Two subjects

in the OLP had wound infection events (wound infection staphylococcal in both) that led to study withdrawal; one of these events was considered by the investigator to be related to the study medication.

**AEs related to Hypersensitivity**

Hypersensitivity symptoms have been reported in subjects applying Oleogel-S10 in the pivotal clinical study in EB (BEB-13 DBP and OLP: n=12 of 223 subjects [5.4%]) and in subjects in the supportive clinical studies in partial-thickness wounds (2 of 425 subjects [0.5%]). Twelve subjects exposed to Oleogel-S10 during the DBP or OLP of BEB-13 experienced a total of 16 AEs that coded to the narrow Hypersensitivity SMQ (i.e., anaphylactic reaction, hypersensitivity, eczema, contact dermatitis, atopic dermatitis, rash, dermatitis, urticaria, allergic cough, and bronchospasm). All but 2 of the 16 events were grade 1 or grade 2 in severity; 2 events were grade 3 (rash, anaphylactic reaction). One event (grade 3 rash) was classified as serious; this was also the only hypersensitivity event that led to study discontinuation. A total of 4 AEs that coded to the Hypersensitivity SMQ were considered by the investigator to be probably/possibly related to Oleogel-S10. These events were urticaria (1 subject), rash (2 subjects), and eczema (1 subject).

**AEs related to Haemorrhage**

A total of 23 AEs in 15 subjects exposed to Oleogel-S10 were coded to terms included in the narrow haemorrhage terms (excluding laboratory terms) SMQ. These events included 5 events of epistaxis (3 subjects); 3 events of rectal haemorrhage (3 subjects); 3 events of haematuria (2 subjects); 3 events of wound haemorrhage (2 subjects); 2 events of hematemesis (2 subjects); 2 events of haematochezia (2 subjects); 1 event of blood urine present (1 subject); 1 event of gastrointestinal haemorrhage (1 subject); 1 event of blood loss anaemia (1 subject); 1 event of hemoperitoneum (1 subject) and 1 event of heavy menstrual bleeding (1 subject). All but 4 of the 23 events were grade 1 or grade 2 in severity; 2 events were grade 3 (wound haemorrhage, hemoperitoneum), and 2 events were grade 4 (blood loss anaemia, gastrointestinal haemorrhage). Only 1 subject showed any worsening in severity; a subject who experienced wound haemorrhage initially had a grade 1 event that worsened to grade 3.

Eight events were classified as serious (2 rectal haemorrhage [grade 1, 2], wound haemorrhage [grade 3], haematuria [grade 2], blood loss anaemia [grade 4], gastrointestinal haemorrhage [grade 4], hemoperitoneum [grade 3], and hematemesis [grade 2]), although one of the events (haematuria) was declassified to nonserious on second occurrence.

Of the 23 AEs that coded to the narrow standard SMQ of haemorrhage terms (excluding laboratory terms), only 2 were considered to be related to study medication (2 events of wound haemorrhage in the same subject, one of which was an SAE); this was also the only haemorrhage event that led to study discontinuation (in the DBP). This was also the only haemorrhage event that worsened in intensity (from Grade 1 to Grade 3). The event of worsening wound haemorrhage could be explained in the context of underlying disease.

**AEs related to Anaemia**

The major hematologic comorbidity in EB patients is anemia. Anemia is present from the second year of life onwards in the majority of patients with RDEB and JEB [Reimer 2020]. During the DBP of BEB-13, the incidence of the PT of anemia (any grade) and severe anemia was higher in the Oleogel-S10 group compared to the control gel group (any grade: 7.3% vs. 3.5%; Grade 3: 4.6% vs. 0%). At the final database lock, an analysis of anemia-related AEs showed that 70 anemia-related PTs (i.e., anemia, iron deficiency anemia, Coombs positive hemolytic anemia) were reported in 45 subjects exposed to Oleogel-S10 during the DBP or OLP. These included 64 events of anemia in 42 subjects, 4 events of iron deficiency anemia in 3 subjects, and 1 event of blood loss anemia and 1 event of Coombs positive hemolytic anemia in 1 subject (who also experienced several events of anemia). All of these anemia-related AEs were considered unlikely related to the study medication by both the investigator and the

Applicant. Nineteen events in 12 subjects were classified as SAEs. Most of the subjects who had an anemia-related AE had low hemoglobin levels at baseline and/or anemia documented in their medical history. Of note, most PTs of anemia reported in subjects treated with Oleogel-S10 in the DBP or OLP occurred in subjects from South America (45 subjects reported anemia of which 29 were South American [64.4%]), where anemia is a public health issue [Vázquez 2019].

**AEs related to Application/Administration Site Reaction**

In the OLP, the incidence of such events was 2.0% in the Oleogel-S10 group and 2.9% in the former control gel group.

***CHMP comment***

Final safety data for the 205 subjects who have participated in the OLP of BEB-13 (final database lock date of 01 July 2022) has been presented in the Clinical Overview and in the Summary of Clinical Safety (SCS).

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. However, the reason for changing the frequency of wound complication from 11.6% to 11.2% in EB patients in SmPC section 4.8 is not clearly presented. Therefore, the MAH is requested to provide further information on the data and calculations supporting this change. **(OC)**

Two reports of wound haemorrhage were reported (in the same subject), one of which was a serious reaction. Both were assessed as related to study medication. The SAE resulted in discontinuation from the study. Consideration should be given to including wound haemorrhage in the description of selected events paragraph detailing wound complications in SmPC section 4.8. **(OC)**

## 7.2.3. Serious adverse event/deaths/other significant events

A total of 9 subjects (4.4%) died during the OLP: 7 (7.0%) subjects in the former Oleogel-S10 group and 2 (1.9%) subjects in the former control gel group. One of these subjects died due to a non-treatment-emergent AE of sepsis with an onset date >30 days (45 days) after last date of study medication administration. None of the deaths were considered related to study treatment, and all were anticipated with regards to disease course.

**Table 11 Deaths in BEB-13 Study**

| (EB Sub-type) | Age (yrs)/ Sex | Cause of Death Investigator Term (MedDRA PT or CTCAE Term) | Study Day of Adverse Event Onset | Study Day of Last Treatment | Study Day of Death | Relation-ship to Study Drug |
|---|---|---|---|---|---|---|
| **BEB-13, Epidermolysis Bullosa**[a] | | | | | | |
| (RDEB) | 15/M | EB progression (disease progression) | OLP Day 30 | OLP Day 30 | OLP Day 30 | Unlikely |
| (RDEB) | 10/F | sepsis (sepsis) | OLP Day 269 | OLP Day 269 | OLP Day 271 | Unlikely |
| (RDEB) | 11/M | heart failure (cardiac failure) | OLP Day 251 | OLP Day 250 | OLP Day 290 | Unlikely |

| (EB Sub-type) | Age (yrs)/ Sex | Cause of Death Investigator Term (MedDRA PT or CTCAE Term) | Study Day of Adverse Event Onset | Study Day of Last Treatment | Study Day of Death | Relation-ship to Study Drug |
|---|---|---|---|---|---|---|
| (RDEB) | 18/F | acute renal failure (acute kidney injury) | OLP Day 102 | OLP Day 101 | OLP Day 118 | Unlikely |
| (RDEB) | 52/F | pneumonia (pneumonia) | OLP Day 92 | OLP Day 91 | OLP Day 93 | Unlikely |
| (JEB) | 6 months / F | sepsis (sepsis) | 45 days after study withdrawal | OLP Day 90 (treatment/study with-drawal) | 45 days after study with-drawal | Unlikely |
| (RDEB) | 10/F | cardiorespiratory arrest (cardiorespiratory arrest) | 29 days after End of Study | OLP Day 729 | 29 days after End of Study | Unlikely |
| (RDEB) | 35/M | intestinal ischemia (intestinal ischaemia) | OLP Day 729 | OLP Day 722 | OLP Day 734 | Unlikely |
| (RDEB) | 14/M | severe pneumonia (pneumonia) | OLP Day 665 | OLP Day 663 | OLP Day 667 | Unlikely |

Abbreviations: EB=epidermolysis bullosa; F=female; JEB=junctional epidermolysis bullosa; M=male; MedDRA=Medical Dictionary for Regulatory Activities; RDEB=recessive dystrophic epidermolysis bullosa; PT=Preferred Term.
[a]EB subtypes are noted in parentheses under the subject ID number.

50 of the 205 subjects (24.4%) reported a total of 116 serious adverse events (SAEs) in the OLP. Two subjects had SAEs considered by the investigator to be related to the study medication. 2 subjects had an SAE (rash in 1 subject and wound infection in the other subject) that was considered related to Oleogel-S10; the rash was the only treatment-related SAE that led to withdrawal from the OLP. Three subjects had SAEs of Squamous cell carcinoma (SCC), none of which were considered to be drug-related by the investigator.

**Table 12 Summary of Serious Adverse Events by System Organ Class and Preferred Term Reported for ≥2 Subjects Overall, Phase 3 BEB-13 Study in EB; Open-Label Phase (Safety Analysis Set)**

| | Former Oleogel-S10 (N=100) n (%) E | Former Control Gel (N=105) n (%) E | All Subjects (N=205) n (%) E | *All Subjects N=205 n (%) E DLP 21 April 2021* |
|---|---|---|---|---|
| Subjects with at least one SAE | 26 (26.0) 70 | 24 (22.9) 46 | 50 (24.4) 116 | *44 (21.5) 85* |
| Infections and infestations | 13 (13.0) 23 | 9 (8.6) 14 | 22 (10.7) 37 | *18 (8.8) 26* |
| Septic shock | 2 (2.0) 2 | 1 (1.0) 2 | 3 (1.5) 4 | - |
| Wound infection | 1 (1.0) 1 | 2 (1.9) 3 | 3 (1.5) 4 | *3 (1.5) 4* |
| Bacteraemia | 2 (2.0) 2 | 0 | 2 (1.0) 2 | *2 (1.0) 2* |

| | Former Oleogel-S10 (N=100) n (%) E | Former Control Gel (N=105) n (%) E | All Subjects (N=205) n (%) E | *All Subjects N=205 n (%) E DLP 21 April 2021* |
|---|---|---|---|---|
| COVID-19 | 2 (2.0) 2 | 0 | 2 (1.0) 2 | - |
| Pneumonia | 1 (1.0) 1 | 1 (1.0) 1 | 2 (1.0) 2 | - |
| Gastrointestinal disorders | 8 (8.0) 18 | 10 (9.5) 12 | 18 (8.8) 30 | *15 (7.3) 23* |
| Oesophageal stenosis | 4 (4.0) 9 | 6 (5.7) 6 | 10 (4.9) 15 | *9 (4.4) 14* |
| Dysphagia | 1 (1.0) 1 | 1 (1.0) 1 | 2 (1.0) 2 | - |
| Rectal haemorrhage | 0 | 2 (1.9) 2 | 2 (1.0) 2 | - |
| Blood and lymphatic system disorders | 4 (4.0) 8 | 6 (5.7) 8 | 10 (4.9) 16 | *8 (3.9) 13* |
| Anaemia | 4 (4.0) 7 | 6 (5.7) 8 | 10 (4.9) 15 | *8 (3.9) 13* |
| Metabolism and nutrition disorders | 2 (2.0) 3 | 3 (2.9) 4 | 5 (2.4) 7 | *3 (1.5) 5* |
| Malnutrition | 1 (1.0) 1 | 2 (1.9) 2 | 3 (1.5) 3 | *2 (1.0) 2* |
| Dehydration | 1 (1.0) 1 | 1 (1.0) 1 | 2 (1.0) 2 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 3 (3.0) 3 | 0 | 3 (1.5) 3 | *3 (1.5) 3* |
| Squamous cell carcinoma of skin | 3 (3.0) 3 | 0 | 3 (1.5) 3 | *3 (1.5) 3* |
| Musculoskeletal and connective tissue disorders | 2 (2.0) 2 | 0 | 2 (1.0) 2 | *2 (1.0) 2* |
| Pseudosyndactyly | 2 (2.0) 2 | 0 | 2 (1.0) 2 | *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.

**Squamous Cell Carcinoma**

Cutaneous SCC is the most serious complication of EB, with metastatic SCC being the most common cause of death during adulthood in RDEB patients. The incidence of SCC increases significantly with age. Data on 2,745 consecutively enrolled patients in the National Epidermolysis Bullosa Registry from September 1986 through April 2002 have shown that the cumulative risk of a first SCC is highest in patients with generalized severe RDEB, with 80.2% developing a first SCC by age 45 and 90.1% by age 55 [Fine 2009]. In BEB-13, 4 subjects had an AE of SCC; all were adult subjects (20-49 years) with generalized severe (3) or generalized intermediate (1) RDEB. All 4 events of SCC were SAEs and were considered by the investigator to be unlikely related to study medication. Two SCC lesions had not been treated with Oleogel-S10 and thus were considered not related to study medication by the Applicant. The other 2 cases of SCC, which occurred in subjects 46 and 49 years of age, had Oleogel-S10 applied to the area prior to the SCC diagnosis; therefore, these 2 events were considered to be possibly related to Oleogel-S10 based on the temporal relationship to study treatment. This causality assessment of a 'possible' relationship was a conservative assessment, primarily referring to the temporal association, as there is no evidence for a cancerous proliferative effect of Oleogel-S10. Outcomes of the 4 SCC AEs were recovered (n=2), recovered with sequelae (n=1), and ongoing (n=1). Three of the 4 subjects discontinued the study due to the SCC.

***CHMP comment***

In comparison to the safety data from the OLP at the time of approval of Filsuvez, 3 additional deaths have been reported. None of these deaths were considered related to Filsuvez.

50 of the 205 subjects (24.4%) reported a total of 116 serious adverse events (SAEs) in the OLP. Only 2 patients had SAEs considered by the investigator to be related to the study medication. These 2 SAEs were included in the safety data provided already before the approval of Filsuvez.

Since the intended action of Filsuvez gel is to promote wound healing, the CHMP considered at the time of approval 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. The MAH has included additional pharmacovigilance activities in the RMP which will include both a specific skin malignancies questionnaire and a registry-based study i.e., the Filsuvez Observational Safety and Effectiveness Evaluation Registry-based study in EB (FOStER-EB) [(AEB-21)].

### 7.2.4. Laboratory findings

In the DBP and OLP of BEB-13, mean changes from baseline in haematology and biochemistry parameters from baseline to Day 90 and from Day 90/ EDBP to Month 12 and Month 24/EOLP were generally small and not clinically relevant.

During the OLP, vital signs and ECGs were only obtained at Month 24/EOLP. In subjects with available data, there were no clinically meaningful changes from EDBP to EOLP in vital signs or ECG results.

## *7.3. Discussion*

At the time of approval of Filsuvez, the BEB-13 24-months single arm open-label phase (OLP) was still ongoing and the applicant provided interim safety data with data lock point of 21 April 2021. On 21 April 2021, out of 205 patients who entered the OLP, 144 (70%) had completed the month 12 visit, and 68 patients (33%) completed the month 24 visit. The last subject last visit in the OLP was 27 May 2022 and the database lock was 01 July 2022. Thus, the final study report of BEB-13 submitted for this variation fills the gap from 21 April 2021 to 1 July 2022.

Final safety data for the 205 subjects who have participated in the OLP of BEB-13 (final database lock date of 01 July 2022) has been presented. The updated Clinical Overview and Summary of Clinical Safety (SCS) submitted for this variation includes data from the completed BEB-13 study that fills the gap from the interim data provided for the MA of Filsuvez up to 21 April 2021. Based on the results, the MAH has enclosed the updated SmPC (PI Annex I) with changes introduced in sections 4.8 and 5.1. These changes are discussed below.

In addition, the MAH took the opportunity to introduce minor change in Annex II section C on the requirements for submission of PSURs. This change is agreed.

Filsuvez is considered a locally applied, locally acting gel with limited systemic absorption. The additional data provided from the finalised OLP does not change this conclusion. 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.

In comparison to the safety data from the OLP at the time of approval of Filsuvez, 3 additional deaths have been reported. None of these deaths were considered related to Filsuvez.

50 of 205 patients (24.4%) reported a total of 116 serious adverse events (SAEs) in the finalised OLP. Only 2 patients had SAEs considered by the investigator to be related to the study medication. These 2 SAEs were included in the safety data provided already before the approval of Filsuvez.

Since the intended action of Filsuvez gel is to promote wound healing, the CHMP considered at the time of approval 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. Therefore, the MAH has included additional pharmacovigilance activities in the RMP which will include both a specific skin malignancies questionnaire and a registry-based study i.e., the Filsuvez Observational Safety and Effectiveness Evaluation Registry-based study in EB (FOStER-EB) [(AEB-21)].

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. However, the reason for changing the frequency of wound complication from 11.6% to 11.2% in EB patients in SmPC section 4.8 is not clearly presented. Therefore, the MAH is requested to provide further information on the data and calculations supporting this change. **(OC)** In addition, two reports of wound haemorrhage were reported (in the same subject), one of which was a serious reaction. Both were assessed as related to study medication. The SAE resulted in discontinuation from the study. The MAH is requested to consider if wound haemorrhage should be included in the description of selected events paragraph detailing wound complications in SmPC section 4.8. **(OC)**

There are no new safety issues from laboratory findings.

In the SCS, the MAH has presented the extent of exposure for patients in the OLP was in median duration 727 days and maximum duration 841 days. In the DPB, the Oleogel-S10 exposure was in median duration 91 days and maximum duration 140 days. In the updated SmPC section 5.1, the median durations of Filsuvez treatment for all patients in the DBP and OLP have been combined and updated from 695 to 733 days and the maximum duration of treatment from of 924 days to 931 days. The MAH is requested to present the data and calculations in support of this change. **(OC)**

In addition, the median number of tubes introduced in the SmPC section 5.1 has not been clearly presented in the SCS. The applicant refers to BEB-13 CSR Addendum Post hoc Table 14.1.5.24. The MAH is requested to present data from the DBP and the OLP combined (preferably in one table) and the following calculations for the data combined to be included in SmPC section 5.1. **(OC)** This is also requested for the median daily extent of exposure and median cumulative extent of exposure (grams). **(OC)**

Overall, the safety database of Filsuvez in JEB and DEB patients is small, however, EB is a rare designated orphan disease and the constraints in recruitment due to the rare condition is acknowledged. The demographics and baseline characteristics of the OLP population were similar to those of the overall study population that participated in the DBP. As all subgroups were small in the BEB-13 study dataset, it is agreed that the interpretation of subgroup data was limited.

In conclusion, there are no new safety issues raised from the submitted data in this variation. There are no objections to the minor change in frequency of wound complications in SmPC section 4.8 is and the exposure data in SmPC section 5.1, however, the MAH has been requested to clarify how these changes were extracted from the results of the finalised BEB-13 study, **see RSI**.

# 8. PRAC advice

Not applicable.

# 9. Changes to the Product Information

As a result of this variation, sections 4.8 and 5.1 of the SmPC are updated. No changes have been introduced in the Package Leaflet (PL).

Minor changes are made to the Annex II conditions as detailed in the recommendations section above.

Please refer to Attachment 1 which includes the Product Information.

# 10. CHMP Request for supplementary information

## *10.1. Major objections*

None.

## *10.2. Other concerns*

1. The reason for changing the frequency of wound complication from 11.6% to 11.2% in EB patients in SmPC section 4.8 has not been clearly presented. Therefore, the MAH is requested to provide further information on the data and calculations supporting this change.
2. The MAH is requested to present the BEB-13 DBP and OLP combined data and calculations in support of the changes of median duration and maximum duration in SmPC section 5.1.
3. The median number of tubes introduced in the SmPC section 5.1 has not been clearly presented in the SCS. The MAH is requested to present the data from the BEB-13 DBP and OLP combined and the calculations for the data combined to be included in SmPC section 5.1. This is also requested for the median daily extent of exposure and median cumulative extent of exposure.
4. Two reports of wound haemorrhage were reported (in the same subject), one of which was a serious reaction. Both were assessed as related to study medication. The SAE resulted in discontinuation from the study. The MAH is requested to consider if wound haemorrhage should be included in the description of selected events paragraph detailing wound complications in SmPC section 4.8.

# 11. Assessment of the responses to the CHMP request for supplementary information

## *11.1. Major objections*

None.

## *11.2. Other concerns*

## *Clinical aspects*

**Question 1**

The reason for changing the frequency of wound complication from 11.6% to 11.2% in EB patients in SmPC section 4.8 has not been clearly presented. Therefore, the MAH is requested to provide further information on the data and calculations supporting this change.

**Summary of the MAH's response**

The reason for the change of frequency of wound complication from 11.6% to 11.2% in EB patients in the SmPC section 4.8 is due to the fact that one subject with an event of wound complication as of the DLP for the current SmPC (15 July 2021) had the causality assessment as related. Now, at the DLP of the CSR addendum (01 July 2022), this subject has had the event assessment for the event of wound complication changed to not related. Therefore, it changed from 26 subjects having related events of wound complication out of 224 subjects (as of DLP of current SmPC) to 25 subjects having related events of wound complication out of 224 (as of DLP of CSR addendum).

However, now with the addition of wound haemorrhage as part of the description of wound complications in section 4.8 (see response to question 4 below) of the SmPC this calculation of frequency of wound complication is impacted. Therefore, there are 25 subjects having related events of wound complication out of 224 (as of DLP of CSR addendum) and there is 1 subject with wound haemorrhage related events. Considering now wound haemorrhage will be captured under the description of wound complications the number of subjects who have experienced a related wound complication event is 25 subjects (with wound complication PT) plus 1 subject (with wound haemorrhage PT) making it 26 subjects out of 224 subjects which brings the frequency percentage back to 11.6%.

**Assessment of the MAH's response**

The MAH's response is considered acceptable. The frequency of wound complication in SmPC section 4.8 will not be changed. Issue resolved.

**Conclusion**

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly.

**Question 2**

The MAH is requested to present the BEB-13 DBP and OLP combined data and calculations in support of the changes of median duration and maximum duration in SmPC section 5.1.

**Summary of the MAH's response**

The data for median daily extent of exposure and cumulative extent of exposure is provided in the following tables:

All patients: Table 14.1.5.5 (Study phase = Overall, pages 6 & 7)

• By age group: Table 14.1.5.17 (Study phase = Overall, pages 18 – 25)

The data for the number of tubes used monthly is provided in the following tables:

• All patients: Table 14.1.5.6 (Study phase = Overall, page 5)

• By age group: Table 14.1.5.24 (Study phase = Overall, pages 4, 7, 10 & 13)

**Assessment of the MAH's response**

The MAH's response is considered acceptable. Issue resolved.

**Conclusion**

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly.

**Question 3**

The median number of tubes introduced in the SmPC section 5.1 has not been clearly presented in the SCS. The MAH is requested to present the data from the BEB-13 DBP and OLP combined and the calculations for the data combined to be included in SmPC section 5.1. This is also requested for the median daily extent of exposure and median cumulative extent of exposure.

**Summary of the MAH's response**

Information on the median number of tubes used per month is included in the updated version of the SCS (Section 2.2.1, page 32) and the tables 14.1.5.6 and 14.1.5.24 which have been provided in response to question 2. The data on the median daily extent of exposure and median cumulative extent of exposure was included in the SmPC at the request of the Agency as part of the marketing authorisation procedure (D120, response to Q75). The MAH believes that the data on the median number of tubes used per month is more informative for healthcare professionals given that Filsuvez is supplied as single-use tubes. Therefore, this information was considered important to include in the revised SCS and SmPC. Nonetheless the data on the median daily extent of exposure and median cumulative extent of exposure was retained for reference in the SmPC and the tables 14.1.5.5 and 14.1.5.17 in which the data has been derived have been provided in response to question 2.

**Assessment of the MAH's response**

The MAH's response is considered acceptable. Issue resolved.

**Conclusion**

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly.

**Question 4**

Two reports of wound haemorrhage were reported (in the same subject), one of which was a serious reaction. Both were assessed as related to study medication. The SAE resulted in discontinuation from the study. The MAH is requested to consider if wound haemorrhage should be included in the description of selected events paragraph detailing wound complications in SmPC section 4.8.

**Summary of the MAH's response**

The MAH proposes including 'wound haemorrhage' in the description of selected events paragraph detailing wound complications in the SmPC section 4.8.

Four wound haemorrhage related events were reported in 3 subjects from the double-blind phase of the BEB-13 trial, of whom 2 received the control gel and 1 received the investigational product.

In BEB-13, wound complication was the most frequently reported AE in both treatment groups during the DBP and in the OLP. As documented in the CSR Addendum, the AEs specific to wound complications were categorised as:

• Increase in wound size compared to baseline (i.e., baseline of DBP)

• Wound reopening

• Increase in wound size compared to the previous visit.

• Other (included increase in wound burden, worsening of EB wound pain, and

wound odour)

• Injury to the wound

• Wound worsening compared to baseline (i.e., baseline of DBP)

Given that in clinical studies wound haemorrhage events were observed both with the control gel and the investigational product, and deemed related by the investigator, it is plausible that the mechanical agitation from the application of the gel onto debrided wounds may be the primary aetiological factor causing wound haemorrhage in these cases.

It is notable that non-clinical safety studies provided no evidence that birch bark extract, the active ingredient, exerts any significant local influence on coagulation factors. Specifically:

• No relevant changes in aPTT or PT were identified with routine blood sampling in studies in which TE was administered intraperitoneally, including studies 13646-00 and 13647-00 (the 2-week dose range finding studies in Sprague Dawley rats and beagles, respectively) and studies 13839-00 and 13904/01 (the 4-week IP studies in in Sprague Dawley rats and beagles, respectively).

• In dermal studies in mini pigs (Studies 34377 and 26742) some minor alterations to aPTT were observed compared to controls, but this occurred only in males and was a reduction of ~10%, which was not deemed relevant.

Given the temporal association between the wound haemorrhage and the administration of the investigational product, the MAH proposes revising the description of wound complications as follows:

*"Wound complication.*

*In studies with EB patients, wound complication comprised different kinds of local complications such as increase in wound size, wound re-opening, increase in wound burden, and injury to the wound. Wound site haemorrhage is a known complication in patients with EB, with severe forms of the condition being at an increased risk for wound haemorrhage. However, in clinical trials wound haemorrhage was reported as possibly related to Filsuvez in one subject based on a temporal association."*

The inclusion of wound haemorrhage under the description of wound complications will affect the calculation of frequency of wound complications. See response to question 1 above for this recalculation.

**Assessment of the MAH's response**

The MAH's response to include 'wound haemorrhage' in the description of selected events paragraph detailing wound complications in the SmPC section 4.8 is considered acceptable. However, the Rapporteur considers the wording too detailed and in relation to the other wound complications in the paragraph, they are all known complications in EB patients. The MAH is requested to reword the text as follows:

*"Wound complication.*

*In studies with EB patients, wound complication comprised different kinds of local complications such as increase in wound size, wound re-opening, increase in wound burden, injury to the wound and wound haemorrhage."*

See also the proposed Changes to the Product Information in a separate document.

**Summary of the MAH's response to the CHMP Rapporteur's responses assessment report**

The MAH agrees with the proposed wording.

**Assessment of the MAH's response to the CHMP Rapporteur's responses assessment report**

Issue resolved.

**Conclusion**

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly.

# 12. Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 14 December 2023.