EU Risk Management Plan for Filsuvez (birch bark extract) (USAN: birch triterpenes)

RMP version to be assessed as part of this application:

RMP Version number: 2.3

Data lock point for this RMP: 14 Jan 2023

Date of final sign off: 14 Jun 2023

Rationale for submitting an updated RMP:

Actions proposed in response to the EMA's PSUSA (EMEA/H/C/PSUSA/00010446/202207) which stated that the last approved RMP (version 2.0) and the Summary of the Risk Management Plan published on the EMA website for birch bark extract covers two medicinal products Episalvan and Filsuvez and safety concerns for both products are reflected in these documents. Considering that on 7 June 2022 the marketing authorisation for Episalvan (birch bark extract) in the European Union has been withdrawn, the PRAC recommends the MAH to update the RMP within the next regulatory opportunity.

EMA's recommendation to the MAH as part of the review of procedure EMEA/H/C/005035/MEA/001 List of Questions (LoQs) to update the RMP regarding revised PASS milestones and study title with the next regulatory opportunity.

Summary of significant changes in this RMP:

- Amendment to the data under Part I: Product overview – removal of Episalvan
- Amendment to the data under Part II: Module SI Epidemiology of the indication and target population – rearranged to focus on EB indication for Filsuvez
- Amendment to the data under Part II: Module SII Non-clinical part of the safety specification – updated of study number
- Amendment to the data under Part II: Module SIII Clinical trial exposure – updated to include Episalvan withdrawal and reference to pivotal and supportive studies for Filsuvez
- Amendment to the data under Part II: Module SIV Populations not studied in clinical trials – removal of pivotal studies for Episalvan
- Amendment to the data under Part II: Module SV Post authorisation experience – updated with recent Filsuvez PSUR information on exposure
- Amendment to the data under Part II: Module SVII Identified and potential risks – removal of risks relating to Episalvan and updated the Identified and potential risks.
- Amendment to the Part II: Module SVIII Summary of safety concerns for Filsuvez for the treatment of Epidermolysis bullosa – removal of risks for Episalvan

- Update to the sections under Part III: Pharmacovigilance plan and II.C.2 Other studies in post-authorisation development plan for Filsuvez for the treatment Epidermolysis bullosa – updated details on registry per approved protocol
- Update to the Sections under Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities) – removal of Episalvan risks, part V.3 updated to remove Foster registry as additional risk minimisation measure for the missing information risk of Use in patients with different skin types regarding ethnic origin / Fitzpatrick skin types
- Update to the sections under Part VI: Summary of the risk management plan – removal of Episalvan reference, updated to remove Foster registry as additional risk minimisation measure for the missing information risk of Use in patients with different skin types regarding ethnic origin / Fitzpatrick skin types
- Part II modules SVII, SVIII; Part III; Part V (V1, V2, V3), Part VI (IIA and IIB) and Annex II – Summary of safety concern, missing information has been updated from "Use in patients with different skin types regarding ethnic origin / Fitzpatrick skin types" to "Use in patients of different race/ethnicity"

Other RMP versions under evaluation: N/A

Details of the currently approved RMP: Version 2.0, Approved on 21 Apr 2022 with the MAA for Filsuvez for the treatment of Epidermolysis bullosa

QPPV name:	Gabriele-Cornelia Fox
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation Chiesi´s QPPV. The electronic signature is available on file.

List of Tables

Abbreviations

AE	Adverse event
AK	actinic keratosis
AUC	Area under the curve
BCC	Basal Cell Carcinoma
BMI	Body Mass Index
C_{max}	Maximum Plasma Concentration
DBP	Double Blind Phase
DBS	Dried blood spot
DDEB	Dominant Dystrophic epidermolysis bullosa
DEB	Dystrophic epidermolysis bullosa
DEBRA	Dystrophic EB Research Association
EB	Epidermolysis bullosa
EBS	Epidermolysis bullosa simplex
EPAR	European Public Assessment Report
EU	European Union
GCP	Good Clinical Practise
GLP	Good laboratory practise
hPK	human primary keratinocytes
HS-RDEB	Hallopeau-Siemens- Recessive Dystrophic epidermolysis bullosa
i.d.	intraduodenal
i.p.	intraperitoneal
i.v.	intravenous
ICD	International Statistical Classification of Diseases and Related Health Problems
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IHC	Immunohistochemistry
JEB	Junctional epidermolysis bullosa
LLOQ	Lower limit of quantification
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
NICE	National Institute for Health and Care Excellence
NOAEL	no observed adverse event limit
OLP	Open Label Phase
PL	Product Leaflet
QPPV	Qualified person for Pharmacovigilance
RDEB	Recessive Dystrophic epidermolysis bullosa
RMP	Risk Management Plan
s.c.	Subcutaneous
SAE	Serious adverse events
SCC	Squamous Cell Carcinoma
SmPC	Summary of Product Characteristics
STSG	split-thickness skin graft
TEN	Toxic Epidermal Necrolysis
TGM	transglutaminase

TK	toxicokinetic
UK	United Kingdom
USA	United States of America
UV	Ultraviolet
WHM	Wound healing model
WHO	World Health Organization

Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Birch bark extract (USAN: birch triterpenes)
Pharmacotherapeutic group(s) (ATC Code)	D03AX13
Marketing Authorisation Holder	MAH: Chiesi Farmaceutici S.p.A.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Filsuvez
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Betulae cortex
	Summary of mode of action: Birch bark extract accelerates wound closure through effects of birch triterpenes on inflammation and epithelialization during wound healing. Cell culture assays with human primary keratinocytes and fibroblasts and *ex vivo* studies with porcine skin show that birch triterpenes modulate inflammatory mediators and are associated with activation of intracellular pathways known to be involved in keratinocyte differentiation and migration.
	Important information about its composition: The active ingredient of Filsuvez is birch bark 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 white, outer part of the birch is used for extraction. The main constituents in birch bark extract are pentacyclic triterpenes that comprise three major triterpene groups, (1) lupane, (2) oleanane, and (3) ursane. Betulin is the major quantified marker substance in the herbal preparation, together with its derivatives, lupeol and betulinic acid. Other quantified triterpene compounds are erythrodiol and oleanolic acid.
Hyperlink to the Product Information	Filsuvez Product Information

Indication(s) in the EEA	Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.
Dosage in the EEA	The gel should be applied to the wound surface at a thickness of approximately 1 mm and covered by a sterile non-adhesive wound dressing or, applied to the dressing so that the gel is in direct contact with the wound. The gel should not be applied sparingly. It should not be rubbed in. The gel should be reapplied at each wound dressing change.
Pharmaceutical form(s) and strengths	Filsuvez is provided as a colourless to slightly yellowish, opalescent, non-aqueous gel containing 10% (w/w) birch bark extract, for cutaneous application. One single use tube contains 9.4 g or 23.4 g of gel. 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.
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication and target population(s)

The Marketing Authorization Holder's (MAH) development program investigated the safety and efficacy of Oleogel-S10 (the development name for Filsuvez gel) in the treatment of partial thickness wounds, including both superficial and deep partial thickness wounds. These wounds included those associated with Epidermolysis bullosa (EB), split-thickness skin graft (STSG) donor site wounds and Grade 2a burn wounds. These are representative of partial thickness wounds (Middelkoop 2014).

Oleogel-S10 received marketing authorization via the centralized procedure under the invented/trade name Episalvan on 14 January 2016 for the treatment of partial-thickness wounds in adults; however, the product was never commercialised in any of the European markets. The European Commission approved a request for the withdrawal of the Episalvan market authorization for commercial reasons.

A European marketing authorization was granted for Filsuvez in June 2022 and was granted in Great Britain in August 2022 for the therapeutic indication "treatment of partial-thickness wounds associated with dystrophic and junctional EB in patients 6 months or older".

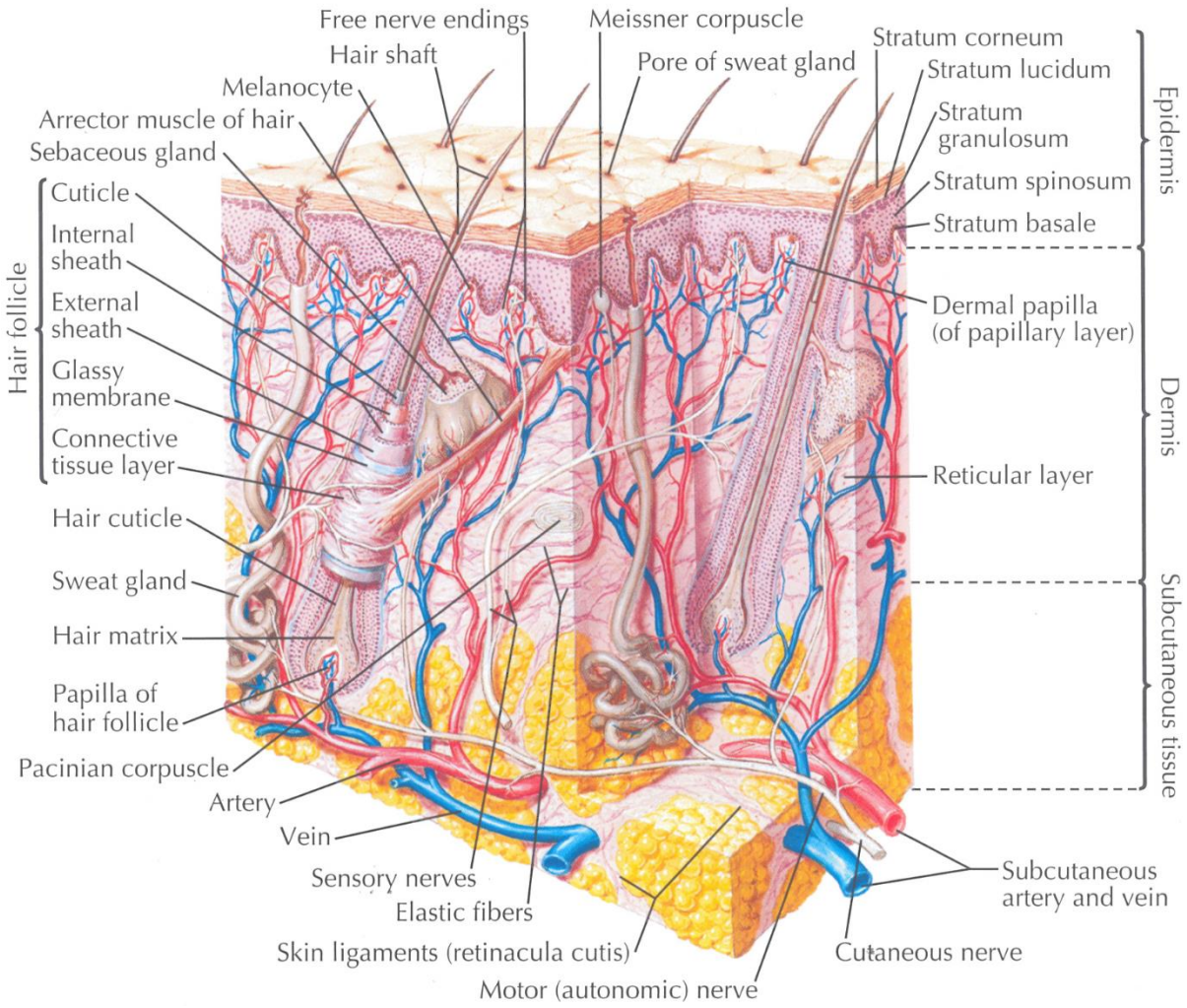
A skin wound is a type of injury in which skin is torn, cut, or punctured, burned, or where blunt force trauma causes a contusion (Singer and Dagum, 2008). The skin has numerous functions, it is barrier to water, microorganism invasion, mechanical trauma, chemicals and ultraviolet light damage. Human skin consists of three layers, epidermis, dermis and subcutis (Figure 1). The epidermis serves as a barrier to infection. The dermis contains the appendages of skin (adnexae) such as hair roots, sebaceous glands and sweat glands. Also, sensory nerve receptors and blood vessels are located within the dermis. Epidermis and dermis are separated by a thin sheet of fibers called the basement membrane. Above the basement membrane basal keratinocytes of the stratum basale and are present around the base of hair follicles in the dermis are located which continuously regenerate the epidermis. Keratinocytes mature, differentiate and progress through the layers of the epidermis until they are finally shed as corneocytes in a life cycle lasting approximately three to four weeks. Based on their prominent abundance in the epidermis keratinocytes are of paramount importance for the re-epithelialization of partial thickness wounds (Doughty, 2012).

Generally, wounds can be classified according to their depth based on the skin layers involved:

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

A further general distinction for wounds is made by their duration of existence, i.e. acute vs. chronic wounds. In general, chronic wounds (e.g. pressure ulcer or diabetic foot ulcer wounds) are wounds that do not heal in an orderly set of stages and in a predictable amount of time. In epidermolysis bullosa >21 days is considered as a chronic wound.

Figure 1: Structure of the Skin



Partial thickness wounds involve loss of the epidermis and to varying degrees extend into the dermis (superficial partial thickness or deep partial thickness wounds).

Source: Anderson, B. E., The Netter collection of medical illustrations: integumentary system. 2nd edition 2012, Elsevier Saunders, Phildaelphia

Epidermolysis bullosa (EB)

Epidermolysis bullosa (EB) is a rare heterogeneous group of genetic skin fragility disorders characterized by blistering and wounds of the skin in response to minor trauma or friction with the involvement of other epithelial surfaces such as the gastrointestinal tract in severely affected patients. It is a lifelong chronic disease which manifests from birth with no established cure or effective treatment for wounds associated EB that provide clinically meaningful benefit to the patient population. Standard of care is primarily symptomatic and supportive management. The lifelong management of wounds is a feature of EB, with severely affected patients changing the wound dressings daily or every second day. Repeated infections, constant trauma, and comorbidities such as compromised nutrition and anemia are reasons for developing chronic wounds (Denyer, 2012). Infected and chronic wounds

are the most frequent complications in the generalised intermediate and severe forms of EB. Consequently, sepsis can be a major complication in these patients (El Hachem, 2014).

Incidence and prevalence

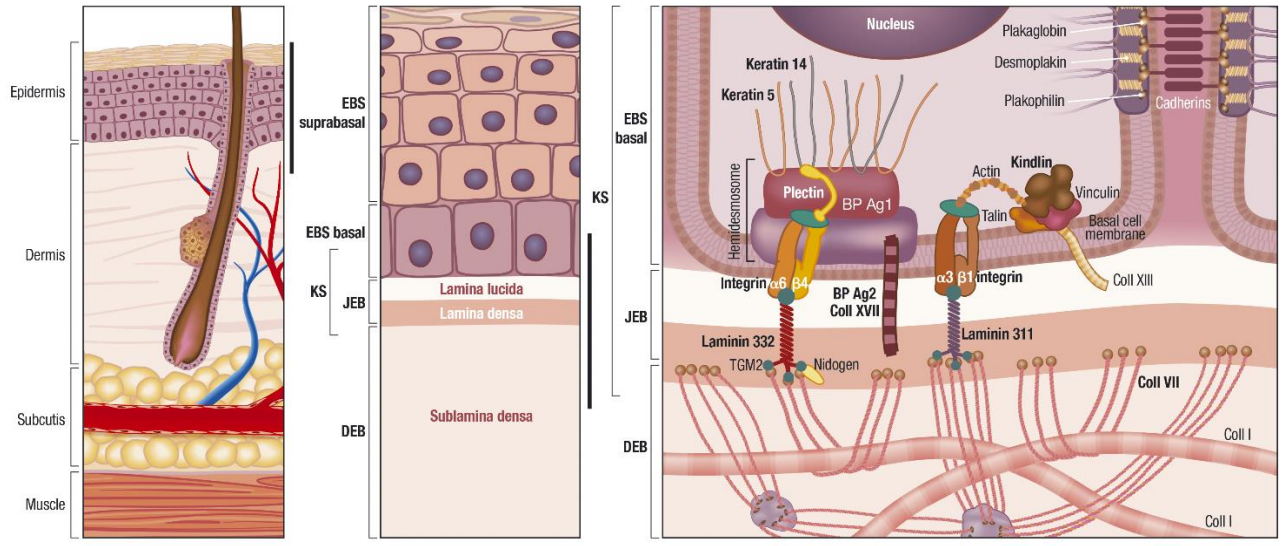
EB is a recognised rare orphan disease and there is a paucity of consistent European disease registry data. However, several European EB investigators have published data from their national registries (e.g. Volz, 2007; Watson, 2010; Castiglia & Zambruno, 2010; Vahlquist and Tasanen, 2010; Hernandez-Martin, 2013; Mellerio, 2010) as well as data published from the United States of America (Fine, 2010). Overall, the data available from European countries are supported by data from the United States National Epidermolysis Bullosa Registry which is a prospective longitudinal study of patients with all sub-types of EB, which included 3,271 patients between January 1986 and December 2002. The data were analysed in 1999 and 2005, both showed a prevalence of 11.07 affected per million (Fine, 2010). It is reasonable to estimate the prevalence of EB (all sub-types) at the upper end of the published European data, of 0.50 in 10,000 people in the EU.

EB is caused by more than 1000 known mutations in 18 genes encoding anchoring proteins of the dermo-epidermal junction (Bruckner-Tuderman, 2012; Schwieger-Briel, 2015). Defects of these proteins lead to different levels of cleavage within the skin according to their location in the dermo-epidermal junction (Fine, 2010).

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

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

Figure 2: Different Cleavage Levels within the Skin of EB Patients



Abbreviations: DEB: dystrophic epidermolysis bullosa; EB: epidermolysis bullosa; EBS: epidermolysis bullosa simplex; JEB: junctional epidermolysis bullosa; KS; Kindlin
Source: JE Stewart, R Brocklehurst © Amryt Pharma 2020

In 2020, an additional consensus report on the classification of EB and other skin fragility diseases was published (Has et al, 2020). This latest consensus report sought to reclassify disorders with skin fragility, with a focus on EB, based on new clinical and molecular data.

Epidermolysis bullosa simplex (EBS) is the most common subtype of EB (approximately 65%), and in the majority of cases causes mild to moderate disease. In the most frequent variant, localized EBS, blistering is usually limited to the hands and feet. There are also more severe variants of EBS, in particular generalised severe EBS (Coulombe et al, 2009), but in general EBS is usually compatible with normal life span (Pillay, 2008). With rare exceptions, EBS is inherited in an autosomal dominant fashion.

Junctional epidermolysis bullosa (JEB) is less frequent (approximately 5%) and has a broad spectrum of severity, from the lethal form of JEB generalised severe to very mild forms often diagnosed later in life. It is always recessively inherited.

Dystrophic epidermolysis bullosa accounts for approximately 30% of inherited EB (Fine, 2016) with 2 subtypes depending on the mutation; dominant DEB (DDEB) and recessive DEB (RDEB). In general, RDEB is more severe and as patients age, they are at a higher risk of developing aggressive squamous cell cancer. Severely affected patients suffer from widespread blistering and painful wounds that cause multiple secondary medical problems, and often lead to physical impairment (Bruckner-Tuderman, 2010). Kindler EB is the rarest form of EB. In this subtype, blistering occurs at various skin depths. It is characterized by generalised blistering at birth and the later development of characteristic poikilodermatous pigmentation and photosensitivity.

Demographics of the population in the proposed indication – EB occurs in racial and ethnic groups throughout the world and there is no gender predilection.

The main existing treatment options: Whilst there is a consensus for skin care for patients with EB (El Hachem et al., 2014), no other European approved therapy exists for treatment of wounds in this disease. Current treatment of EB is symptomatic and aims to reduce the risk of complications such as infection and to manage pain and itching (Pope et al., 2012). Acceleration of wound healing would meet a high unmet medical need and reduce the burden of disease.

Until the approval of Filsuvez in Europe symptomatic and professional wound care was the only therapeutic intervention for EB wounds. In patients with EB, topical antibiotics and antimicrobial dressings are used judiciously to minimize or prevent bacterial colonization. Wound infections, characterized by increasing size, exudate, odor, pain, surrounding erythema, swelling and edema often require treatment with systemic or topical antibiotics. EB patients require higher calorie intake to compensate for the increased energy expenditure required for wound healing. However, EB patients may suffer from oropharyngeal, esophageal and gastrointestinal disease involvement that adversely affects the ability to consume adequate calorie intake and leads to malnutrition that further impairs wound healing. Mineral deficiencies, such as zinc deficiency is common in severely affected patients which are required in the process of healing. A wide range of oral medications are used for the treatment of pruritus secondary to EB including antihistamines, corticosteroids, antiepileptics, tricyclic antidepressants, serotonin 5-HT3 receptor antagonists and benzodiazepines, although there is limited evidence that these are effective. For the treatment of severe recalcitrant itching, even thalidomide and cyclosporine are used. Pain from wounds, which is especially distressing during dressing changes, is managed by the administration of nonsteroidal anti-inflammatory analgesics and opioids depending on individual needs and the severity, chronicity and location of discomfort Goldschneider et al., 2014). In summary, the current treatment of EB wounds is symptomatic, including early treatment of wounds to prevent superinfection and wound protection with non-adhesive dressings to enable wound healing. EB patients take care to minimize trauma and avoid friction which is particularly difficult for young children and adversely affects their quality of life.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

The major consequences of recurrent blistering of the skin in patients with EB are the development of erosions and ulcers with compromised wound healing, while patients with certain subtypes of EB, especially the dystrophic variants, show extensive scarring that can lead to mutilation particularly of the hands and feet (Fine, 2009).

In addition, the co-existence of psychological symptoms such as depression, anxiety and behavioural disorders should be taken into consideration (Fortuna et al., 2017), as they may compromise treatment strategies and worsen symptoms.

The prognosis of EB is highly dependent on the subtype of disease that is present. Most EB patients, particularly those with EBS and DDEB, have normal life expectancies, but significant co-morbidities may complicate the natural progression of the disease. Patients with JEB, particularly those with JEB-generalised severe, are at major risk of death during the first few years of life while patients with RDEB, particularly those with severe generalised RDEB, are at risk of death on or after young adulthood. The highest risk of infant mortality among EB neonates, infants, and young children occurs in JEB-generalised severe, and is most often the result of sepsis, failure to thrive, or tracheolaryngeal obstruction. Overall, despite the disease rarity, inherited EB can cause a huge clinical and socioeconomic impact on patients and their families.

The US National Epidermolysis Bullosa Registry determined the incidence and prevalence of inherited EB stratified by subtype in the USA during a 16-year period (Fine, 2016). 3,280 patients were enrolled and evaluated, and demographics of the study population were considered to be a good representation of patients in the US with this genetic condition and 2,750 patients were sub-classified into major EB subtypes.

The data was used to perform a nested randomly sampled longitudinal sub-cohort to determine the cause-specific risks of death in children with EB in the first 15 years of life (Fine et al., 2008). The data demonstrate that the risk of death among EB infants and children differs markedly by EB subtype in terms of specific cause, magnitude of risk, and timing of onset. It also showed that most children with EB who survive the first 1-2 years of life will live into at least adulthood, provided that meticulous, aggressive medical care is provided.

The distribution of EB subtypes and the percentage of patients in each subtype who died is presented in Table 1.

Deaths in childhood were most common in JEB with 44.7% of all children with JEB generalised severe subtype dying within the first year of life. The major causes of death were failure to thrive and sepsis. Severely affected JEB infants commonly have prolonged hospitalization during the first year of life, and this results in exposure to hospital acquired infections, which often contribute to mortality. These patients have substantial extracutaneous disease, including trachea-laryngeal involvement, however in the nested study the only specific pulmonary cause of death reported on the death certificate was pneumonia which was at low frequency. This may or may not have been a complication of sepsis, alternatively, it may have occurred as a consequence of chronic aspiration pneumonitis secondary to narrowing of the upper airway. The median age of death in patients with JEB, generalised severe subtype was 0.58 year and the short life span was also associated with high morbidity.

Table 1: US EB Registry Table: Distribution by sub-type

EB Subtype	Number of patients	% of patients who had died	Age at time of death (years) Median
JEB, generalised severe	41	65.85%	0.58

JEB, generalised intermediate	186	50.54%	0.34
RDEB, generalised severe	138	37.68%	22.09
RDEB- generalised intermediate	262	9.92%	30.34
DDEB	425	1.41%	64.23

(Source: modified from Table I & Table II of Fine et al., 2008)

Other literature pertaining to JEB generalised severe, is consistent with the US Registry. In total, there were 22 patients with JEB-generalised severe subtype included in the Dutch EB Registry over a 23-year period (1988- 2011) who were followed longitudinally (Yuen et al., 2012). The average age at death was 5.8 months (range 0.5–32.6 months). The causes of death were, in order of frequency: failure to thrive, respiratory failure, pneumonia, dehydration, anaemia, sepsis and euthanasia. The pattern of initial weight gain was a predictor of lifespan in these patients. Invasive treatments to extend life did not promote survival in these patients. The authors concluded that it is important to make the diagnosis as soon as possible after birth so that the management can be shifted from active treatment to palliative care. Dystrophic EB Research Association of America (DeBRA) published data on 5-year period in which 71 children were born with JEB, in which there was a high prevalence of morbidity and infant mortality (Kelly- Mancuso et al 2012). The mean age of death was 5 months, and worst in patients with generalised severe JEB. The data from EB House Austria is similar with a mean life span of 5.08 months for patients with JEB. Finally, the Australia & New Zealand epidemiology registry enrolled 259 patients with EB between January 2006 and December 2008 (Kho et al 2010). JEB generalised severe subtype patients had a very high mortality (n=10/11), with most deaths occurring in infancy with the commonest causes being sepsis and failure to thrive. The next highest mortality rate was seen in patients with generalised severe RDEB (n= 4/17) predominantly in early adulthood due to metastatic skin cancer with the mean age at death at 29.4 years old (range 23-35).

The progression of the clinical course of disease is difficult to appreciate unless subjects are monitored for long periods of time, such as in epidemiology registries, however this is hampered by the low prevalence of EB, and indeed DEB and JEB account for less than 30% therein. Within RDEB the patients with generalised severe subtype have the most clinically severe manifestations and usually have blistering from birth. The skin is extremely fragile and susceptible to injury with minor trauma or friction. The blisters heal with scarring the most devasting of which results in adhesions between digits, webbing and pseudosyndactyly. Oral, genital, anal and ocular mucosa may be affected with erosions and scarring. The ability to open the mouth can be restricted, the tongue less mobile and oesophageal strictures are common, these may lead to nutritional impairment. Thus, the constellation of symptoms in affected individuals result in reduced food intake, protein loss, anemia, and impaired growth. In the clinical course of this disease, individuals become severely disabled and a shortened lifespan due to secondary complications, and there is an increased risk of squamous cell skin cancer (Bruckner-Tudermann et al, 2010).

In summary, the natural history of severely affected EB patients, such as RDEB generalised severe, is associated with multi-organ disease involvement. The US EB Registry shows the reduction in life expectancy for these patients and sepsis was documented as a cause of death in RDEB in the first 15 years of life, although uncommon (Fine et al., 2008). The median age at the time death was 22.09 years in RDEB, generalised severe, and during the 16-year period of the US EB Registry, 37.68% with this subtype had died.

Important co-morbidities:

There is a high incidence rate of repeated wound infections and non-melanoma skin tumours and repeated infections in patients with EB. Other common clinical findings in patients with EB include dental caries, oesophageal strictures, pseudosyndactyly or mitten deformities, nutritional deficiencies, and psychosocial morbidity (Fine & Mellerio., 2009).

Repeated infections

Infected and chronic wounds belong to the most frequent complications in the generalised intermediate and severe forms of EB (El Hachem, 2014). Extensive areas of bare skin show loss of stratum corneum barrier and allow microbial penetration. The accumulation of lymph and moisture in the surface increases bacterial growth. Severe subtypes of JEB generalised severe correlate with immunological abnormalities, including reduced production of lymphocytes. Along with poor nutritional status, there is decreased resistance to infections. The most commonly isolated microorganisms in wound cultures from EB patients encompass Staphylococcus sp., Streptococcus sp., Diphtheroids, P. aeruginosa, and Candida sp.; the presence of ≥4 bacterial groups is associated with significant delayed wound healing (Brandling-Bennett and Morel, 2010).

Patients usually show greater susceptibility to develop sepsis, with a high risk of death in early childhood. Prevention of infection is the preferred strategy. Therefore, with extensive bare areas or areas of crusting, strict care must be taken. This regimen includes the use of topical antibiotics. Self-adhesive dressing is a good choice to keep the areas covered.

Non-Melanoma skin tumours

There is a high incidence of developing skin carcinoma in patients with EB and usually occurs in multiple primary sites of chronic lesions.

In patients with DEB, especially in severely affected RDEB, there is a significant risk of aggressive squamous cell carcinoma (SCC) of the skin. Typically, SCC's develop at site of chronic wounds and scarring, in particular, at extremities (Conderalli et al., 2019). Unlike in the general population, in DEB patients, there is no predilection for photo exposed areas. This high risk shows that early detection and treatment of SCC has great importance in the management of adults with RDEB, considering the development of severe and recurrent lesions or chronic skin ulcerations and erosions.

The peak of incidence of SCC increases dramatically in the second and third decades of life. These lesions may recur frequently even with aggressive surgical excision. Studies on the pathogenesis of SCC in patients with RDEB suggest that cancer occurs due to decreased expression of type VII collagen in the NC1 domain. Type VII collagen is required for Ras-driven human epidermal tumorigenesis by means of tumor-stroma interactions and promote neoplasia; retention of NC1 sequences in a subset of RDEB patients may contribute to their increased susceptibility to SCC (Ortiz-Urda, 2005).

According to figures from the USA National EB registry, the cumulative risk of developing at least one SCC for patients with RDEB-generalised severe increases with age. At age 35, patients have a 67.8% chance of developing an SCC and this rises to 90.1% by the age of 55. Cumulative risk of death from SCC in patients with RDEB-generalised severe, who developed at least one SCC was 57.2% by the age of 35 and raised to 87.3% by the age of 45 (Conderalli et al., 2019).

This risk is also present in other EB variants (DDEB) and in other RDEB sub-types but they are less common and occur later into adulthood.

EBS-DM patients have a substantial risk of developing basal cell carcinoma (BCC). Possibly, repeated injury to keratinocytes promotes tumorigenesis. The risk of BCC is low in other subtypes of EBS. The risk of melanoma and BCC in other subtypes is comparable to that of the general population (Boeira, 2013).

Indications considered relevant models for EB:

Completed clinical studies with Oleogel-S10 relevant for the treatment of wounds associated with inherited EB include studies performed in subjects with EB as well as in indications that are considered to be relevant models for EB (i.e., partial-thickness split-thickness skin graft [STSG] donor site wounds

and Grade 2a burn wounds). Since the general mechanisms of wound healing are the same in the skin of EB patients as in wounded healthy skin, efficacy data from the three Phase 3 studies that supported the Episalvan Marketing Authorization Application (MAA) were also used to support Filsuvez MAA.

Partial Thickness Wounds of the Skin

Partial thickness wounds are shallow wounds involving epidermal loss and partial loss of the dermal layer and are usually approximately 0.2 cm in depth. They are moist and painful because of loss of the epidermal covering and the resultant exposure of abundant nerve endings in stratum granulosum as well as pain receptors throughout. The wounds may be caused by accident (e.g., burns, abrasions, contusions) or may have an iatrogenic cause (e.g., split-thickness skin grafting, ablative laser skin resurfacing, radiation wounds). In epidermolysis bullosa, the skin is fragile and minor friction or trauma results in wounds, usually partial thickness.

Split-Thickness Skin Graft (STSG) Donor Site Wounds

Split-thickness skin grafting is the transplantation of a patient's own cutaneous tissue harvested from an area of normal healthy skin, used to replace an area of skin loss or injury and is one of the most commonly performed operations in plastic and reconstructive surgery. Indications for split-thickness skin grafting include reconstruction after the surgical removal of cutaneous malignancies, replacement of tissue lost in full-thickness burns, and covering chronic non-healing cutaneous ulcers (Black and Black, 2012; McCartan and Dinh, 2012). The partial thickness wound of the STSG graft donor site heals by re-epithelialization. Often the graft donor site is slow to heal, and it is the source of most postoperative pain (Voineskos et al., 2009).

The STSG donor site, as an iatrogenic partial thickness wound created in a surgical setting, represents a highly standardized, homogeneous, and clean wound. It is therefore considered a model wound for partial thickness wounds of all types (Middelkoop 2014; Gottrup et al., 2000; Voineskos et al., 2009; Brölmann et al., 2013). A notable example of the STSG donor site as a model wound is represented by skin lesions caused by the rare hereditary disease dystrophic epidermolysis bullosa (DEB), for which STSG donor site wounds are considered the best available model wound. The general principles of wound healing progression apply, although in case of EB the skin will remain prone to new injuries. Consequently, STSG donor sites can be used in clinical studies to generate insights into wound healing which are of relevance to all partial thickness wounds (Middelkoop 2014; Gottrup et al., 2000).

Grade 2a Burn Wounds

Burns are classified according to the depth of injury into 1st degree (epidermal with redness and erythema), Grade 2a (superficial partial thickness extending to dermis), Grade 2b (deep partial thickness extending to dermis, and unable to regenerate epidermis within 3 weeks), 3rd degree (full thickness, extending through entire dermis) and 4th degree (charred).

Grade 2 burns represent partial thickness wounds with the potential to regenerate the epidermis. However, within the first days after injury, even for experienced burn surgeons it is difficult to estimate the time required for the healing process. After 3 to 7 days post-injury, the assessment and estimate of wound healing time becomes more precise. Clinical assessment can be further refined with laser Doppler imaging (Merz et al., 2010; Kaiser et al., 2011) which is validated for as early as 2 days after injury, but in most European countries these diagnostic devices have not yet been made available as a standard in burn centers.

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

Toxicity

Single-dose Toxicity:

Single dose toxicity studies with birch triterpenes were conducted in mice and rats following subcutaneous (s.c.) and intraperitoneal (i.p). administration (Study Nos. 13487/00, 13488/00, 13597/00 and 13598/00). Birch triterpenes was well tolerated by both species when administered as single i.p. or s.c. injections at doses up to 2000 mg/kg. The LD_{50} values for the male and female animals at 24 hours and 14 days after i.p. administration could not be calculated as no mortality was observed (>2000 mg/kg; highest tested dose).

Repeated-dose toxicity:

Oral and parenteral exposures

Repeated-dose studies were performed in rats (14-day and 4-week) and dogs (14-day) via the i.p. route of administration (Study No. 13646/00; 13839/00 and 13647/00) which showed no systemic test substance related changes, except for local findings (peritonitis) expected due to the insolubility of birch triterpenes. Indirect effects related to peritonitis included the reduction of body weight and food consumption in both rats and dogs and changes in blood parameter (increase in leucocytes and platelets counts decrease in reticulocytes) as well as increased activities of alkaline phosphatase and lactate dehydrogenase in dogs. Indirect effects were observed in rats at 500 mg/kg (14-day) or 540 mg/kg (4-week) and in dogs at 50 mg/kg and above. 4-week s.c. administration of birch triterpenes to dogs resulted in pronounced inflammatory reaction at the injection site which was considered to be related to the insolubility and possible accumulation of the triterpenes (Study No. 13904/00). No direct test item related changes were observed at repeated applications of up to 300 mg/kg/day.

Oral gavage administration of birch triterpenes to Crl:WI (Han) rats, once daily for 26 weeks at dose levels of 10, 30 or 100 mg/kg/day was well tolerated (Study No. ZDA0015). The no observed adverse event limit (NOAEL) was considered to be 100 mg/kg/day. At this dose, mean maximal plasma concentration of betulin during week 26 was 459 ng/mL in males, and 719 ng/mL in females and mean systemic exposure of betulin (Area under the curve; AUC) was 4,650 ng*h/mL in males, and 3,730 ng*h/mL in females, respectively.

Dermal exposures

In mice, Oleogel-S10 was well tolerated, with no evidence of systemic toxicity or local irritation when dermally applied daily (non-occluded) at a dose of 0.1 mL/mouse/day (approx. 10 µl/cm^2, corresponding to 0.093 g Oleogel-S10 per 0.035 kg/mouse, 2.66 g Oleogel-S10/kg or 266 mg birch triterpenes/kg) to the shaved skin of the animal's back (Study No. ZDA0016 and ZDA0017). The only notable effect was a 58% increase in body weight gain in females compared with controls, which was not considered to be test article related. TK analysis revealed measurable quantities of betulin in the blood of mice up to 8 hours after dosing. Maximum mean concentrations observed on Day 1 were 392 ng/mL in males and 717 ng/mL in females and 339 ng/mL in males and 284 ng/mL in females on Day 86, respectively.

In minipigs, no evidence for systemic toxicity was observed when Oleogel-S10 was applied to intact or wounded skin (split-thickness skin grafts with a depth of 0.4 to 0.6 mm) over a period of 28 days (1.5 g Oleogel-S10/kg, or 150 mg birch triterpenes/kg) (Study No. 26742). Locally, no test item-related

changes were observed in Oleogel-S10, gel-treated sites of intact skin. On Oleogel-S10, gel treated abraded skin, an increased incidence and severity of lympho-histiocytic inflammatory cell infiltration in association with the presence of multinucleate giant cells was noted at the end of the treatment period. The inflammatory cell infiltrates and giant cells were typically present in the superficial dermis, but occasionally aggregates of giant cells were also located in the deeper dermis. Some of the giant cells contained eosinophilic material. At the end of the recovery period, marginally increased severity of lympho-histiocytic inflammatory cell infiltration, in association with the presence of multinucleate giant cells were noted in the Oleogel-S10, gel treated abraded skin sites of female animals. No such finding was observed in male animals though. The inflammatory signs were considered to be caused by the presence of low soluble test item but were not considered adverse since they were of low-grade severity, and no clinical signs were observed.

The morphometric investigation of immunohistochemistry (IHC)-stained histological slides indicated a reduction of Ki67-positive epithelial cells after 28-day Oleogel-S10 treatment compared to control skin in both male and female minipigs.

When Oleogel-S10 gel was applied to wounded skin, betulin and betulinic acid concentrations were below lower limit of quantification (LLOQ) (5 ng/mL). On intact minipig skin, most of the samples were below LLOQ with respect to both betulin and betulinic acid. Measurable betulin concentrations were detected in single animals (7 out of 12 animals) at single time points: 33 out of 216 samples were above 5 ng/mL (6.07 – 36.6 ng/mL). The data suggest a tendency towards an increase in plasma levels with treatment duration. Betulinic acid was detected in 3 out of 12 animals (≤8.15 ng/mL).

In a chronic dermal toxicity study in minipigs Oleogel-S10 was applied topically once daily (500 cm^2, approx. 10% of the total body surface area, daily dose approx. 3 g Oleogel-S10/kg or 300 mg birch triterpenes/kg) for 39 weeks to intact skin (Study No. 34377). At the end of the 9-month treatment period no signs of systemic toxicity were observed.

Throughout the study local tolerance reactions were noted, including slight to severe isolated focal red spots and/or slight to severe erythema in all animals treated with 15 mL sunflower oil (vehicle) and in most of the animals treated with 50 mL Oleogel-S10. The incidence and severity of the changes were more pronounced in the animals treated with 15 mL sunflower oil/animal (vehicle control group 2) compared to the animals treated with 50 mL Oleogel-S10/animal. The application volume of the vehicle was reduced to 5 mL/animal from week 10 for males and week 11 for females. Erythema and red spots at the application sites had completely subsided in male and female animals treated with 50 mL Oleogel-S10/animal as of test week 29 (males) or test week 37 (females). Slight signs of local intolerance were still noted for all 6 male animals and for 2 of 6 female animals treated with 5 mL sunflower oil/animal (vehicle control group) at the end of the 39-week treatment period.

Punch biopsy skin samples obtained at week 14 showed several changes in epidermis, dermis and subcutis in vehicle and Oleogel-S10, gel treated animals. There was no difference in the incidence or severity of these changes between vehicle and Oleogel-S10, gel treated animals. At the end of the treatment period at week 39, epidermal hyperplasia, orthokeratotic hyperkeratosis, dermal lymphocytic and/or neutrophilic infiltration, and pustules in the stratum corneum were noted in vehicle and Oleogel-S10, gel at comparable incidence, considered related to the vehicle or to the mere fact that the administration site was covered with an oily material for several hours per day. Histopathology evaluation of skin samples at week 39 showed epidermal hyperplasia, pustule formation, inflammatory cell infiltration and the presence of foamy vacuolated cells. These findings were present in all animals receiving Oleogel-S10 and were graded at minimal to moderate in terms of severity. Four weeks after the cessation of treatment, the findings were observed only at minimal severity, indicating regression. These microscopic changes are considered to be due to the physical effects of the long-term application of the lipophilic (oily) test material.

TK analysis of Betulin showed no Betulin on Test Day 1 and low levels on Test Days 28 and 91 ranging from 6.27 ng/mL to 184 ng/mL. Betulin levels seem to increase slightly with time.

A higher number Ki67-positive cells was observed in males treated with the vehicle control (but not females). Males of the test-item group also showed an increase in Ki67 positive cells, which was statistically significant compared to untreated animals, but lower when compared to the vehicle sunflower oil group. Females did not show increased KI67 levels after treatment with the test item.

Relevance to Human use:

There were no safety-relevant findings for human use identified.

Peritonitis is an artefact due to i.p. / s.c. administration of the test item with no relevance to humans, since the clinical route of application is topical, dermal use. Peritonitis was neither observed in a repeated dermal study in minipigs, nor in any clinical investigation with Oleogel-S10. The NOELs after repeated dosing in rats and dogs cover the total human dose on a mg / kg basis (155 mg/kg) and the systemic exposure after i.p. / s.c. covers the worst-case assumption in humans after topical use.

The inflammatory response at s.c. injection site seen in dogs is an artefact due to the s.c. administration of the test-item with no relevance to humans, since the clinical route of application is topical, dermal. Inflammation was neither observed in a repeated dermal study in minipigs, nor in any clinical investigation with Oleogel-S10.

The inflammatory reaction seen in the topical treatment of abraded skin was related to the insolubility of the triterpenes. Giant cells are typically observed in foreign body reactions and are formed by the aggregation of individual macrophages in order to remove foreign substances. Therefore, inflammatory reactions were considered to be caused by the presence of low soluble test item and not being a direct reaction (adverse effect) triggered by the birch triterpenes, gel treatment itself. These findings showed some regression though not complete recovery after the 14 day off-treatment period. Because of the overall low severity of the skin lesions in the dermal toxicity studies in minipigs, and the absence of associated clinical and macroscopic changes, findings at Oleogel-S10 treated sites are not considered adverse and of any toxicological importance. More importantly, in clinical studies with birch triterpenes no increase in inflammation was observed following long-term treatment of wounded skin. Accordingly, relevance of this reaction to human use is considered low.

Pharmacokinetics

Using human, minipig, mouse and rat hepatocytes, the extent of metabolism of betulin after 5 hours of incubation was almost complete, ranging between 97 and 100% (G-A-VIT-19-050). In human hepatocytes, biotransformation of betulin revealed four structurally identified metabolites with relative abundances (normalized to parent drug at time 0 h) ranging between 10.2% and 26.9%. M2, formed by oxygenation, methylation, and sulfation, was the most abundant one (26.9%), followed – in rank order – by M4 (sulfation, 19.0% abundance), M5 (glucuronidation, 12.0% abundance), and M3 (sulfation, 10.2% abundance).

Three of the human metabolites, i.e., M2, M3, and M5 were found in at least one animal species (mouse and minipig), the two latter to a similar or even higher extent. Merely M4, a phase II conjugate formed via sulfation, was not detectable in mouse, rat, or minipig hepatocytes. However, since this metabolite represents a phase II metabolite with no structural alert, it is not considered of toxicological concern.

CYP phenotoyping experiments with Bactosomes™ showed that Betulin is metabolized by four CYP isoforms with the following rank order: CYP3A5 ≈ CYP3A4 >> CYP2C8 > CYP2C19 with a relative contribution of 70%, 30%, 0.1%, and 0.04%, respectively (G-A-VIT-19-059; G-A-VIT-19-060). Non-CYP enzymes were found to play the predominant role in the hepatic metabolism of Betulin.

Betulin showed a direct inhibition of CYP2C8 (test substrate amodiaquine) and CYP3A (test substrates testosterone and midazolam) with IC_{50} values of 0.60 µM (266 ng/mL), 0.17 µM (75 ng/mL), and 0.62 µM (275 ng/mL), respectively in human hepatocytes (G-A-VIT-19-057). In addition, betulin caused a very slight induction of CYP3A4 mRNA (2.7-fold) (G-A-VIT-19-058).

No dedicated studies evaluating the risk of Betulin on transporter-mediated drug interactions was performed, as Betulin showed high passive diffusion in a preliminary study using Caco-2 cells that is expected to overrun/mask potential active efflux transport [Study No. G-A-VIT-20-032].

Relevance to Human use:

There were no relevant findings.

Genotoxicity and Carcinogenicity

Genotoxicity: Genotoxicity of birch triterpenes was assessed using a variety of *in vitro* (AMES, Study No. 13542/00; mutagenic activity, Study No. 13543/00) and *in vivo* (micronucleus in mice, Study No. 13544/00) assays. No evidence for genotoxicity was recorded in *in vitro* studies. Birch triterpenes (suspended in sesame oil) showed no clastogenic properties in the mouse bone marrow micronucleus study, tested up to the maximum tolerated dose of 500 mg/kg bw i.p. However, Betulin and Betulinic acid plasma levels have not been evaluated in Study No. 13544/00.

Carcinogenicity: No carcinogenicity studies have been performed with Oleogel-S10 gel.

In the animal studies described above, no benign or malignant neoplasms were observed at the sites of application of Filsuvez. Epidermal hyperplasia was noted at the treatment sites following the administration of Filsuvez for 13 or 39 weeks. This finding was characterised by an increased number of cells in the lower epidermis, however there was no evidence of any unusual features such as cellular atypia and the epidermis showed normal cellular stratification. This appearance is not consistent with pre-neoplasia and is typically observed as part of a normal regenerative process.

Histopathological examinations in minipigs as part of the 28-day study (Study No. 26742) do not point to a tumour-promoting effect, neither in intact nor in wounded minipig skin. In the repeated dose toxicity study in minipigs, treatment with Oleogel-S10 for 28 days did not result in an increase of the proliferative marker Ki67, either on healthy or abraded skin.

In *in vitro* studies, (see Module 2.6.2), neither birch triterpenes or its components demonstrated any induction of proliferation of human primary keratinocytes (hPK) that, when kept under defined cell culture conditions, represent the proliferating and early-differentiated cells of the epidermis (basal keratinocytes).

In addition, in an *ex vivo* porcine wound healing model (WHM) birch triterpenes did not induce proliferation.

Also, in *in vivo* studies in actinic keratosis patients with birch triterpenes a decrease / normalization of aberrant Ki67 expression was seen. In a repeated dose toxicity study in minipigs treatment with Oleogel-S10 for 28 days did not result in an increase of Ki67, neither on healthy nor abraded skin as applicable. In a follow-up 39-week repeated dose dermal toxicity study in minipigs males of the test-item group showed an increase in Ki67 positive cells, which was statistically significant compared to untreated animals, but lower when compared to the vehicle sunflower oil group.

Relevance to Human use:

There were no relevant findings.

Reproductive and Developmental Toxicity

Reproductive and developmental toxicity studies with birch triterpenes (up to 100 mg/kg) were performed following oral administration in rats. No impact on male and female fertility (Study No. ZDA0012), embryo-fetal development (Study No. ZDA0010 and ZDA0011) and pre- and postnatal development (ZDA0013) was observed. Exposure to Betulin was analyzed using dried blood spot (DBS) ranged between 144 – 1,090 ng/mL following treatment with birch triterpenes. The highest dose was considered the NOEL in these studies.

Relevance to Human use:

There were no relevant findings.

Juvenile Toxicity

An oral juvenile repeated dose toxicity study (including respective dose range finding) with birch triterpenes in rats, administration once daily from Day 10 of age to at least Day 63 of age, did not point to any adverse effects on growth and development up to dose levels of 30, 100 or 300 mg/kg/day (Study No. ZDA0005 and ZDA0006). The NOAEL was the highest tested dose of 300 mg/kg/day. Highest C_{max} levels of 1,120 ng/mL and 1,140 ng/mL were reported for males and females, respectively, of animals received 100 mg/kg/day on Day 10 of age. On Day 63 of age C_{max} was between 249 ng/mL and 371 ng/mL in all animals.

Relevance to Human use:

There were no relevant findings.

Local Tolerance

Skin sensitization was assessed in guinea pigs according to Magnusson and Kligman (Study No. 13545/00). Birch triterpenes revealed no indication of sensitizing properties following intracutaneous (0.0001-5% birch bark extract suspended in sesame oil) or topical (0.1 – 15% birch triterpenes suspended in sesame oil) administration. In addition, an *in vitro* bovine corneal opacity and permeability (BCOP) assay with Oleogel-S10, gel did not show any signs of eye irritation or corrosion [Study No. 34488].

Relevance to Human use:

There were no relevant findings.

Safety pharmacology

A GLP *in vitro* hERG assay [Study No. A2726] indicated that betulin is devoid of potential to block potassium currents, responsible for cardiac repolarization up to a concentration of 190.13 nM (84.1 ng/ml), the highest feasible concentration in this test system. This concentration is also in the same range as highest Betulin values observed in venous plasma samples obtained in clinical trials with Oleogel-S10 [Section 2.7.2, Chapter 2.2].

No test item related effects have been observed on cardiovascular (peripheral, pulmonal and capillary blood pressure, heart rate, QT interval, cardiac output, stroke volume, systolic left ventricular pressure, dp/dt max, central venous pressure and blood gas analysis; up to 300 mg birch triterpenes/kg in beagle dogs), central nervous (sleeping time; up to 300 mg birch triterpenes/kg; mice), gastrointestinal (spontaneous, intestinal motility, up to 300 mg birch triterpenes/kg; mice) and renal (diuresis; up to 500 mg TE/kg in rats) parameters (Study Nos. 13536/00, 13537/00, 13538/00, 13539/00 and 13541/00).

Standard safety pharmacology parameters (respiratory and circulatory systems) were further evaluated in acute dose toxicity studies in mice and rats (up to 2000 mg birch triterpenes/kg) and in repeated dose toxicity studies in rats (up to 540 mg birch triterpenes/kg), dogs (up to 300 mg birch

triterpenes/kg) and minipigs (up to 150 mg birch triterpenes/kg) as part of monitoring clinical symptoms. In addition, in the 2-week dose range finding and the 4-week repeated dose toxicity study in dogs (up to 300 mg birch triterpenes/kg) ECG recordings were carried out. In all studies, no test-item related adverse effects were observed up to the highest tested dose (see Module 2.6.6).

Other toxicity-related information or data

In an *in vitro* phototoxicity study (3T3-NRU assay; 1.0 µg/mL birch triterpenes) revealed neither a cytotoxic nor a phototoxic potential (Study No. 26888). A photosensitization study in guinea pigs (0.5 mL of 10% birch triterpenes in sunflower oil) did not reveal any photosensitizing properties (Study No. 26889).

Relevance to Human use:

There were no relevant findings.

Part II: Module SIII - Clinical trial exposure

SIII.1 Brief overview of development

Oleogel-S10 was the name used for birch bark extract during the clinical/non-clinical development programme for the treatment of partial thickness wounds in adults (EB and non-EB indications). The clinical safety was evaluated in a total of 540 patients with different underlying diseases. The initial development focussed on studies to support the marketing authorisation for Episalvan. The MAA for Episalvan included a total of 10 clinical studies, which were conducted in Austria, Bulgaria, Czech Republic, France, Germany, Greece, Latvia, Poland, Spain, Sweden, Switzerland and UK. Two hundred and eighty (280) patients were enrolled in pivotal Phase III trials in addition to 34 patients in phase II trials in partial thickness wounds and 226 patients in supportive studies. Oleogel-S10 received marketing authorization in the European Union (EU) via the centralized procedure under the invented/trade name Episalvan on 14 January 2016 for the treatment of partial-thickness wounds in adults; however, the product was never commercialized in any of the European markets. Subsequently, the European Commission approved a request for the withdrawal of the Episalvan market authorization for commercial reasons.

Oleogel-S10 was subsequently evaluated in a clinical/non-clinical development programme for the treatment of epidermolysis bullosa.

Clinical studies of Oleogel-S10 were performed in patients with EB in a Phase II trial (BEB-10, which was also included as a supportive study for the MAA of Episalvan) in one country and a Phase III trial (BEB-13) in 26 countries. Oleogel-S10 was shown to be effective, safe and well-tolerated in EB patients in both Phase II and Phase III trials. Oleogel-S10, with the brand name Filsuvez®, has received an orphan designation (EU/3/10/845) for the treatment of EB in the EU on 23 Feb 2011. Orphan designation was maintained during the marketing authorisation application for Filsuvez.

In April 2022 a positive opinion recommending the approval of orphan designation for Filsuvez for the treatment of EB was adopted by the Committee for Orphan Medicinal Products (COMP). A European marketing authorization was granted for Filsuvez in June 2022 and was granted in Great Britain in August 2022 for the therapeutic indication "treatment of partial-thickness wounds associated with dystrophic and junctional EB in patients 6 months or older".

The designs of the 11 clinical efficacy and safety studies are summarized in Table 2 below. These studies were compliant with Good Clinical Practice (GCP).

Table 2: Completed and Ongoing Clinical Studies

Study Number Country Study Status	Title of Study	Study Treatment(s) and Duration of Treatment Duration of Follow-Up	Total number of patients exposed
Treatment of epidermolysis bullosa			
BEB-13 (EASE Study) 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, United Kingdom, Ukraine, United States of America Completed	Double Blind Phase Double-blind, Randomised, Vehicle-controlled, Phase III, Efficacy and Safety Study with 24-month Open-label Follow-up of Oleogel-S10 in Patients with Inherited Epidermolysis Bullosa	Oleogel-S10 plus non-adhesive wound dressing vs. control gel plus non-adhesive wound dressing applied directly to the wound or wound dressing every 1 to 4 days during dressing changes for 90 days (DBP). Target wounds and all other EB partial thickness wounds were treated during the DBP. If a wound was confirmed as closed, it was not necessary to continue to apply study medication to that wound. Oleogel-S10 was applied in the same manner to all EB partial-thickness wounds for up to 24 months during OLP. Subjects were followed during the 24-month OLP (Follow-up period).	109

Study Number Country Study Status	Title of Study	Study Treatment(s) and Duration of Treatment Duration of Follow-Up	Total number of patients exposed
BEB-13 (EASE Study) 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, United Kingdom, Ukraine, United States of America Completed	Open Label Phase Double-blind, Randomised, Vehicle-controlled, Phase III, Efficacy and Safety Study with 24-month Open-label Follow-up of Oleogel-S10 in Patients with Inherited Epidermolysis Bullosa	Oleogel-S10 plus non-adhesive wound dressing vs. control gel plus non-adhesive wound dressing applied directly to the wound or wound dressing every 1 to 4 days during dressing changes for 90 days (DBP). Target wounds and all other EB partial thickness wounds were treated during the DBP. If a wound was confirmed as closed, it was not necessary to continue to apply study medication to that wound. Oleogel-S10 was applied in the same manner to all EB partial-thickness wounds for up to 24 months during OLP. Subjects were followed up during the 24-month OLP (Follow-up period).	205*
BEB-10 (EBCS Study) Germany Completed	Phase II, Open, prospective, controlled case series documentation to compare intra-individually the efficacy and tolerance of Oleogel-S10 versus non-adhesive wound dressing alone in accelerating the epithelialisation of skin lesions in patients with Epidermolysis bullosa (EB) hereditaria	Oleogel-S10 plus non-adhesive wound dressing vs. non-adhesive wound dressing alone. The eligible wound (half) was topically treated with Oleogel-S10 and covered with wound dressing (Mepilex®) on Day 0. Wound dressings were changed about every 24 to 48 hours until discharge from hospital or until the end of treatment at Day 14 in 'recent wounds' or Day 28 in 'chronic wounds.' No follow-up beyond Day 14 or 28.	10

Study Number Country Study Status	Title of Study	Study Treatment(s) and Duration of Treatment Duration of Follow-Up	Total number of patients exposed
Treatment of split-thickness skin graft donor site wounds			
BSH-12 Austria, Bulgaria, Czech Republic, Finland, Germany, Poland Completed	Open, blindly evaluated, prospective, controlled, randomised, multicentre, phase III clinical trial to compare intra-individually the efficacy and tolerance of Oleogel-S10 versus standard of care in accelerating the wound healing of split-thickness skin graft donor sites.	Oleogel-S10 plus non-adhesive wound dressing vs. non-adhesive wound dressing alone at each dressing change (every 3 to 4 days) until full wound closure or up to 28 days. Treatment allocation to the halves of the wound was randomly assigned. Subjects attended follow-up visits at 3- and 12-months post treatment.	107
BSG-12 France, Greece, Latvia, and Spain Completed	Open, blindly evaluated, prospective, controlled, randomised, multicentre, phase III clinical trial to compare intra-individually the efficacy and tolerance of Oleogel-S10 versus standard of care in accelerating the wound healing of split-thickness skin graft donor sites.	Oleogel-S10 plus non-adhesive wound dressing vs. non-adhesive wound dressing alone until full wound closure or up to 28 days. Treatment allocation to the halves of the wound was randomly assigned. Subjects attended follow-up visits at 3- and 12-months post treatment.	112
BSH-10 Germany Completed	Open, Prospective, Controlled, Randomised, Multicentre Phase II Clinical Trial to Compare Intra-Individually the Efficacy and Tolerance of Oleogel-S10 versus Moist Wound Healing Dressing Alone in Accelerating the Epithelialization of Split Thickness Skin Graft Donor Site	Oleogel-S10 applied to Mepilex moist dressing vs. conventional treatment with Mepilex moist dressing only. Subjects were simultaneously given 2 treatments, one on each half of the SSG wound site, for 14 days. Subjects attended a follow-up visit at 3 months post treatment.	24
Treatment of Grade 2a burn wounds			
BBW-11 Germany, Sweden, Switzerland and UK Completed	Open, blindly evaluated, prospective, controlled, randomised, multicentre, phase III clinical trial to compare intra-individually the efficacy and tolerance of Oleogel-S10 versus standard of care in accelerating the healing of Grade 2a partial thickness burn wounds.	Oleogel-S10 plus non-adhesive wound dressing vs. Octenilin plus non-adhesive wound dressing applied every other day until full wound closure or for up to 21 days. Treatment allocation to the 2 halves of the wound (or 2 comparable wounds) was randomly assigned. Subjects attended follow-up visits at 3- and 12-months post treatment.	61

Study Number Country Study Status	Title of Study	Study Treatment(s) and Duration of Treatment Duration of Follow-Up	Total number of patients exposed
Treatment of actinic keratosis skin lesions			
BAK-08 (BETA trial) Germany, Greece Completed	Phase II, Randomized, multi center, double blind study to compare the efficacy and tolerability of Oleogel-S10 for 3 months versus placebo only in patients with mild to moderate actinic keratoses located at the face and head	4 treatment groups as follows: Group A treated with Oleogel-S10 once/day for 3 months Group B treated with Oleogel-S10 twice/day for 3 months Group C treated with Placebo (Petroleum jelly) once/day for 3 months Group D treated with Placebo (Petroleum jelly) twice/day for 3 months Subjects returned for a follow-up visit at Week 18 (4.5 months or 1.5 months post treatment).	111
Huyke, et al., 2006, Treatment of actinic keratoses with birch bark extract: a pilot study. Germany, Completed	Open, prospective, parallel group proof of concept pilot study to determine the efficacy of birch bark extract in the treatment of actinic keratoses	2 Treatment Groups: Oleogel-S10 alone Oleogel-S10 cryotherapy Oleogel-S10 treatment period was 2 months.	28
Huyke, et al., 2009, BAK-04 Treatment of actinic keratoses with a novel betulin based oleogel; A prospective, randomized, comparative pilot study. Germany, Completed	Phase IIa, Randomized, prospective monocenter comparative pilot study to determine the efficacy of birch bark extract in the treatment of actinic keratoses	3 Treatment Groups: Oleogel-S10 alone Oleogel-S10 cryotherapy Cryotherapy alone Oleogel-S10 treatment period was 2 months.	30
Treatment with Atopic Dermatitis			

Study Number Country Study Status	Title of Study	Study Treatment(s) and Duration of Treatment Duration of Follow-Up	Total number of patients exposed
BCA-001 Germany Completed	Phase I, Placebo-controlled, double-blind, randomized proof of concept clinical study to investigate the efficacy and tolerability after three weeks treatment and one week regression phase of a 4 % birch bark extract containing topical preparation in a contralateral comparison in patients with atopic dermatitis in a subchronic state	Approximately 1.5 cm of the test substance (4% birch bark extract vs placebo gel) was administered twice daily over a 3-week period	33
Treatment of psoriasis			
BC-002 Germany Completed	Phase I, 12-day placebo and active controlled, double-blind, randomised proof of concept clinical study to investigate the efficacy of 4% birch bark extract (containing 90% Betulin) ointments in a psoriasis plaque test	125 µl of the test product administered for 7 days for 24 each using large Finn chambers Test products: 1. Birkencreme A (active ingredient; 4% tripertenes of birch bark containing 90% Betulin as a main component and betulinic acid and Lupeol as minor components) 2. Birkencreme G (active ingredient; 4% tripertenes of birch bark containing 90% Betulin as a main component and betulinic acid and Lupenol as minor components) 3. Placebo without emulsion	24

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

*100 of these patients were previously included in the Oleogel-S10 arm of the Double Blind Phase of BEB-13. 105 out of 114 patients included in the Control gel arm of the Double Blind Phase of BEB-13 continued in the Open Label Phase. A total of 205 patients entered the Open Label phase.

Table 3 Patient exposure in clinical trials by Gender, Racial and Age Group

	BEB-13 (OLP)*	BEB-13 (DBP)	BEB-10	BSH-12	BSG-12	BSH-10	BBW-11	BAK-08	Huyke, et al., 2006),	Huyke, et al., 2009),	BCA-001	BC-002
INDICATION	**EPIDERMOLYSIS BULLOSA**	**EPIDERMOLYSIS BULLOSA**	**EPIDERMOLYSIS BULLOSA**	**SKIN GRAFT DONOR SITE**	**SKIN GRAFT DONOR SITE**	**SKIN GRAFT DONOR SITE**	**BURN WOUNDS**	**ACTINIC KERATOSIS**	**ACTINIC KERATOSIS**	**ACTINIC KERATOSIS**	**ATOPIC DERMATITIS**	**PSORIASIS**
NUMBER OF PATIENTS EXPOSED (N)	**205***	**109**	**10**	**107**	**112**	**24**	**61**	**111**	**28**	**30**	**33**	**24**
MALE / FEMALE (%)	61/39	62/38	70/30	64 / 36	66 / 34	67 / 33	69 / 31	80 / 20	18/10	Unk	7/26	20/4
RACIAL GROUP (NUMBER OF PATIENTS)												
Asian	10	0	Unk	0	0	Unk	5	Unk	Unk	Unk	Unk	Unk
Black	3	0	Unk	0	1	Unk	4	Unk	Unk	Unk	Unk	Unk
White	169	95	Unk	107	98	Unk	51	Unk	Unk	Unk	Unk	Unk
Other	23	14	Unk	0	11	Unk	1	Unk	Unk	Unk	Unk	Unk
Unknown	0	0	Unk	0	2	Unk	0	Unk	Unk	Unk	Unk	Unk
TOTAL	**205**	**109**	**10**	**107**	**112**	**24**	**61**	**111**	**28**	**30**	**33**	**24**

	BEB-13 (OLP)*	BEB-13 (DBP)	BEB-10	BSH-12	BSG-12	BSH-10	BBW-11	BAK-08	Huyke, et al., 2006),	Huyke, et al., 2009),	BCA-001	BC-002
Age, years (NUMBER OF PATIENTS)												
0 years to <4 years	16	7	0	0	0	0	0	0	Unk	Unk	0	0
≥4 years to <12 years	81	42	3	0	0	0	0	0	Unk	Unk	0	0
≥12 years to <18 years	50	25	2	0	0	0	0	0	Unk	Unk	0	0
≥18 years to <65 years	58	33	5	67	89	24	55	10	Unk	Unk	32	21
≥65 years	0	2	0	40	23		6	101	Unk	Unk	1	3
Median (years)	N/A	13	20	56	49	65	41	72	69	Unk	33	44.5
Range (years)	N/A	1–71	6-48	18-86	19-90	22-80	18-79	56-88	51-80	Unk	18-68	21-69
Total	**205**	**109**	**10**	**107**	**112**	**24**	**61**	**111**	**28**	**30**	**33**	**24**

Abbreviations: OLP = Open Label Phase, DBP = Double Blind Phase

*100 of these patients were previously included in the Oleogel-S10 arm of the Double Blind Phase of BEB-13. 105 out of 114 patients included in the Control gel arm of the Double-Blind Phase of BEB-13 continued in the Open Label Phase. A total of 205 patients entered the Open Label phase.

For all studies, estimated exposure is actual exposure data.

Given the fundamental differences in study design and patient populations within the clinical dataset, it was not possible to pool the exposure data across studies.

The studies of Oleogel-S10 varied in design (e.g., many do not include a separate control group), duration of treatment, and study population (EB versus non-EB). Specifically, the non-EB Phase 3 studies performed in adult patients with partial-thickness wounds (BSG-12, BSH-12, and BBW-11) enrolled generally healthy subjects with single wounds, many of which had been surgically created (split-thickness graft donor sites). Furthermore, supportive studies for Filsuvez employed an intra-subject comparison of Oleogel-S10 vs. a standard of care control in either 2 similarly sized wounds, or a single large wound that was divided in half and comparisons made between the 2 halves. In addition, the non-EB studies generally evaluated a much shorter treatment duration than the EB Phase 3 study.

Therefore, the duration of exposure in person time and exposure days is presented below in the pivotal study for Filsuvez and separately in a pooled analysis for the supportive studies for Filsuvez.

Table 4.Extent of Exposure in Pivotal Trial for Filsuvez (Phase 3 Study BEB-13 Double-Blind Phase and Open Label Phase)

		DBP			OLP[a]		
		Oleogel-S10 N=109 n (%)	**Control Gel N=114 n (%)**	**All Subjects N=223 n (%)**	**Former Oleogel-S10 N=71 n (%)**	**Former Control Gel N=74 n (%)**	**All Subjects N=145 n (%)**
Treatment duration [days][b]	n	109	114	223	71	74	145
	Mean (SD)	89.0 (18.34)	86.8 (23.64)	87.9 (21.20)	537.1 (257.65)	515.6 (278.13)	526.1 (267.58)
	Min	2	2	2	14	7	7
	Median	91.0	91.0	91.0	720.0	721.0	721.0
	Max	140	161	161	841	780	841
Actual treatment duration overall [days][c]	n	109	114	223	71	74	145
	Mean (SD)	89.0 (18.43)	86.4 (23.88)	87.7 (21.38)	535.7 (258.88)	511.1 (279.59)	523.1 (268.99)
	Min	0	0	0	14	7	7
	Median	91.0	91.0	91.0	720.0	718.5	720.0
	Max	140	161	161	841	780	841

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

[a] Exposure data are calculated only for subjects who have reached study completion or discontinued early.

[b] 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.

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

Table 5. Duration of exposure in supportive studies for Filsuvez

Wound type / Study	**Number of days of study drug exposure**							
	N	Mean	STD	Min	1st Quartile	Median	3rd Quartile	Maximum
STSG wound (BSG-12/BSH-12)	219	18.5	6.8	3	13.0	16.0	23.0	34
Grade 2a burn wound (BBW-11)	61	10.4	4.9	2	7.0	9.0	13.0	23
Total	280	16.7	7.2	2	11.5	15.0	21.0	34

Table 6. Duration of exposure for Filsuvez (Pooled supportive studies)

Duration of Exposure	Persons	Person time (subject days)*
Total	280	4,676

*calculated from mean and number of exposed persons, see Table 4

Table 7. Duration of exposure for Filsuvez(Other supportive studies)

Duration of Exposure	Persons	Person time (subject days)
Total	482	16,215

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Pregnancy and Lactation

Reason for exclusion: Potential risk of teratogenic or fetotoxic events; Potential exposure to child via breast milk

Is it considered to be included as missing information? Yes

Rationale: The risk was not identified during non-clinical studies, but pregnant and lactating women were excluded from clinical trials. There were no pregnant patients exposed to Oleogel-S10. It is unknown if Oleogel-S10 is excreted in human milk.

Current and /or former malignancy including basal cell carcinomas and squamous cell carcinomas

Reason for exclusion: Excluded for patient safety. Immunosuppressive therapy and cytotoxic chemotherapy within 60 days prior to study enrolment was one of the exclusion criteria. In addition, associated metastasis with cutaneous involvement and the high risk of secondary infections has a significant impact on patient safety.

Is it considered to be included as missing information? No

Rationale: This will be described as an important potential risk and will be included as a warning in the prescribing information

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes.

Due to the small patient size exposed, the clinical development programme is unlikely to detect certain types of adverse reactions with an incidence rate of less than 1:1000. However, the safety data gathered so far demonstrate a safety risk consistent with a favourable overall risk / benefit ratio.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes.

Table SIV.2: Exposure of special populations included or not in clinical development programmes

Type of special population	Exposure
Pregnant women	Pregnant women were not included in the clinical development programme, however, one patient was exposed to the control gel in the BEB-13 clinical trial during the first trimester. The subject was discontinued from the clinical trial.
Breastfeeding women	Not included in the clinical development program

Type of special population	Exposure
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program
Population with relevant different ethnic origin	Not applicable.
Subpopulations carrying relevant genetic polymorphisms	Not applicable

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Exposure to commercial product is estimated in patient years based on unit sales. The following formula is sued:

Number of mg sold (mg) ÷ average daily dose (1450.8 mg per day)

÷ 1 year (365) = number of patient years

For patient exposure through an expanded access programme, absolute patient numbers are used.

SV.1.2 Exposure

As of the DLP of 14 Jan 2023, Filsuvez® Gel has been provided commercially in Austria (named patient sales), Colombia (named patient sales), Germany (launched), Greece (named patient sales) and Spain (named patient sales).

Patient exposure to Filsuvez® was estimated as:

• Interval commercial patient exposure estimate: 6.73 patient years for the current period (15 July 2022 to 14 January 2023)

• Cumulative commercial patient exposure estimate: 34.12 patient years for cumulative period (14 January 2016 to 14 January 2023)

Additionally, patient exposure for patients who are supplied product through an expanded access program (e.g. free of charge supply) is based on absolute patient numbers. There were 31 new patients who received product during the interval reporting period. Cumulatively there have been 125 patients exposed to birch bark extract through Compassionate use/Expanded access programs in the EMEA (113), UK (5) and ROW (7).

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

The potential for misuse of birch bark extractor use for illegal purposes is unlikely and has not been identified to date.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial EU RMP submission for Filsuvez (birch bark extract)

Details of important identified and potential risks are as follows:

Important identified risks	None
Important potential risks	Squamous cell carcinoma and other skin malignancies
Missing information	Use in patients with different skin types regarding ethnic origin / Fitzpatrick skin types

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the EU RMP for Filsuvez (birch bark extract):

Wound infection

Reason for not including an identified or potential risk in the list of safety concerns in the EU RMP for Filsuvez (birch bark extract)::

Wound infection with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable (in relation to the severity of treated wounds):

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the EU RMP for Filsuvez (birch bark extract):

Important Identified Risk : None

Important Potential Risk : Squamous cell carcinoma and other skin malignancies

Risk-benefit impact:

There is a high incidence of developing aggressive SCC in patients with EB. (Fine et al, 2009). It usually occurs in multiple primary sites of chronic lesions, particularly in patients with DEB, especially in severely affected RDEB. SCCs in RDEB patients occur at a much higher rate than all other EB subtypes and the risk of SCC increase with age: According to Fine et al 2009, SCC was highest in patients with RDEB Generalised Severe with at least one occurrence in 7.5% of patients by the age of 20 years, 67.8% by age 35, 73.4% by age 40, 80.2% by age 45, and 90.1% by age 55. In cases of DEB, there is no predilection for photo exposed areas.

In the pivotal BEB-13 trial for EB, four cases of SCC amongst study subjects were noted of which 2 cases of SCC were categorised as possibly related by the Sponsor in association with Oleogel-S10 therapy due to temporal association. Both were patients with RDEB, one generalised Severe and one generalised intermediate, and over 45 years of age and the investigator considered the SCC as not related to Oleogel-S10, consistent with the clinical course of their EB.

Missing information : Use in patients with different skin types regarding ethnic origin / Fitzpatrick skin types

Limited numbers of non-Caucasian patients have been enrolled in the pivotal trials. Also limited Fitzpatrick skin types have been addressed in clinical studies.

SVII.2 New safety concerns and reclassification with a submission of an updated EU RMP for Filsuvez (birch bark extract):

None

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks:

Important Identified Risk: None

Important Potential Risk : Squamous cell carcinoma and other skin malignancies

(Skin malignant tumors SMQ, Skin neoplasms, malignant and unspecified SMQ)

Potential mechanisms: The intended action of Oleogel-S10 / Filsuvez in EB is to accelerate wound healing.

The four overlapping phases of healing are described as (des Jardins- Park et al, 2019):

I. **Haemostasis**: (0–6 hrs) The primary response to injury (clot formation).
II. **Inflammation**: (0–5 days) Elimination of pathogens and debris.
III. **Proliferation & Deposition:** (4-21 days) The reparative phase – including proliferation/ migration of fibroblasts & keratinocytes, deposition of matrix, and epithelialisation.
IV. **Remodelling:** (21 days - ≥1 year) Reorganisation and restoration of skin integrity.

It is known that when normal cellular regulatory mechanisms are disrupted (in particular, the p53 and p21 tumour suppressor genes at the cell cycle checkpoints), aberrant, uncontrolled proliferation can lead to carcinogenesis. In the general population, this occurs in the skin as low-risk SCC in later life and usually as a result of ultraviolet (UV) exposure. In EB (particularly RDEB), it is common, and occurs *independently* of UV exposure. Repeated cycles of tissue wounding, healing and breakdown are believed to be an important contributory factor.

Almost all patients with the RDEB subtype will be expected to present with SCC at some point in their lifetime; indeed, it is recognised as the primary cause of death in these patients. The severe and aggressive form in these patients has been explained by molecular changes in the local micro-environment, including prolonged inflammation, fibrosis and scar formation. Increased production of TGF-β, and a lack of anchoring via Collagen VII leads to loss of integrin-interactions, perpetuates a myofibroblast phenotype, excess matrix deposition and eventual conversion towards cancer-associated fibroblast like cells. Proteomic studies indicate that the deletion of Col7 in RDEB predisposes the fibroblasts to dysregulated matrix deposition and complications including tumorigenesis. In turn, this additionally creates an environment conducive to keratinocyte transition to carcinoma cells (Conderelli et al, 2019). The loss of Col7 interactions in RDEB keratinocytes serves to enhance migration and invasion, impair differentiation and stimulates epithelial – mesenchymal transition. Reduction in adhesion proteins including tissue transglutaminase (TGM) (Kuttner et al., 2014) and LM332, as well

as hyperactivation of the inflammatory cytokine, IL-6 (Qaio et al 2018), each play a role, as does microbial infection and bioburden (Hooste et al., 2015; Nystrom et al, 2018; van der Kooi-Pol et al., 2013).

Woefle et al., 2010 indicates that triterpenes inhibit the growth of cancer cells *in vitro*. In a 3-month study of actinic keratosis (AK), a pre-cancerous condition of the skin epithelia, a down-regulation or normalisation of ki67 expression was reported in the presence of TE, together with promotion of keratinocyte terminal differentiation. These and previous results (Huyke et al., 2009) point towards a potential therapeutic role for TE in prevention of neoplasia.

Ebeling et al., 2014 indicate a transient up-regulation of the pro-inflammatory response to healing (as evidenced by stabilisation of cyclo-oxygenase-2, IL-6 and IL-8 mRNA and protein), as well as stimulation of keratinocyte migration in the scratch assay model, with minimal effect on proliferation.

In the long-term study of topically applied Oleogel-S10 to the skin of minipigs (Module SII above), no formation of neoplastic or pre-neoplastic lesions were observed.

In conclusion, whilst the above suggests that the known mechanism of action of Filsuvez would not promote neoplasia or pre-neoplastic lesions, the intended long-term therapy duration for Filsuvez might be an issue of clinical relevance, so this risk has been retained.

Evidence source(s) and strength of evidence: In the pivotal trial, a total of 4 patients experienced SCC of skin. In 2 patients (both adults, 1 with RDEB generalised severe and 1 with RDEB generalised intermediate) Oleogel-S10 was not applied to the lesion that transformed into SCC. In 2 further patients (1 with RDEB generalised severe and 1 with RDEB generalised intermediate, aged over 45 years of age) Oleogel-S10 had been applied to the lesion that transformed into SCC.

Characterisation of the risk: The wounds, where the SCC had been diagnosed, had not been treated with Oleogel-S10 in two out of four patients. All events were assessed as unlikely related to Oleogel-S10 by the investigator, while the MAH assessed 2 of the events of SCC as possibly related based on the temporal relationship. All of SCC events were assessed as severe under Grade 3 severity criteria.

The outcome was reported as recovered (n=2), recovered with sequalae (n=1) and ongoing (n=1). Three out of 4 patients discontinued the study due to the SCC.

Risk factors and risk groups: RDEB especially with severe diagnosis, and EB patients with prior SCC

Preventability: Physicians should regularly monitor patients with the purpose of detecting and managing patients with skin lesions suspected to be cancerous or pre-cancerous and withdraw treatment if applicable.

Impact on the risk-benefit balance of the product: Depending on how the SCC develops and how early it is diagnosed, it can have mild to severe impact on the patient's quality of life.

Despite the primary genetic defects underlying each inherited EB type, all EB patients share skin and/or mucosal fragility and blistering. Mutations in genes coding for specific components of the epidermal-dermal junction strongly compromise the healing process particularly in the most severe and disabling EB sub-types, and, in turn, skin erosions and blisters evolve into chronic wounds, inflammation and fibrosis (Cianfarani, 2017). Therefore, the relationship between the risk of occurrence of epithelial cancers such as squamous cell carcinoma of skin and the unremitting and altered wound healing process of severe EB patients is evident by means of the aberrant activation of wound healing pathways (Foster, 2018). These events are responsible for the onset of highly disabling and even life-threatening disease complications including SCC (Cianfarani, 2017). In light of the physio-pathological pathways involved in the manifestation of SCC in concordance with the genetic

susceptibility of EB patients, the risk-benefit balance for Filsuvez is deemed positive in relation to the severity of the indication(s) treated.

Public health impact: The potential public health impact is considered low.

SVII.3.2. Presentation of the missing information

Missing information : Use in patients of different race/ethnicity

Limited numbers of non-Caucasian patients have been enrolled in the pivotal trials.

Anticipated risk/consequence of the missing information:

There is a theoretical risk that such patients have a higher risk of side effects against birch bark extract.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns for Filsuvez (birch bark extract)

Summary of safety concerns for Filsuvez (birch bark extract)	
Important identified risks	None
Important potential risks	Squamous cell carcinoma and other skin malignancies
Missing information	Use in patients of different race/ethnicity

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Chiesi will monitor the safety profile of birch bark extract as per routine pharmacovigilance and signal management processes. These processes include signal detection/ assessment activities (in a timely manner) and adverse reaction reporting for which the risk minimisation information in the product information is adhered to by prescribers, (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised). It also includes continued monitoring and systematic review of available safety data, which includes review of particular safety issues of concern for periodic reports. Routine pharmacovigilance activities beyond adverse reaction reporting and signal management are not proposed.

Specific adverse reaction follow-up questionnaires for safety concerns in Table SVIII.1:

- Follow-Up Questionnaire for Skin Malignancies

Other forms of routine pharmacovigilance activities for safety concerns in Table SVIII.1:

Monitoring the risk of SCC using the 'Skin neoplasms, malignant and unspecified (SMQ)' and 'Skin malignant tumours (SMQ)' via the routine pharmacovigilance activities (during monthly Signal management activities).

III.2 Additional pharmacovigilance activities

Chiesi will monitor safety concerns for birch bark extract amongst patients with epidermolysis bullosa under additional pharmacovigilance activity though the proposed Filsuvez Observational Safety and Effectiveness Evaluation Registry- based Study in EB. Specific safety concerns addressed by the proposed Registry-based study are outlined under *III.3 Summary Table of additional Pharmacovigilance activities.*

Filsuvez Observational Safety Registry Based Study (FOSteR)

Study short name and title: A long-term non-interventional study to assess the incidence of skin malignancies in patients with dystrophic and junctional epidermolysis bullosa receiving treatment with Filsuvez (FOSteR)

Rationale and study objectives: The study is designed with a primary objective to estimate the incidence of first skin malignancy during follow-up in patients with DEB and JEB receiving treatment with Filsuvez in real-world clinical practice.

In the general population, the risk of skin cancer is inversely correlated with the amount of melanin present in skin. The correlation is weak and not linear, and there are numerous factors that influence the risk of developing skin cancer. The MAH will collect data on race/ethnicity to describe any possible related patterns between race/ethnicity and Filsuvez exposure to help understand the distribution of patient characteristics. Fitzpatrick skin types will not be collected in this study due to difficulties in collecting this information according to feasibility assessments.

Study design: This is a non-interventional, multi-country, cohort study based on primary data collection and secondary use of patient registry data. The study will have an approximately 2-year enrolment period, followed by a 5-year follow-up period. However, since EB is a rare disease and skin malignancy a rare event, the enrolment rates will be monitored, and the enrolment and study periods may be modified based on actual enrolment rates and Filsuvez uptake.

Data is collected when patients attend their standard care visits, which for most patients is expected to occur approximately annually. For EB registries, data is collected through the usual registration and collection practice of the respective registries.

The DEB and JEB patients will be assessed for exposure to Filsuvez and followed up for occurrence of skin malignancies from the date of study enrolment (index date) to the date of discontinuation (death, discontinuation from site or registry, physician's decision in sites, withdrawal of consent, emigration, lost to follow-up, or end of the study).

Study size and population:

Study size estimations were carried out for the primary outcome (first skin malignancy) by varying incidence rates (IR) between 1 and 10 per 100 person-years, with margins of error from 0.1 to 0.5 and follow-up values of 1, 2 and 3 years. With an estimated IR (based on literature reports of skin malignancy in RDEB patients) of 4 events per 100 person-years, for a target margin of error of 0.25 (6.25% of the IR), the estimated target size of 123 Filsuvez-exposed patients with a follow-up contribution of 2 years per patient across all study countries, would be appropriate. For a follow-up of

1 year and 3 years per patient, an estimated sample size of 246 and 82 Filsuvez-exposed patients are required, respectively.

Population considered for the inclusion in the study are patients with a confirmed diagnosis of DEB or JEB and alive during the enrolment period. Two types of data sources are planned for this study with a site-based primary data collection from specialised EB centres, and data collection from existing EB disease registries [such as Registro EB (Italy) and Dutch EB Registry (Netherlands)].

Study milestones:

- Registration in the EU PAS register: Within 30 days after protocol endorsement by European Medicines Agency (EMA)
- Anticipated start of data collection: Q2 2024
- Anticipated end of data collection: Q2 2031
- Interim reports will be generated every 24 months (2026, 2028, 2030)
- Final report of study results: 2032

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities.

Study name/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Filsuvez Observational Safety Registry Based Study (FOSteR) ongoing	To estimate the incidence of first skin malignancy during follow-up in patients with DEB and JEB receiving treatment with Filsuvez in real-world clinical practice.	• Important potential risk: Squamous cell carcinoma and other skin malignancies • Missing information: Use in patients of different race/ethnicity	Registration in the EU PAS register	Within 30 days after protocol endorsement by EMA
			Estimated start of data collection	Q2 2024
			Estimated end of data collection	Q2 2031
			Submission of Study Interim reports	Generated every 24 months (2026, 2028, 2030)

Study name/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
			Final report of study results	2032

Part IV: Plans for post-authorisation efficacy studies

There are no post-authorisation efficacy studies planned.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Indication	Routine risk minimisation activities
Important Potential Risk Squamous cell carcinoma and other skin malignancies	Epidermolysis bullosa	Routine risk communication: *SmPC section 4.4* *PL section 2* Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine
Missing information Use in patients of different race/ethnicity	Epidermolysis bullosa	Routine risk communication: *None* Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Indication	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risk Squamous cell carcinoma and other skin malignancies	Epidermolysis bullosa	Routine risk communication: *SmPC section 4.4* *PL section 2* Other routine risk minimisation measures beyond the Product Information: Not Applicable Legal status: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: Follow-Up Questionnaire for Skin Malignancies Monitoring the risk using 'Skin neoplasms, malignant and unspecified (SMQ)' and 'Skin malignant tumours (SMQ)' during monthly Signal management activities **Additional pharmacovigilance activities**: Filsuvez Observational Safety Registry Based Study (FOSteR)

Safety concern	Indication	Risk minimisation measures	Pharmacovigilance activities
Missing information Use in patients of different race/ethnicity	Epidermolysis bullosa	Routine risk communication: *None* Other routine risk minimisation measures beyond the Product Information: Not Applicable Legal status: Prescription only medicine	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Filsuvez Observational Safety Registry Based Study (FOSteR)

Part VI: Summary of the EU risk management plan for Filsuvez (birch bark extract)

This is a summary of the risk management plan (RMP) for Filsuvez. The RMP details important risks of Filsuvez, and how more information will be obtained about Filsuvez's risks and uncertainties (missing information).

Filsuvez's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Filsuvez should be used.

This summary of the RMP for Filsuvez should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new safety concerns or changes to the current ones will be included in updates of Filsuvez's RMP.

I. The medicine and what it is used for

Filsuvez is authorised for epidermolysis bullosa (see SmPC for the full indication). It contains birch bark extract as the active substance, and it is given topically.

Further information about the evaluation of Filsuvez's benefits can be found in Filsuvez's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage Filsuvez | European Medicines Agency (europa.eu).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Filsuvez, together with measures to minimise such risks and the proposed studies for learning more about Filsuvez's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

If important information that may affect the safe use of birch bark extract is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Filsuvez are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Filsuvez. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and

needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• Squamous cell carcinoma and other skin malignancies
Missing information	• Use in patients of different race/ethnicity

II.B Summary of important risks

Important identified risk : None

Important Potential Risk : Squamous cell carcinoma and other skin malignancies	
Evidence for linking the risk to the medicine.	In the pivotal trial, a total of four patients experienced SCC of skin, one patient in the double-blind phase and three in the open label phase (based on interim safety analysis set). The wounds where the SCC was diagnosed had not been treated with Oleogel-S10 in two out of four patients, the other 2 cases occurred in patients at known high risk of developing SCC as had RDEB generalised severe and were over 45 years of age. All events were assessed as unlikely related to Oleogel-S10 by the investigator, while the MAH assessed 2 of the events of SCC as possibly related based on the temporal relationship. All of SCC events were assessed as severe under Grade 3 severity criteria. The outcome was reported as recovered (n=2), recovered with sequalae (n=1) and ongoing (n=1). Three out of 4 patients discontinued the study due to the SCC.
Risk factors and risk groups	Patients with prior of history of skin cancers; particularly in patients with RDEB especially severe.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4; Warnings and Precautions PIL section 2 Prescription only medicine
Additional pharmacovigilance activities	Filsuvez Observational Safety Registry Based Study (FOSteR)

Missing information : Use in patients of different race/ethnicity	
Risk minimisation measures	Routine risk minimisation measures None Prescription only medicine
Additional pharmacovigilance activities	Filsuvez Observational Safety Registry Based Study (FOSteR)

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation.

There are no studies which are conditions of the marketing authorisation or specific obligation of Filsuvez.

II.C.2 Other studies in post-authorisation development plan

Filsuvez Observational Safety Registry Based Study (FOSteR)

Study short name and title: A long-term non-interventional study to assess the incidence of skin malignancies in patients with dystrophic and junctional epidermolysis bullosa receiving treatment with Filsuvez (FOSteR).

Rationale and study objectives: The study is designed with a primary objective to estimate the incidence of first skin malignancy during follow-up in patients with DEB and JEB receiving treatment with Filsuvez in real-world clinical practice.

In the general population, the risk of skin cancer is inversely correlated with the amount of melanin present in skin. The correlation is weak and not linear, and there are numerous factors that influence the risk of developing skin cancer. The MAH will collect data on race/ethnicity to describe any possible related patterns between race/ethnicity and Filsuvez exposure to help understand the distribution of patient characteristics. Fitzpatrick skin types will not be collected in this study due to difficulties in collecting this information according to feasibility assessments.

Study design: This is a non-interventional, multi-country, cohort study based on primary data collection and secondary use of patient registry data. The study will have an approximately 2-year enrolment period, followed by a 5-year follow-up period. However, since EB is a rare disease and skin malignancy a rare event, the enrolment rates will be monitored, and the enrolment and study periods may be modified based on actual enrolment rates and Filsuvez uptake.

Data is collected when patients attend their standard care visits, which for most patients is expected to occur approximately annually. For EB registries, data is collected through the usual registration and collection practice of the respective registries.

The DEB and JEB patients will be assessed for exposure to Filsuvez and followed up for occurrence of skin malignancies from the date of study enrolment (index date) to the date of discontinuation (death, discontinuation from site or registry, physician's decision in sites, withdrawal of consent, emigration, lost to follow-up, or end of the study).

Study size and population:

Study size estimations were carried out for the primary outcome (first skin malignancy) by varying incidence rates (IR) between 1 and 10 per 100 person-years, with margins of error from 0.1 to 0.5 and follow-up values of 1, 2 and 3 years. With an estimated IR (based on literature reports of skin malignancy in RDEB patients) of 4 events per 100 person-years, for a target margin of error of 0.25 (6.25% of the IR), the estimated target size of 123 Filsuvez-exposed patients with a follow-up contribution of 2 years per patient across all study countries, would be appropriate. For a follow-up of 1 year and 3 years per patient, an estimated sample size of 246 and 82 Filsuvez-exposed patients are required, respectively.

Population considered for the inclusion in the study are patients with a confirmed diagnosis of DEB or JEB and alive during the enrolment period. Two types of data sources are planned for this study with a site-based primary data collection from specialised EB centres, and data collection from existing EB disease registries [such as Registro EB (Italy) and Dutch EB Registry (Netherlands)].

Study milestones:

- Registration in the EU PAS register: Within 30 days after protocol endorsement by European Medicines Agency (EMA)
- Anticipated start of data collection: Q2 2024
- Anticipated end of data collection: Q3 2031
- Interim reports will be generated every 24 months (2026, 2028, 2030)
- Final report of study results: 2032

Part VII: Annexes

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Annex 4 - Specific adverse drug reaction follow-up forms

Follow up Questionnaire for Skin Malignancies

Targeted Questionnaire -Filsuvez: Skin Malignancies

Patient Information					
Patient Initials:	Gender: ☐ Male ☐ Female	Date of Birth:	Age:	Height: ☐ inches ☐ cm	Weight: ☐ lbs ☐ kg
Race/ Ethnicity: ☐ White ☐ Black/African American ☐ Asian ☐ Hispanic ☐ Other……					
Adverse Event (s)					
[List verbatim terms]					

[Choose / customize the appropriate sections below as appropriate for the ICSR]

Epidermolysis Bullosa (EB) subtype	Classification	Comments
☐ Junctional EB	☐ Generalized severe ☐ Generalized intermediate ☐ Localized ☐ Other	
☐ Dystrophic EB ☐ Recessive dystrophic EB ☐ Dominant dystrophic EB		
☐ EB simplex		
☐ Kindler EB		

Other Medical History, including Surgical Procedures ☐ None			
Condition	Start Date	Stop Date	Comments
		☐ Ongoing	
		☐ Ongoing	
		☐ Ongoing	

Chiesi/ Co-suspect Product Information				
Name			Start Date	Stop Date
Filsuvez				☐ Ongoing
Indication		Dose	Frequency	Route
Location(s) of application				
Lot Number:	Exp. Date:			
Action Taken:	Drug Stop Date	Event Stop?	Drug Restart Date	Event Re-appear?
☐ Dose not changed				
☐ Dose increased				
☐ Dose decreased				
☐ Drug interrupted		☐ Yes ☐ No		☐ Yes ☐ No
☐ Drug withdrawn		☐ Yes ☐ No		
☐ Unknown				
Co-suspect Drug Name			Start Date	Stop Date
☐ None				☐ Ongoing
Indication		Dose	Frequency	Route
Action Taken:	Drug Stop Date	Event Stop?	Drug Restart Date	Event Re-appear?
☐ Dose not changed				
☐ Dose increased				
☐ Dose decreased				
☐ Drug interrupted		☐ Yes ☐ No		☐ Yes ☐ No
☐ Drug withdrawn		☐ Yes ☐ No		
☐ Unknown				

Skin Malignancy Information			
The type of skin malignancy		Start Date	Stop Date
☐ Squamous cell skin cancer (SCC) ☐ Basal cell skin cancer ☐ Cutaneous malignant melanoma ☐ Other:	☐ New diagnosis ☐ Recurrence ☐ Metastatic		
Was Filsuvez applied to the area in which the skin malignancy developed?		Start Date	Stop Date
☐ Yes (if yes, please specify start and stop dates of treatment) ☐ No			
Location of skin malignancy:	Features of the area: ☐ Area of non-healing or partial thickness wounds ☐ Area of scarring due to EB ☐ Other:		
Was the event confirmed by biopsy or histopathological examination? ☐ Yes ☐ No	Stage: Grade:	Is the event related to Filsuvez? ☐ Related ☐ Not related ☐ Possibly related ☐ Unassessable ☐ Unlikely related ☐ Unknown	
Risk factors			
☐ Previous cutaneous SCC ☐ Occupational ☐ Immunosuppression ☐ Non healing ulcer ☐ Excessive sun exposure ☐ Actinic keratoses ☐ Genetic disease (other than EB): ☐ Other tumors (either benign or malignant): ☐ Other:			
Treatment of skin malignancy			
Outcome			
☐ Recovered with sequelae ☐ Not recovered ☐ Recovering ☐ Recovered ☐ Fatal			
If hospitalized, please include the hospital discharge summary.		Admission Date	Discharge Date
If outcome is fatal, please provide a copy of the death certificate.		Date of Death	Autopsy Performed?
			☐ Yes ☐ No

Other Adverse Event Information ☐ None		
Verbatim term	Start Date	Stop Date
Can you confirm that the event occurred? ☐ Yes ☐ No	Is the event related to Filsuvez? ☐ Related ☐ Not related ☐ Possibly related ☐ Unassessable ☐ Unlikely related ☐ Unknown	
If yes, please provide a specific diagnosis		
Event specific treatment		
Outcome		
☐ Recovered with sequelae ☐ Not recovered ☐ Recovering ☐ Recovered ☐ Fatal		
If hospitalized, please include the hospital discharge summary.	Admission Date	Discharge Date
If outcome is fatal, please provide a copy of the death certificate.	Date of Death	Autopsy Performed?
		☐ Yes ☐ No

Laboratory Tests ☐ None		
Name / Type of Test	Date of test	Results (including units)
	Normal Range	Assessment
		☐ Normal ☐ Abnormal
Name / Type of Test	Date of test	Results (including units)
	Normal Range	Assessment
		☐ Normal ☐ Abnormal
Name / Type of Test	Date of test	Results (including units)
	Normal Range	Assessment
		☐ Normal ☐ Abnormal
Biopsy/Histopathology	Date of Biopsy	Taken from:
		☐ Skin ☐ Secondaries
Biopsy results:		

Concomitant Medication(s) ☐ None			
Name		Start Date	Stop Date
			☐ Ongoing
Indication	Dose	Frequency	Route
Name		Start Date	Stop Date
			☐ Ongoing
Indication	Dose	Frequency	Route
Name		Start Date	Stop Date
			☐ Ongoing
Indication	Dose	Frequency	Route

If the patient received Filsuvez during a clinical trial, please specify the name and contact information for the investigator:	
Physician Name:	
Physician Street Address:	
Physician City, State, Zip Code:	
Physician Telephone:	
Physician Fax:	

Additional questions / queries		
N	Query / Comment	Response
1.		
2.		
3.		

Signature	
Please sign here to indicate that the information is completed and correct to the best of your knowledge.	
Signed:	Date:

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable