Medicinrådet

Bilag til Medicinrådets vurdering af birkebarkekstrakt til epidermolysis bullosa

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. birkebarkekstrakt
2. Forhandlingsnotat fra Amgros vedr. birkebarkekstrakt
3. Ansøgers endelige ansøgning vedr. birkebarkekstrakt

Note.to.DMC.assessment.report.of.Filsuvez

Epidermolysis bullosa (EB) is a rare and severe skin disease, which significantly impacts the quality of life for both patients and their families. Caring for patients with EB is also time-consuming and costly and often requires significant support from relatives. There is currently no specific treatment for EB and the need for new treatments is therefore very high. Very few other diseases report as low average quality of life and combined with the high mortality, the total health loss (e.g. QALY loss) in EB is very high, higher than most other diseases, including most end stage cancer diseases.

These aspects should lead to an increased willingness to pay for an additional QALY.

Uncertainty and relevance of clinical benefit

As for all new products at introduction, there is uncertainty about the effectiveness and cost-effectiveness, particularly in the long-term. This is even more pronounced in rare diseases. The evidence base and uncertainty must however be assessed in the context of the disease.

For Filsuvez, the phase III clinical trial is the largest trial conducted so far in this disease and shows statistically significant results on the primary endpoint, an endpoint which follows regulatory authority recommendation in this disease area. In addition, there is already at launch a real-world study with 2-years follow-up which supports the trial findings and shows even better effectiveness than the trial results.

Therefore, in the context of this rare disease, we believe that the evidence of clinical benefits is more substantial than could be expected.

Cost-effectiveness analysis assumptions

DMC has in most cases made the most conservative assumptions for the parameters changed in the economic model. The DMC base case scenario may therefore be seen as worst-case scenario. Our opinion is that decisions about resource use in health care, particularly for rare diseases where the evidence base is more limited, should be based on the most likely scenario not the worst case. Given DMC very conservative assumptions, the uncertainty mainly goes in one direction, i.e. reality will most likely be better than DMC base case.

Uncertainty should in this case not negatively impact the accepted ICER or decision, the very conservative assumption by DMC leads to low uncertainty and low risk of worse outcome and should therefore instead lead to a higher willingness to pay for an additional QALY.

Dosing and treatment cost

The DMC analysis is assuming a much higher drug dosing and treatment cost than the manufacturer base case. The mean trial dosing was biased by a few outliers with very high drug use, and we therefore think that using median or restricted mean, without these worst outliers, is a better reflection of future doses in Danish clinical practice.

In addition, both clinical expert opinion and data from a real-world study show that the dosing used in real-world is lower and also is reduced more over time than observed in the clinical trial. The DMC report also describes that the dose using in Danish clinical practice will be lower. But,

despite this, DMC applies the trial mean dose and even extrapolates the first 3 months dose to the full first year and by that applies a dose scenario that is even higher than overserved in the trial.

The DMC dose assumption is therefore not a realistic and most likely assumption about dosing in Danish clinical practice.

Hospital cost

EB is associated with high costs, not only related to dressing changes. The manufacturer uses a European multi-country study on EB patients, because, as the case often is with rare diseases, no data on the cost of treating EB in Denmark was a available. Using data from an actual study, although from other countries, gives a better estimate of what the resource use/cost in Denmark would be than basing it on assumptions from clinicians. This is due to the rarity of the disease where individual clinicians in Denmark meet very few patients and therefore have a limited view of full disease consequences and resources used.

In addition, as a validation approach, data was extracted from the Landspatientregistret in Denmark and found 279 hospital stays for 39 patients with DEB between 2021 and 2023. This means 2.4 hospital stays per year per patient, which corresponds to an annual cost between 50,000 and 142,000 DKK, which is higher than the hospital cost assumed in the analysis. DMC assumed zero hospital cost for the patients, mainly because a Danish estimate based on clinical experts was not applied.

Removing hospital costs completely is not a realistic and most likely assumption about EB hospital costs in Denmark.

Estimate of budget impact

DMC assumes 100% uptake of Filsuvez, i.e. that all 50 of the patients fulfilling the label criteria would directly be treated in year 1. This is not realistic, we are not aware of any treatment that had a 100% uptake in the first year. A realistic assumption would be a slow uptake over the first few years and that maybe half of the theoretically eligible population would be treated with Filsuvez. This would lead to less than half of the budget impact estimated by DMC. It was also not fully clear if the DMC budget impact calculation has taken into account the much higher discontinuation rate DMC assumes in the cost-effectiveness analysis.

New manufacturer scenario

After reviewing the DMC base case analysis, we have performed an analysis with an adjusted base case scenario, where two of the most unrealistic and unlikely assumptions made by DMC are adjusted. This means that the following changes are made:

- The dose of Filsuvez is based on the manufacturer scenario of using the restricted mean from the trial, but the assumption about 20% lower dose in clinical practice is removed
- 50% of the hospital cost assumed in the manufacturer base case analysis is applied (instead of 0% as in DMC base case)

Applying these changes leads to an incremental cost per QALY gained of about 3.5 MDKK, instead of the 6.3 MDKK in DMC base case analysis.

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07.05.2025

DBS/KLE

Forhandlingsnotat

Dato for behandling i Medicinrådet	18.06.2025
Leverandør	Chiesi Farmaceutici S.p.A
Birkebarkekstrakt (Filsuvez)	Filsuvez (Birkebarkekstrakt)
Ansøgt indikation	Behandling af sår af delvis tykkelse ved dystrofisk og junktional epidermolysis bullosa hos patienter over 6 måneder.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris for Filsuvez (Birkebarkekstrakt).

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (paknings-størrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Filsuvez	100 mg/g 30 x 23,4 g gel	68.298,61	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Hvis Medicinrådet *ikke* anbefaler Filsuvez, indkøbes lægemidlet til AIP.

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrerende lægemidler til Filzuvez.

Vyjuvek (beremagene geperpavec), en genterapi til behandling af epidermolysis bullosa, forventes godkendt af EMA i maj 2025. Vyjuvek har endnu ikke anmodet om vurdering i Medicinrådet.

Ved denne aftale vil de årlige lægemiddeludgifter pr. behandlet patient i gennemsnit være som vist i tabel 2.

Tabel 2: Årlige lægemiddeludgifter pr. behandlet patient i gennemsnit.

Lægemiddel	Styrke (pakningsstørrelse)	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling/år (SAIP, DKK)
Filsuvez	100 mg/g 30 tuber á 23,4 g gel	30 tuber/måned	[redacted]	[redacted]

*Jf. vurderingsrapporten s. 35. er det gennemsnitlige antal tuber pr. patient pr. måned i opstartsåret 29,7 og i andet år 29,3. For praktiske formål anvendes 30 tuber pr. måned.

Informationer fra forhandlingen

[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering		Link til status
England	Anbefalet		Link til anbefaling
Sverige	Ikke anbefalet		Link til beslutning

Opsummering

[redacted]

Medicinrådet

Instructions for companies

This is the template for submitting evidence to the Danish Medicines Council (DMC) as part of the appraisal process for a new medicinal product or a new indication for an existing medicine. The template is not exhaustive.

Please note the following requirements:

- When preparing their application, companies must adhere to the current version of the DMC's methods guide.
- Always use the current (latest updated) version of this template downloadet from the DMC's website.
- Headings, subheadings and appendices must not be removed. Tables must not be deleted or edited, unless it is explicitly stated in the text.
- Text in grey and [in brackets] is only for example purposes and must be deleted.
- All sections in the template must be filled in. If a section or an appendix is not applicable, state "not applicable" (N/A) and explain why.
- The main body of the application must not be longer than 100 pages (including the title page, contact information and references – excluding appendices).
- The formatting is not to be altered and all cross-references must work.
- All applications must comply with the general data protection regulations, find more information on DMC's data policy here.
- Submissions in either Danish or English are accepted.

The assessment process cannot be initiated before all the requirements are met.

Documentation to be submitted

The following documentation must be sent to the DMC's email medicinraadet@medicinraadet.dk:

- Application in word format*
- Application in PDF format*
- Health economic model including budget impact model in one Excel file, with full access to the programming code. The model must include relevant sheets from the DMC Excel template 'Key figures including general mortality' available on the DMC's website.
- The European Public Assessment Report (EPAR) should be submitted. Send a draft version if the final one is not published at the time of submission, and send the final version as soon as possible.

Confidential information and blinding

The Danish Medicine Council publishes the application (including attachments) on the website together with the recommendation.

The applicant has the option to blind any confidential information in the application incl. appendices.

Medicinrådet

The application and paper/appendices

If there is confidential information in the application or note/appendices, the company must submit two versions of both the application and note/appendices:

- a version for the DMC's case processing, where the confidential information is marked with [redacted].
- a version for publication on the DMC's website, where the confidential information is blinded with black marking. The DMC publishes this version.

It is the pharmaceutical companies that must ensure that the blinding is sufficient, so that the confidential information cannot be read when the document is edited.

Therefore, the applicant must ensure that the confidential information is sufficiently redacted blinded for publication on the DMC's website. This can be done, for example, by covering the text/information to be redacted with a black marker simultaneously replacing the underlying text with crosses ("XXX"), so that the text/information cannot be read when editing the document.

Read about redaction of confidential information on the DMC's website.

About macros in Excel

Due to IT security requirements, Excel files containing macros must be authorized and signed by the applicant before being submitted to the DMC. Find more information here.

Version log

Version log		
Version	**Date**	**Change**
2.5	10 September 2024	Section 3.4 and 3.4.1: new information regarding ATMP (Advanced Therapy Medicinal Products). Section 6.1.1 and 8.1: Updated text regarding data-cut. Section 4, 8, 10 and 12: Clarification regarding cost-minimization analysis.
2.4	5 July 2024	Section 11: Clarification in the text regarding costs and changes in the tables 26 and 30.
2.3	1 June 2024	Clarification regarding redaction of confidential information, clarification regarding EPAR, clarification regarding literature search and changes in the text regarding costs. New information about Joint Nordic assessments has been added.
2.2	3 November 2023	'Pharmaceutical' is exchanged with 'medicine'. Tabel 26 is new.
2.1	1 September 2023	Section 4.2: Updated information about discount rate (The DMC applies a discount rate of 3.5 % for all years) Section 10.1.3: Clarification regarding EQ-5D-5L and Danish preference weights Section 11.1: Updated information about Excel sheet 'Key Figures'
2.0	15 June 2023	New application template
1.3	6 December 2022	Clarification regarding new IT security requirements concerning macros in Excel files has been added, see page 1.
1.2	20 June 2022	Clarification of the introduction, including instructions on how to complete the form.
1.1	9 February 2022	Appendix K and onwards have been deleted (company-specific appendices) Color scheme for text highlighting table added after table of contents Section 6: Specific requirements for literature search Section 7: Stated it explicitly that statistical methods used need to be described Section 8.3.1: Listed the standard parametric models

Version log		
		Section 8.4.1: Added the need for description of quality of life mapping Appendix A: Specified that the literature search needs to be specific for the Danish context and the application Appendices B and D: Stated it explicitly that statistical methods need to be described in the tables in the appendices
1.0	27 November 2020	Application form for assessment made available on the website of the Danish Medicines Council.

Application for the assessment of Filsuvez (birch bark extract) for treatment of partial-thickness wounds associated with dystrophic and junctional epidermolysis bullosa in patients 6 months and older

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

Contact information	
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Name (External representation)	**[Name / company]**
Title	
Phone number	[Include country code]
E-mail	

[If a company wishes to use external representation in relation to the application for evaluation of a new medicine / extension of indications, the following power of attorney must be completed and sent to medicinraadet@medicinraadet.dk.]

Table of contents

Tables and Figures

Abbreviations

Term	Definition

AE	Adverse event
ANCOVA	Analysis of covariance
BSA	Body surface area
BSAP	Body surface area percentage
CCM	Current clinical management
cm^2	Square centimetre
DEB	Dystrophic epidermolysis bullosa
EB	Epidermolysis bullosa
EBDASI	Epidermolysis Bullosa Disease Activity and Scarring Index
EBS	Epidermolysis bullosa simplex
EQ-5D	EuroQol 5-Dimension
EQ-5D-Y	EuroQol 5-Dimension Youth
EQ-5D-5L	EuroQol 5-dimension 5 level
g	Gram
HRQoL	Health-related quality of life
ICER	Incremental cost effectiveness ratio
iscorEB	Instrument for Scoring Clinical Outcomes of Research for Epidermolysis Bullosa
JEB	Junctional epidermolysis bullosa - other
mm	millimetre
N, n	Number
OLP	Open-label phase
QALY	Quality adjusted life year
RDEB	Recessive dystrophic epidermolysis bullosa
SD	Standard deviation
SE	Standard error
SMR	Standardised mortality ratio
TTO	Time trade-off

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Filsuvez
Generic name	Birch bark extract
Therapeutic indication as defined by EMA	Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older
Marketing authorization holder in Denmark	Chiesi Farmaceutici S.p.A
ATC code	D03AX13
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	21 June 2022
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	NA
Orphan drug designation (include date)	Yes, 23 February 2011
Other therapeutic indications approved by EMA	NA
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	No, assessment process already started in Sweden and Chiesi expects Filsuvez to be supplied via a mix of hospital / pharmacy dispensing (different local payers) and funding process and mechanisms will vary by Country.
Dispensing group	NBS
Packaging – types, sizes/number of units and concentrations	25 ml sterile tube containing 23.4 g of gel per tube 30 x 23,4 g gel

Overview of the medicine	
	100 mg/g

2. Summary table

Summary	
Indication relevant for the assessment	As per the EMA indication
Dosage regiment and administration	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.
Choice of comparator	Standard of care. Filsuvez is the first approved medicine for EB.
Prognosis with current treatment (comparator)	EB is a genetically complex disease. Patients with JEB and RDEB have more fragile skin than other EB subtypes. Patients with EB have debilitating wounds often accompanied by pain and severe itching and more serious complications, such as skin cancer, upper airway occlusion, renal failure, and premature death may be present in patients with more severe subtypes of EB. Sepsis following wound infection have been identified as one of the main causes of death in children with EB. The mean survival for patients with severe JEB is estimated to be only 8.4 months, and nearly 28 years for patients with severe RDEB.
Type of evidence for the clinical evaluation	Head-to-head study vs blinded control gel
Most important efficacy endpoints (Difference/gain compared to comparator)	Total body wound burden (Body surface are percentage, BSAP) reduced from 12.1% to [redacted]% for all patients by Month 24 in EASE and reduced from 27.3% to 10.4% in a real-world study.
Most important serious adverse events for the intervention and comparator	6.4% in the Filsuvez group and 5.3% in the control gel group experienced serious adverse events (SAEs), but only one SAE (wound haemorrhage) was considered to be related to study treatment in a patient randomised to Filsuvez.
Impact on health-related quality of life	An average utility increase per % reduction in BSAP of [redacted] is estimated
Type of economic analysis that is submitted	Cost-utility, Markov model

Summary	
Data sources used to model the clinical effects	EASE trial extension and real-world study
Data sources used to model the health-related quality of life	EASE trial extension and real-world study
Life years gained	[redacted]
QALYs gained	[redacted]
Incremental costs	[redacted]
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	The model outcome is most sensitive to variations in utility gain and cost of treatment associated with Filsuvez treatment.
Number of eligible patients in Denmark	Incidence: Uncertain, possible 2-3 DEB and JEB patients per year Prevalence: approx 50 DEB and JEB
Budget impact (in year 5)	[redacted]

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

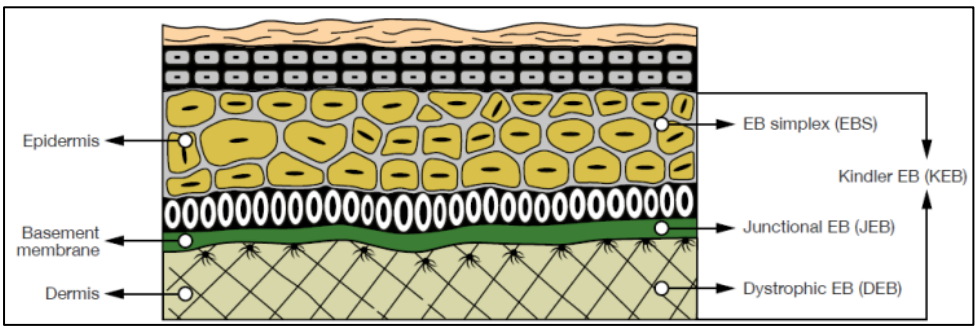
3.1 The medical condition

EB is a genetically complex disease, with over 1,000 mutations. The four major subtypes are dystrophic EB (DEB), which can be either dominant (DDEB) or recessive (RDEB), junctional EB (JEB), EB simplex, and Kindler EB (KEB; formerly known as Kindler syndrome) (Vahidnezhad 2019), however only DEB (inclusive of RDEB and DDEB) and JEB are relevant to the scope of this application.

The different EB subtypes reflect the underlying protein abnormality that leads to loss of skin integrity, with JEB and DEB (the most severe subtypes of EB) typically affecting

deeper layers of skin. Therefore, the level of skin cleavage is considered when discerning the EB subtype of a patient.

Figure 1: Cross-section of skin and corresponding major EB types



EB: epidermolysis bullosa
Source: DEBRA 2024

Additional factors are also considered, including ultrastructural manifestations, location of wounds and blisters, frequency, and severity of extracutaneous complications, inheritance patterns and genetic mutations detected. DEB and JEB, usually present from birth and so are often diagnosed at birth or in early childhood (Fine 2008).

Pathophysiology of DEB and JEB

The primary function of skin is to act as a protective barrier against the environment. Therefore, if the skin barrier is broken, the complex process of wound healing is employed to restore epidermal barrier function (Cianfarani 2017). This occurs in four sequential steps:

- Haemostasis: the blood loss following epithelial injury is halted by the formation of a fibrin clot

- Inflammation: Platelets within the fibrin clot release pro-inflammatory cytokines (e.g. COX-2, tumour necrosis factor-α, IL-2, IL-4, IL-6, and IL-8), initiate a controlled inflammatory response which promotes re-epithelialisation

- Cell proliferation: The re-epithelialisation, which begins when immune cells migrate to the wound site and actively proliferate to form new tissue (Cianfarani 2017). As the wound begins to heal, dead tissue (eschar) accumulates at the surface of the skin and eventually sheds as new tissue is formed.

- Tissue remodelling: Fibroblasts and endothelial cells release growth factors to induce myofibroblast differentiation and collagen replacement, promoting wound closure and skin remodelling (Cianfarani 2017).

Patients with JEB and DEB exhibit dysfunction in multiple stages of the wound healing process, including delayed epithelialisation, persistently elevated cytokine levels and disordered keratinocyte migration, resulting in an altered wound healing profile (Bardhan 2020, Mellerio 2023).

Clinical manifestations

Wounds and blisters

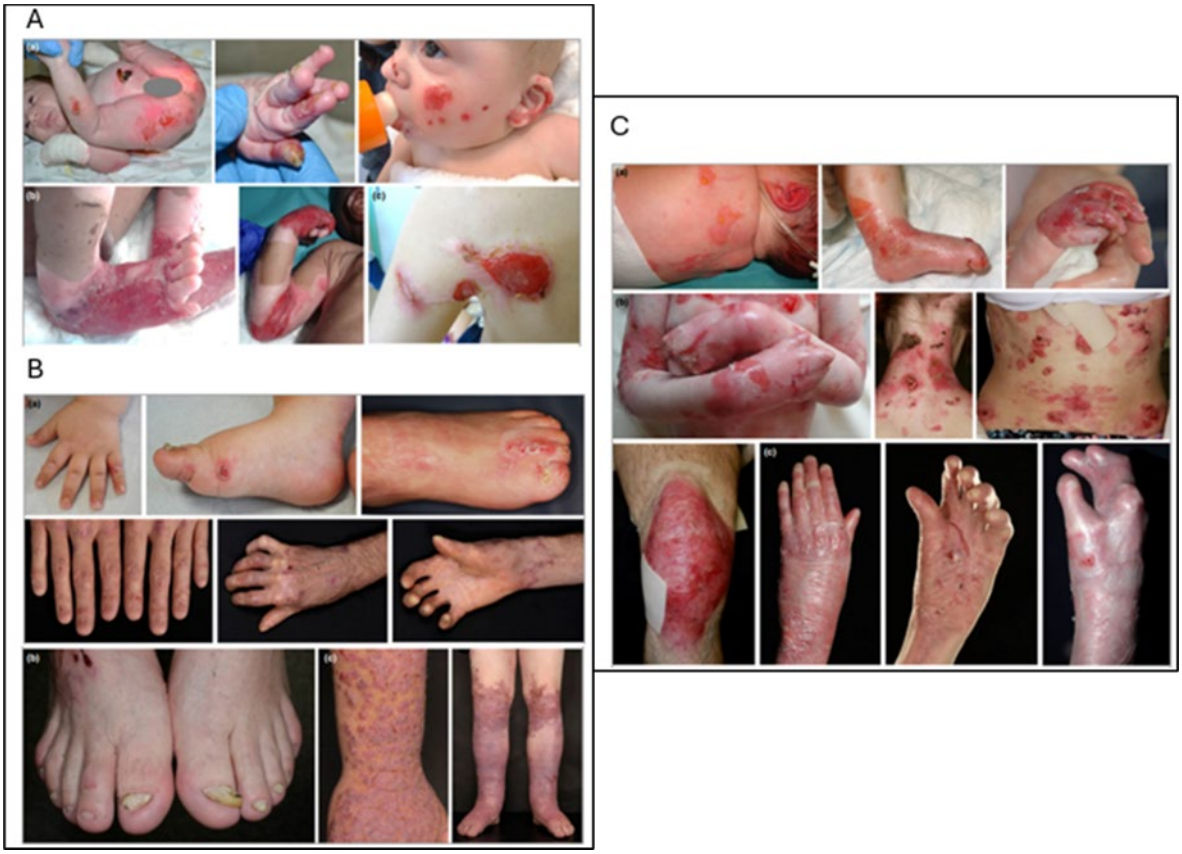
EB is characterized by cutaneous and extracutaneous wounds and blisters, which can potentially affect all mucus membranes, and any organ lined with epithelial tissue; the slightest touch or frictional movement can cause painful tearing of the skin or membrane (Bardhan 2020). Pain and itch associated with wounds is common and when scratched by patients they can worsen and prolong open wounds, resulting in cycles of impaired wound healing that leave patients susceptible to bacterial colonisation and infection. Sepsis following wound infection is associated with increased mortality, especially in neonates with severe forms of JEB or RDEB. Additional serious complications in patients with JEB and DEB include skin cancer, upper airway occlusion, renal failure and premature death.

When wounds remain unhealed for long periods of time (typically after six weeks of standard care), they often become referred to as chronic (Schwieger-Briel 2015, Tang 2021). Unhealed wounds often break down again, resulting in patients presenting with several wounds of varying age and healing ability, leading to a substantially high wound burden. Most patients with EB can have chronic wounds that remain open for 12 weeks or longer as well as recurrent wounds that heal but blister again easily (Bardhan, 2020, Tang 2021). Chronic wounds tend to be substantially larger than recurrent wounds, as well as more painful.

Patients with DEB and JEB have widespread unremitting blistering which contributes to the substantial wound burden associated with EB. In a survey conducted by Bruckner et al in 2020, 25% of patients with JEB, 36% of patients with DDEB, and 58% of patients with RDEB reported having >30% of their body covered in wounds (Bruckner 2020). In addition, patients with RDEB have on average three chronic wounds and 11 recurrent wounds at a given time (Tang 2021).

Demonstrative images of DEB and JEB wounds are provided in the figure below, representing a mix of adult and paediatric patients (Fine 2019).

Figure 2: Images of patients with JEB (a), DEB (b), intermittent RDEB (b) and Severe RDEB (c)



A) Images of children with JEB; B) Images of patients with DEB and intermediate RDEB; C) Images of patients with severe RDEB

Source: Has 2020

Bruckner and colleagues (Bruckner 2020) reported that wound management can take more than 4 hours per day. The time required for wound care differed by EB subtype; patients with RDEB reported spending the longest amount of time on wound care whereas caregivers of patients with both JEB and RDEB reported spending the most time on wound care (Bruckner 2020). Wounds also have a high impact on the humanistic burden of the disease as wound management require extensive dressing procedures, which are frequent, time consuming and painful, with many patients requiring opioids and anxiolytics to relieve the pain and anxiety associated with dressing changes (Bruckner 2020, Goldschneider 2014).

Pain and itch

Pain and itch are common and disabling symptoms for patients with EB (Bardhan 2020). In patients with RDEB, over 75% of patients reported experiencing neuropathic pain (von Bischhoffshausen 2017).

Patients with EB often experience acute pain due to wounding but can also suffer chronic pain. While pain and itch often arise from the condition itself, patients also experience

pain due to current wound management practices such as bathing, dressing changes and blister lancing, and other clinical procedures (Denyer 2017).

Infections

Wound infection and bacterial colonisation are common in patients with EB, especially those with more severe and generalised subtypes who have a large number of chronic wounds such as JEB and DEB. When bacterial levels have reached that of critical colonization, EB wound healing may become impaired. Beyond colonization, wound infection in EB is characterised by increasing wound size, exudate, odour, and pain, with surrounding areas marked by erythema, swelling, and oedema. While infection occurs in almost all EB wounds patients with more severe subtypes of EB (such as JEB and DEB) may be more susceptible due to anaemia, poor nutrition, and immunosuppression secondary to systematic disease.

Common bacterial organisms that have been isolated from EB wounds include gram-positive, gram-negative, and anaerobic species. In addition, several antibiotic-resistant strains of bacteria including methicillin-susceptible Staphylococcus aureus (MSSA), methicillin-resistant Staphylococcus aureus (MRSA), Klebsiella pneumoniae, Streptococcus spp., and Pseudomonas aeruginosa are commonly isolated organisms. The resulting consequences of bacterial infection are a state of impaired wound healing, characterised by reduced keratinocyte migration/differentiation, impaired epithelial regeneration, scarring and fibrosis, hypergranulation and an hypercatabolic state due to increased energy expenditure to maintain homeostasis.

Sepsis, arising from cutaneous infection or the use of intravenous lines or indwelling ports on chronically colonised or infected surrounding skin, has been associated with increased mortality, especially in neonates or infants with JEB or RDEB; death from sepsis occurs in 11-20% of patients with JEB by 1 year of age and in 8% of patient with severe RDEB by 35 years of age (Fine 2008).

Comorbidities

In addition to partial-thickness wounds and associated pain, ich, infection and bacterial colonisation, patients with JEB and DEB suffer from additional severe complications related to the condition. These also represent an increased risk of premature death.

E.g., chronic wounds that are subject to repeated mechanical trauma lead to tissue inflammation, extracellular matrix remodelling, dermal fibrosis, and microenvironment alterations, all of which may contribute to the pathogenesis of the development and recurrence of squamous cell carcinoma (SCC) in patients with EB (Condorelli 2019). Particularly in RDEB, SCCs are recurrent, metastasizing, and therapy-resistant, and represent a leading cause of mortality and reduced life expectancy.

Impact on life expectancy

The subtype of EB has a direct impact on disease prognosis (Fine 2010). While patients with DDEB typically have normal life expectancies, those with JEB and RDEB are at risk for premature death. The mean survival estimates range from 8.4 months with severe JEB (JEB-S), to 28 years for severe RDEB (RDEB-s), to 40 years with RDEB to almost normal life expectancy with DDEB (DesJardins-Park 2019, Fine 2010, Petrof 2022).

Common causes of death include failure to thrive, sepsis, pneumonia, respiratory failure and SCC (Fine 2008).

Impact on quality of life

EB severely affects Quality of life (QoL) for both patients and their families. Patients (both children and adults) living with EB have a lower health-related QoL (HRQoL) compared to those without EB, an impact that increases with severity of disease (Bardhan 2020, Bruckner 2020). EB impacts all aspects of patients´ daily activities such as toileting, feeding, bathing, dressing, grooming and walking. Fine et al. (2004) used a standardised questionnaire to assess the level of independence for 140 randomly chosen children with EB. Of patients with JEB and RDEB, 27% to 61% were 'somewhat dependent' while up to 27% of patients with JEB and RDEB were totally reliant on others for their daily activities (Fine 2004).

In addition, patients may struggle to cope with learning to live with disfigurement, physical impairment, loneliness, and low self-esteem, particularly given how unpredictable disease progression is for individuals with EB, which can all contribute to reduced QoL. Children with EB in particular often spend a lot of time during their early years in the hospital, particularly children with JEB, where they are often hospitalised for long periods of time due to failure to thrive.

Caring for patients with EB can be distressing, as daily bathing, blister lancing/draining, and dressing changes can be very painful, and anxiety-provoking, particularly for parents caring for young children, as well as extremely time consuming. Furthermore, 66.7% of carers reported that assistance was always required with wound care regimens (Bruckner 2020) reported that the patients with a higher degree of severity require support from a second carer as well.

When assessed through EQ-5D, caregivers reported a score of 0.64 for carer 1 and 0.7 for carer 2; this is lower than carers for patients with severe dementia which reported an EQ-5D score of 0.82 (Reed 2017, Morgan n.d.).

The burden of EB is expressed in a 2-minute video highlighting what EB is and the serious impact of EB on a child's and their carers life:

Figure 3: Understanding EB (QR code link to video)

3.2 Patient population

There is limited information about the EB population in Denmark, but it is believed to be similar to the general international EB population. Due to the rarity of EB, limitations in literature and variation in reporting guidelines, defining the exact prevalence of EB is challenging, with significant disparity across countries. According to the genodermatosis database the prevalence of DEB and JEB was in 2022 about 60 patients in Denmark (clinical expert opinion, 2024). A study by Kristensen et al (Kristensen 2019) assessed first-time diagnoses of congenital epidermolysis bullosa in the Danish National Patient Registry and the Danish Pathology Registry and found 32 cases at three hospital departments during time period 1977 to 2015. Extrapolating this data to national level may indicate a total EB incidence of about 4-5 case per year, but only part of these would be DEB and JEB patients.

Table 1 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark	2-3	2-3	2-3	2-3	2-3
Prevalence in Denmark	Approx. 60	Approx. 60	Approx. 60	Approx. 60	Approx. 60
Global prevalence	Unknown/ varying	Unknown/ varying	Unknown/ varying	Unknown/ varying	Unknown/ varying

The epidemiology of this disease in Denmark is uncertain, and so is estimation of the proportion of eligible patients. We have assumed that 50 out of the 60 DEB and JEB patients would be eligible.

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	50	50	50	50	50

3.3 Current treatment options

Currently there is no curative treatment for EB (El Hachem 2014). The clinically established guidelines for current management of EB focus on routine care managed by a multidisciplinary team. Wound management is the primary aspect of disease

management, with strategies focused on reducing risk of new injury, minimising complications and improving QoL as much as possible (El Hachem 2014).

The main treatment for EB is different methods of wound care to enhance wound healing together with treatments to reduce pain, itch and other discomforts arising from the wounds and the care of wounds as well as prevent the forming of new wounds. The goal of the treatment is to reduce the size of the wounds, increase the time of healing, and reduce the number of dressings needed to care for the wounds.

The current clinical management of DEB and JEB partial-thickness wounds is heterogeneous but commonly consists of using a variety of non-adhesive dressings and bandages, topical antimicrobials, topical steroids, and a variety of other topical agents, all of which are not licensed specifically for use in the management of EB wounds. Hygiene advice is often also provided; bathing is often tolerated more than showering and can be used to cleanse, reduce the trauma of dressing changes, and allow supplemental antibacterial cleaning by using diluted acetic acid or bleach.

To reduce the symptoms, such as pain, pruritus, and itch arising from the condition itself as well as the procedures, patients use treatments such as:

- Analgesics, such as acetaminophen, nonsteroidal anti-inflammatory drugs and opioids
- Moisturisers are commonly used to address the pain in patients with EB (Goldschneider 2014)
- Pharmacological treatments that have been used for severe recalcitrant itch include gabapentin, amitriptyline, ondansetron, thalidomide, ciclosporin, Antihistamines, and opioids
- Antibiotics and other relevant treatments to treat infections.

In addition, a number of surgical procedures are also commonly used as part of the management of severe EB, including oesophageal dilatation, insertion of a gastrostomy tube, surgery to manage contractures (e.g. of the hands), excision of skin cancers, amputations, regional lymph node dissection, insertion of central venous access, and tracheostomy.

International consensus guidelines from the Dystrophic Epidermolysis Bullosa Research Association (DEBRA) are used internationally to address current wound management strategies; patients are encouraged to use atraumatic and non-adhesive dressings and individualize wound management strategies that balance efficacy, QoL, and cost-effectiveness (Denyer 2017).

In summary, EB is a rare and debilitating lifelong condition with a devastating impact on patient and caregiver QoL (El Hachem. 2014). Without the availability of curative treatment, current management of EB has been largely focusing on wound care and preventative measures. The frequent, often daily, dressing changes to manage chronic wounds and unremitting blistering is a painful process, with many patients requiring opiate medication to address the discomfort (Goldschneider 2014).

The inflammation and infection associated with EB reinforces a state of impaired wound healing associated with debilitating and potentially fatal complications while surgical interventions may be required for mitten deformities, oesophageal strictures and gastronomy tube replacement or repair (Denyer, Pillay and Clapham 2017). Overall, the current management of EB is time consuming and burdensome for patients, health care system and caregivers.

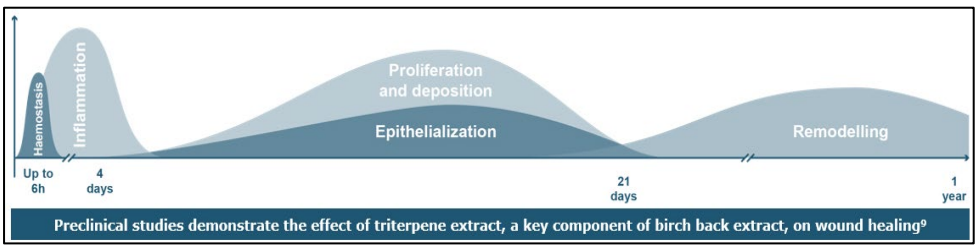
3.4 The intervention

Filsuvez contains birch bark extract topical gel comprising a technologically advanced pharmaceutical formulation of birch triterpenes, including betulin, betulinic acid, erythrodiol, lupeol and oleanolic acid, mixed with sunflower oil creating a non-aqueous topical gel (EMA 2023). The gel has thixotropic properties that facilitate easy application, retention at wound site and ease of use within an individual's routine dressing changes (EMA 2023). One gram 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

While the mode of action of Filsuvez for the treatment of wounds associated with EB is not specifically defined, birch triterpenes and betulin have been shown to modulate inflammatory mediators and activate intracellular pathways known to be involved in keratinocyte cellular processes (Schweiger-Briel 2019, EMA 2023). More specifically, Filsuvez modulates three key phases of wound healing involving; inflammation, new tissue formation, and new epidermal barrier formation (Illustrated in figure below):

- Within hours: transient modulation of inflammatory mediators e.g. COX-2, IL-6 and IL-8 takes place immediately upon application, and stimulating cellular activity through PGDF, TGF-b and VEGF (Ebling 2014).
- Within days: promotion of keratinocyte, fibroblast and endothelial cell migration to the wound site fills the defect. Changes in the cytoskeleton network and cell surface receptors, enabling cellular migration, also occur within days of application (Ebling 2014, Schweiger-Briel 2019).
- Within weeks: the enhancement of keratinocyte differentiation, with skin cells from the basal layer differentiating into epidermal skin cells and forming the epidermal barrier; this is at least partly via upregulation of TRPC6 (Schweiger-Briel 2019).

Figure 4: Filsuvez wound healing mechanism



Birch triterpenes have been shown in multiple literature sources to exhibit a range of beneficial effects (Ebling 2014, Schweiger-Briel 2019). The effects exhibited propose a route to help alleviate the burdensome impacts EB has on its patients and caregivers. The formulation of BTs supports the inflammatory process in a number of ways; stabilising the regulation of inflammatory cytokines and pro-inflammatory mediators, while also pushing the wound healing process from the inflammatory phase into the re-epithelialisation phase (Ebling 2014).

The promotion of keratinocyte migration, differentiation and epithelialisation drives skin remodelling and reformation of the protective epithelial barrier. Therefore, further enhancing the potential for increased wound healing and possibly leading to lower risk of infection, a reduction in dressing change frequency and thus, diminished levels of pain (Kern 2019, Kern 2023). This in turn, indirectly alleviates many burdensome life-altering factors affecting patients and carers of EB.

The overall purpose of the treatment is to improve wound healing, prevent disease complications and optimise the quality of life of patients.

Overview of intervention	
Indication relevant for the assessment	Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older
ATMP	N/A, not an ATMP
Method of administration	Filsuvez is available as a gel that should be applied to the wound surface at a thickness of approximately 1 mm and covered by a wound dressing. The medicine can also be applied directly to the wound dressing.
Dosing	Filsuvez is available as a gel that should be applied to the wound surface at a thickness of approximately 1 mm and covered by a wound dressing. The medicine can also be applied directly to the wound dressing.
Dosing in the health economic model (including relative dose intensity)	[redacted]
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	The gel should be reapplied at each wound dressing change and should be applied until the wound is completely healed. If symptoms persist or worsen after use, or if wound complications occur, the patient's condition should be fully

Overview of intervention	
	clinically assessed prior to continuation of treatment, and regularly re-evaluated thereafter.
Necessary monitoring, both during administration and during the treatment period	Monitor for Important identified risks: • Allergic reaction / Hypersensitivity (in patients with Partial thickness wounds) Monitor for Important potential risks: • Wound infection Prolonged healing of burn wounds and risk of hypertrophic scarring if surgery is delayed (in patients with Partial thickness wounds) • Squamous cell carcinoma and other skin malignancies (in patients with Epidermolysis Bullosa)
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Genetic testing is not a requirement for initiation of treatment with Filsuvez
Package size(s)	30 tubes x 23,4 g gel/tube

3.4.1 Description of ATMP

N/A, not an ATMP

3.4.2 The intervention in relation to Danish clinical practice

The introduction of Filsuvez gel as part of routine clinical management of DEB and JEB in Denmark would represent a step change in EB treatment. As discussed above, currently there is no curative treatment for EB and wound management is the primary aspect of current disease management. Filsuvez gel would be used in combination with current wound management and will therefore not replace a specific treatment. However, the treatment effect of Filsuvez gel is expected to improve wound healing and thereby reduce the amount of standard wound management, e.g. number of dressings, and possible also disease complications.

3.5 Choice of comparator(s)

The comparator in the pivotal trial program was standard of care non-adhesive wound dressing alone and continued dressing changes at least every 4 days. This standard of care treatment is believed to in line with current treatment practice in Denmark.

In the cost-effectiveness model, Filsuvez is compared to the current clinical management (CCM) of DEB and JEB (Filsuvez + CCM vs CCM alone), in line with clinical trial program as well as Danish clinical practice. It should be noted however that the clinical trial

comparator included a control gel which is not available in clinical practice, but which likely has some beneficial properties.

CCM is heterogeneous but commonly consists of using a variety of non-adhesive dressings and bandages, topical antimicrobials, topical steroids, and a variety of other topical agents, all of which are not licensed specifically for use in the management of EB wounds. Hygiene advice is often also provided; bathing is often tolerated more than showering and can be used to cleanse, reduce the trauma of dressing changes, and allow supplemental antibacterial cleaning by using diluted acetic acid or bleach.

Additional recommendations for the management of cutaneous manifestations may include lancing and draining of intact blisters since EB blisters are not self-limiting, action to address colonisation and infection of wounds such as the use of antiseptics and topical/systemic antimicrobials mentioned above, efforts to treat intense pruritus, and protection from further cutaneous trauma. Pain management, including pharmacological and non-pharmacological interventions, is also key to tackling both background pain and procedural pain experienced during wound management practices such as bathing, dressing changes, blister lancing, surgical procedures, treatment for squamous cell carcinomas (SCC), and other clinical procedures.

Current treatment is burdensome, with often daily or every other daily wound dressing changes, most requiring caregiver help. Depending on the type of EB and whether the wound is infected, there could be as many as two to three dressings of the same wound during the day. The wound dressing-change procedure may take more than four hours, severely restricting the lives of patients and their caregivers (Bruckner 2020). In addition to being burdensome, the wound caring process is associated with pain, where patients with more severe disease require the use opiates to alleviate the procedural pain (Eng 2021).

Overview of comparator	
Generic name	N/A (not a single pharmaceutical)
ATC code	N/A (not a single pharmaceutical)
Mechanism of action	N/A (not a single pharmaceutical)
Method of administration	Consists of non-adhesive dressings and bandages, topical antimicrobials, topical steroids, and a variety of other topical agents
Dosing	N/A (not a single pharmaceutical)
Dosing in the health economic model (including relative dose intensity)	N/A (not a single pharmaceutical)

Overview of comparator	
Should the medicine be administered with other medicines?	N/A (not a single pharmaceutical)
Treatment duration/ criteria for end of treatment	No end of treatment
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	N/A (not a single pharmaceutical)

3.6 Cost-effectiveness of the comparator(s)

Not available

3.7 Relevant efficacy outcomes

Choice of relevant outcomes

The primary endpoint used in EASE trial to determine efficacy is the proportion of patients with first complete closure of the target EB wound within 45 ± 7 days of treatment. The assessment for the primary endpoint follows the U.S. Food and Drug Administration (FDA) Guidance for Industry 'Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment'. However, selecting appropriate endpoints in wound-healing trials has been found difficult in the past. FDA has listed four different kinds of endpoints that are acceptable for deriving clinical benefit in wound healing. These include: incidence of complete wound closure; speed of wound closure; facilitation of surgical wound closure; and "quality of healing," which encompasses cosmesis and skin function. However, in EB, these endpoints generate a number of problems. For incidence and speed of complete wound closure, the relapsing, remitting course of EB means that some wounds never fully close. Facilitation of surgical closure is not relevant to EB because of the wide area of involvement whereby wounds resemble partial thickness wounds rather than incisions (Kern 2019). A number of secondary endpoints were included in EASE trial as well, as described below.

This also means that other endpoints that the primary in EASE may be more clinically relevant in EB and better reflect the impact of the treatment on patients.

Statistical consideration

For the primary endpoint, the proportion of patients with first complete closure of the EB target wound within 45 ± 7 days based on clinical assessment by the investigator in the Oleogel-S10 and placebo treatment groups was compared using the Cochran-Mantel-Haenszel (CMH) test, stratified by EB sub-type and target wound size class. Due

to the interim analysis, the final statistical analyses of the primary endpoint was performed based on the Cui, Hung, Wang approach using a weighted statistic. The secondary endpoint of the proportion of patients with first complete closure of the EB target wound as analyzed in the same manner as the primary endpoint. The percentage change from baseline in EB target wound size was analyzed at each visit using an analysis of covariance (ANCOVA) model including treatment group and EB sub-type as fixed effects and size of target wound at baseline as a covariate. The 95% confidence intervals for the difference in least squares means between treatment groups was calculated. Additionally, treatments was compared using a two-sided Wilcoxon Rank Sum test stratified by EB sub-type (van Elteren test). The changes from baseline in total body wound burden, in body surface area percentage (BSAP) of total body surface area (TBSA) affected by EB partial thickness wounds, in the impact of wounds on sleep, and the treatment response were analyzed correspondingly. The incidence rates of wound infection between treatments was compared using a CMH test considering the strata of EB sub-type and target wound size class.

For the primary endpoint, an individual with missing data was defined as not having achieved complete closure. For the key secondary endpoint, participants were censored at the date last known to have not achieved complete closure. Missing data for all other endpoints were imputed according to last observation carried forward.

3.7.1 Definition of efficacy outcomes included in the application

Table 3 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Proportion of patients with first complete target wound closure within 45±7 days determined by clinical assessment (primary endpoint)	45 days	Wound closure was defined as skin re-epithelisation without drainage and was confirmed by a second observation after 7±2 days.	Clinical trial – clinical assessment. Statistical/measurement consideration described above
Time to first wound closure up to 90±7 days of treatment	90 days	Wound closure was defined as skin re-epithelisation without drainage and was confirmed by a second observation after 7±2 days.	Clinical trial – clinical assessment. Statistical/measurement consideration described above
Proportion of patients with first complete closure within day 90	90 days	Wound closure was defined as skin re-epithelisation without drainage and was confirmed by a second observation after 7±2 days.	Clinical trial – clinical assessment. Statistical/measurement consideration described above

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Incidence of wound infection within 90 (±7) days	90 days	The incidence of EB target wound infections between Baseline (DBP D0) and D90 or EDBP was assessed based on the total number of patients with an EB target wound infection, as evidenced by AEs and/or the use of topical and/or systemic antibiotics, and the total number of patients	Clinical trial – clinical assessment. Statistical/measurement consideration described above
Maximum severity of wound infection between baseline and 90 (±7) days	90 days	Target wound infections between baseline (DBP D0) and D90 or EDBP were assessed for maximum severity (maximum severity was evaluated if a subject had a wound infection event evidenced by AEs).	Clinical trial – clinical assessment. Statistical/measurement consideration described above
Change from baseline in total body wound burden (TBWB) at day 90	90 days	The evaluation of total body wound burden (TBWB) was based on clinical assessment using Section I (Skin) of the Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI). The EBDASI skin activity (blistering/erosions/crusting) was scored from 0 to 10 for each of 10 anatomical locations (excluding the anogenital and buttocks regions). Therefore, the total skin activity score (i.e., TBWB) could range from 0 to 100, with lower scores indicative of less wound burden.	Clinical trial – clinical assessment. Statistical/measurement consideration described above
Change from baseline in body surface area percentage (BSAP)	Up to 24 months	Body surface area percentage (BSAP) of TBSA affected by EB partial-thickness wounds as evidenced by clinical assessment based on the Lund and Browder chart	Clinical trial – clinical assessment. Statistical/measurement consideration described above

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Change from baseline in weekly dressing changes (post-hoc analysis)	90 days	Frequencies are calculated based on the response at each visit	Clinical trial – clinical assessment. Statistical/measurement consideration described above

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Validity of outcomes

The endpoints used have been discussed with regulatory agencies. The choice of primary endpoint was discussed and agreed in the EMA CHMP protocol assistance in 2017 (EMEA/H/SA/2179/1/FU/1/2016/PA/SME/III). Assessing the proportion of patients achieving wound closure within a period of 45 days, rather than time to first wound closure within 90 days was found acceptable. Also, the time point 45 days was preferred to the initially proposed 60 days. The target EB wound was defined as an EB partial-thickness wound of 10 cm2 to 50 cm2 in size and ≥21 days to < 9 months in age. This definition provides reassurance that the wound has not healed for a period of 3 weeks, while still not being a chronic wound aged more than 9 months. A wound size of 10-50 cm2 is deemed relevant. The definition is considered adequate and in agreement with what was discussed in the CHMP PA in 2017.

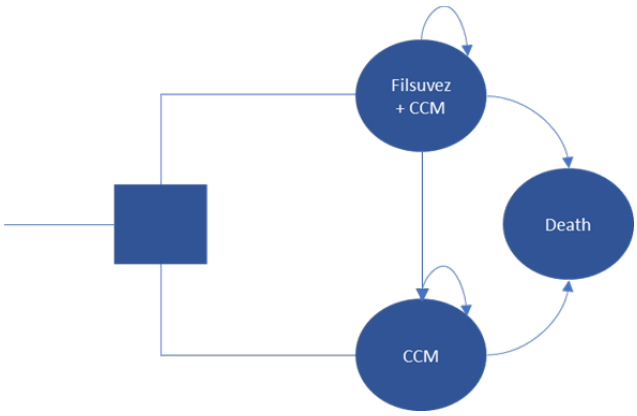
4. Health economic analysis

A model was used to investigate if Filsuvez, in addition to CCM, is a cost-effective treatment compared to CCM alone for treating patients with DEB or JEB aged six months and older in the Danish setting. The CCM comparator comprises clinical management without Filsuvez, including, but not limited to, treatments which can help ease and control infections, pain, and other aspects of EB.

4.1 Model structure

The model is a simple Markov model with three health states: treatment with Filsuvez, treatment with CCM and death. Patients are assumed to be treated either with Filsuvez (unless treatment is discontinued) or CCM alone until death. Patients who discontinue Filsuvez are assumed to revert to using CCM alone, meaning they receive the same costs and benefits (quality of life) as the cohort treated with the comparator, CCM alone. The model structure is presented below.

Figure 5: Model structure



CCM: Current clinical management

4.2 Model features

Perspective

The base case was performed from a restricted societal perspective.

Population

The analysis included all patients described in the label for Filsuvez, people aged six months and older with partial-thickness wounds associated with DEB or JEB. The model follows the patients for a lifetime horizon, including the paediatric and adult patient populations. The age at baseline is six months, and the proportion of females in the model is 39.9%. The population in the model has been parameterized based on age with information relevant to utility, survival and/or costs. This includes age-corrected utilities, background mortality (Danish-specific) and drug use. The distribution of sex was used to estimate mortality.

Intervention

Filsuvez gel (birch bark extract) non-aqueous gel.

Comparators

Filsuvez was compared with the current standard of care, which is referred to as CCM alone. CCM consists of individually tailored symptom relief and complication prevention measures as described above.

Outcomes

The model estimates the total costs for the treatment with Filsuvez + CCM and CCM alone. Treatment benefits (or harms) are measured using quality-adjusted life years (QALYs). Incremental differences are reported and summarized using an ICER.

Time horizon and cycle length

The time horizon implemented in the model is a lifetime horizon of 100 years, deemed necessary to capture all the relevant costs and benefits from Filsuvez treatment, in line with the Danish medicines council (DMC) guidelines. The cycle length used in the model is one year and half-cycle correction is applied. Scenarios with different time horizons are presented as well.

Discounting

The discount used throughout the model for both costs and benefits is 3.5% yearly.

Uncertainty

A deterministic sensitivity analysis was performed, and the most influential model parameters were identified. Further, specific scenarios with alternative values for key inputs were evaluated.

Table 4 Features of the economic model

Model features	Description	Justification
Patient population	Patients aged six months and older with partial-thickness wounds associated with DEB or JEB	In line with label
Perspective	Restricted societal perspective	According to DMC guidelines
Time horizon	Lifetime	To capture all health benefits and costs in line with DMC guidelines.
Cycle length	1 year	Appropriate to capture disease progression and consequences
Half-cycle correction	Yes	
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Filsuvez gel (+CCM)	According to trial program
Comparator(s)	Current clinical management (CCM) aloe, consisting of wound healing, symptom relief and complication prevention measures	According to Danish clinical practice.
Outcomes	Quality-adjusted life years (QALYs)	Treatment is expected to impact both survival and quality of life

5. Overview of literature

5.1 Literature used for the clinical assessment

A systematic literature review (SLR) was conducted to identify evidence for the efficacy and safety of Filsuvez gel and/or other interventions considered established clinical management, for the treatment of partial-thickness wounds associated with DEB (DDEB/RDEB) and JEB. The SLR was undertaken according to the principles of systematic reviewing published in the Cochrane Handbook (Higgins 2019). The searches for this SLR were first conducted in June 2022 and updated in April 2024.

One trial was identified as providing evidence relevant to the decision problem based on screening against the predefined PICOS [Population, Intervention, Comparator, Outcomes, Study/ Design] criteria. The EASE trial is a phase III randomised controlled trial providing direct head-to-head evidence of the safety and efficacy of Filsuvez gel compared to a control gel arm (Kern 2019, Kern 2023). However, since the EASE protocol permitted continuation of the participants usual wound care management routine, including use of dressings, bandages, and some topical treatments, this is considered a proxy for CCM alone since there is an absence of any other trial evidence of key wound healing endpoints in DEB and JEB patients receiving only current clinical management.

One additional recently published study of the real-world use of Filsuvez was also added as relevant literature for the clinical assessment (Torres Pradilla 2024).

Table 5 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Kern JS, Sprecher E, Fernandez MF, Schauer F, Bodemer C, Cunningham T, Löwe S, Davis C, Sumeray M, Bruckner AL, Murrell DF; EASE investigators. Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: results from the phase III randomized double-blind phase of the EASE study. Br J Dermatol. 2023 Jan 23;188(1):12-21. doi: 10.1093/bjd/ljac001. PMID: 36689495. Kern JS, Schwieger-Briel A, Löwe S, Sumeray M, Davis C, Martinez AE. Oleogel-S10 Phase 3 study "EASE" for epidermolysis bullosa: study design and rationale. Trials. 2019 Jun 11;20(1):350. doi: 10.1186/s13063-019-3362-z. PMID: 31186047; PMCID: PMC6560757.	EASE	NCT03068780	Start: 29/03/2017 Completion: 27/05/2022	Filsuvez +CCM vs CCM in patients with DEB or JEB

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Torres Pradilla M, Álvarez E, Novoa M, Lozano I, Trujillo M. Oleogel-S10 in Dystrophic Epidermolysis Bullosa: A Case Series Evaluating the Impact on Wound Burden Over Two Years. Adv Ther. 2024 Feb;41(2):867-877. doi: 10.1007/s12325-023-02749-x. Epub 2024 Jan 3. PMID: 38170434; PMCID: PMC10838820.	N/A, no trial name available	N/A, no NCT identifier available	Start: Not available Completion: Not available	Filsuvez + standard care vs standard care

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

A literature search was conducted to identify relevant data on quality of life /health utility. The search revealed that the most informative information source was data from the EASE trial. This data was used to link the BSAP wound burden to health utility.

Table 6 Relevant literature included for (documentation of) health-related quality of life (See section 0)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Kern JS, Sprecher E, Fernandez MF, Schauer F, Bodemer C, Cunningham T, Löwe S, Davis C, Sumeray M, Bruckner AL, Murrell DF; EASE investigators. Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: results from the phase III randomized double-blind phase of the EASE study. Br J Dermatol. 2023 Jan 23;188(1):12-21. doi: 10.1093/bjd/ljac001. PMID: 36689495.	EQ-5D data from open-label phase of EASE trial	Section 10

5.3 Literature used for inputs for the health economic model

A literature search was conducted to identify relevant data for economic input in the model. The review identified two sources which were deemed as most reliable and relevant for the analysis.

Table 7 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Kern JS, Sprecher E, Fernandez MF, Schauer F, Bodemer C, Cunningham T, Löwe S, Davis C, Sumeray M, Bruckner AL, Murrell DF; EASE investigators. Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: results from the phase III	Number of dressing changes	Systematic literature review	Section 6

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
randomized double-blind phase of the EASE study. Br J Dermatol. 2023 Jan 23;188(1):12-21. doi: 10.1093/bjd/ljac001. PMID: 36689495			
Angelis, A., J.E. Mellerio, and P. Kanavos, Understanding the socioeconomic costs of dystrophic epidermolysis bullosa in Europe: a costing and health-related quality of life study. Orphanet J Rare Dis, 2022. **17**(1): p. 346	Cost of treating the disease	Systematic literature review	Section 11
Torres Pradilla M, Álvarez E, Novoa M, Lozano I, Trujillo M. Oleogel-S10 in Dystrophic Epidermolysis Bullosa: A Case Series Evaluating the Impact on Wound Burden Over Two Years. Adv Ther. 2024 Feb;41(2):867-877. doi: 10.1007/s12325-023-02749-x. Epub 2024 Jan 3. PMID: 38170434; PMCID: PMC10838820.	Amount of Filsuvez drug use	Systematic literature review	Section 11

6. Efficacy

6.1 Efficacy of Filsuvez compared to CCM alone for patients with dystrophic or junctional EB

6.1.1 Relevant studies

One study was in the literature review identified as providing evidence relevant to the assessment. The EASE trial is a phase III randomised controlled trial providing direct head-to-head evidence of the safety and efficacy of Filsuvez gel compared to a control gel arm (Kern 2019, Kern 2023).

One additional recently published study of the real-world use of Filsuvez was also added as relevant literature for the clinical assessment (Torres Pradilla 2024).

Table 8 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
EASE - NCT03068780	Double-blind, randomized, vehicle-controlled, phase III	Double-blind phase (DBP) 90 days, open-label phase (OLP) 24 months	Patients with dystrophic EB, junctional EB or Kindler EB	Oleogel-S10 (Filsuvez) with standard-of-care dressings	Control gel with standard-of-care dressings	**Double-blind phase (DBP)** Primary: • Proportion of patients with first complete target wound closure within 45±7 days determined by clinical assessment. Wound closure was defined as skin re-epithelisation without drainage and was confirmed by a second observation after 7±2 days. Secondary: • Time to first wound closure up to 90±7 days of treatment • Incidence of first complete wound closure of EB target wound within 90 (±7) days • Incidence of wound infection within 90 (±7) days • Maximum severity of wound infection between baseline and 90 (±7) days • Change from baseline in total body wound burden as measured through (EBDASI, Section I: Skin, Activity (not Damage), only) Other secondary endpoints included: • Change from baseline in TBWB through BSAP

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
						• Change from baseline in weekly dressing changes (post-hoc analysis) **open-label phase (OLP)** Primary: • N/A, no primary endpoint defined Secondary: • Incidence of Target Wound Infection in the OLP • Maximum Severity of Wound Infection in the OLP (between baseline and Month-24) • Change from baseline in Total Body Wound Burden in the OLP (EBDASI, Section I: Skin, Activity (not Damage), only; Months 3, 12, 24) • Change from baseline in BSAP affected by partial-thickness wounds by Visit (Months 3, 12, 24) • Change from baseline in patients' quality of life as assessed by the EQ-5D (Months 12, 24) Follow-up duration was pre-specified
Torres Pradilla 2024	Observational retrospective medical records review study	Up to 24 months follow-up	Patients diagnosed with dystrophic EB treated	Oleogel-S10 (+standard care)	Standard care at baseline	Total body wound burden and safety for up to 24 months follow-up

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
			with Oleogel-S10 through an early access programme in different regions of Colombia			

6.1.2 Comparability of studies

The EASE trial was a randomized study in controlled clinical trial setting, while Torres Pradilla et al was a real-world observational study.

6.1.2.1 Comparability of patients across studies

Patients in the real-world observational study were slightly older and had more female patients than the EASE trial.

Table 9 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	EASE trial		Real-world study	
	Int	Comp	Int	Comp
Age	13.0 years (median)	12.0 years (median)	19 years (mean)	NA
Gender	68% male	66% male	30.8% male	NA

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

There is limited information about the patient population in Denmark, but the population is believed to be similar to the trial population.

Table 10 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age	Unknown, believed to be in line with clinical trial population	Median age 12 years (Kern 2023)
Gender	Unknown, believed to be in line with clinical trial population	60.1% male (Kern 2023)
Patient weight	Unknown, believed to be in line with clinical trial population	52% underweight, 39% normal weight (Kern 2023)

6.1.4 Efficacy – results per EASE

Although EB is a rare condition, Filsuvez was evaluated in the largest randomised vehicle-controlled trial in EB, the EASE trial, which consisted of two phases (Kern 2019), with a total duration of 27 months:

- A 90-day randomised, double-blind phase (DBP) of Filsuvez gel versus control gel
- A 24-month single-arm open-label phase (OLP), during which all participants received Filsuvez gel

In the double-blind phase, patients are randomized 1:1 to either Filsuvez plus standard-of-care wound dressing or control gel, also with standard-of-care wound dressing, at least once every four days. The control-gel was not a strict vehicle control as it in addition to sunflower oil also included cera flava/yellow wax and carnauba wax in order to match the consistency and visual appearance of Filsuvez.

This is an important consideration as this control gel likely has beneficial properties and the derived value of Filsuvez vs the control gel likely underestimates the benefit of Filsuvez vs current clinical practice (which does not include the control gel).

A total of 223 patients from 49 clinical sites in 26 countries were randomised 1:1 to receive Filsuvez (n=109) or control gel (n=114) (Kern 2023). Both trial arms were instructed to use the standard of care non-adhesive wound dressing and were required to continue dressing changes at least every 4 days until the end of the treatment (Kern 2019). Silver dressings, topical antibiotics or topical steroids were only permitted for application once the target wounds had completed closure with confirmed epithelialisation, because these products have the potential to impact wound healing.

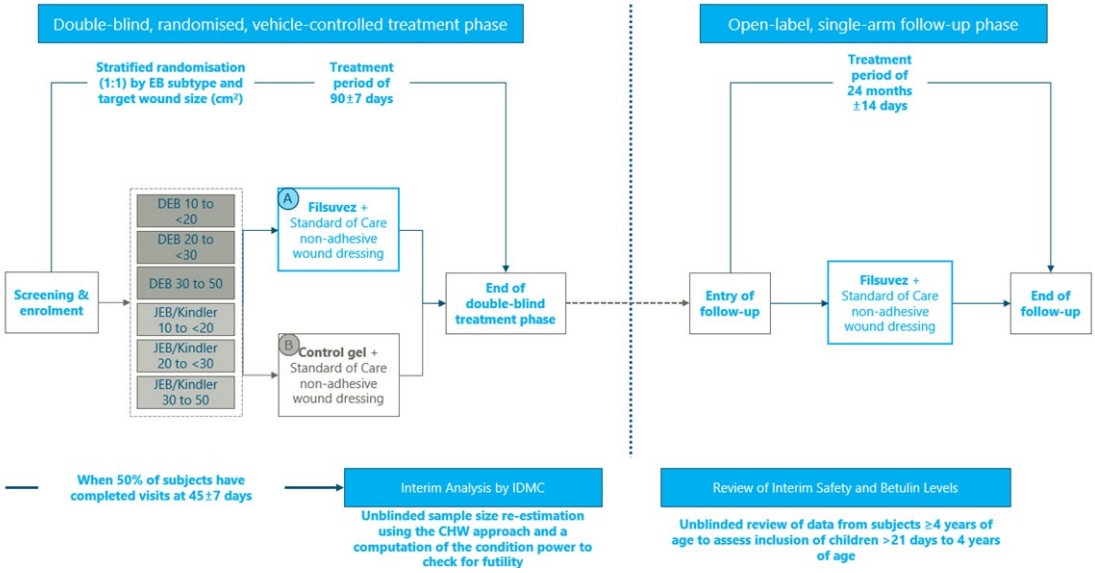
Randomisation was conducted according to blinded patient number, and the randomisation key was held solely by an independent statistician. Patients eligible for study inclusion were stratified by both EB subtype (DEB, JEB or KEB) and target wound size (10 cm2 to <20 cm2, 20 cm2 to <30 cm2 or 30 cm2 to 50 cm2). Patients in both arms were instructed to apply approximately 1 mm of investigational product to all their wounds at each dressing change for 90 days alongside standard of care non-adhesive wound dressing (Kern 2019).

After completion of the DBP, patients in both treatment arms were invited to enter the single-arm open label phase with Filsuvez. The primary rationale of the OLP was to obtain long-term safety data, while efficacy data was consistently collected according to the methods employed in the DBP, as well as some specific efficacy data unique to the OLP. Filsuvez was administered in the same manner as described for the DBP for any partial-thickness wounds on day 0 of the OLP. In total 205 patients entered an additional 24-month, single-arm OLP (Chiesi, data on file 2022).

Eligible patients included male and female patients aged ≥4 years old (reduced to ≥21 days old only after confirmation by an Independent Data Monitoring Committee [IDMC] review of the safety and bioanalytical data at the interim safety review) with DEB, JEB or

KEB and a suitable target wound of 10 cm2 to 50 cm2 in size and ≥21 days to <9 months in age (Kern 2019, Kern 2023).

Figure 6: EASE study design overview (total duration:27 months)



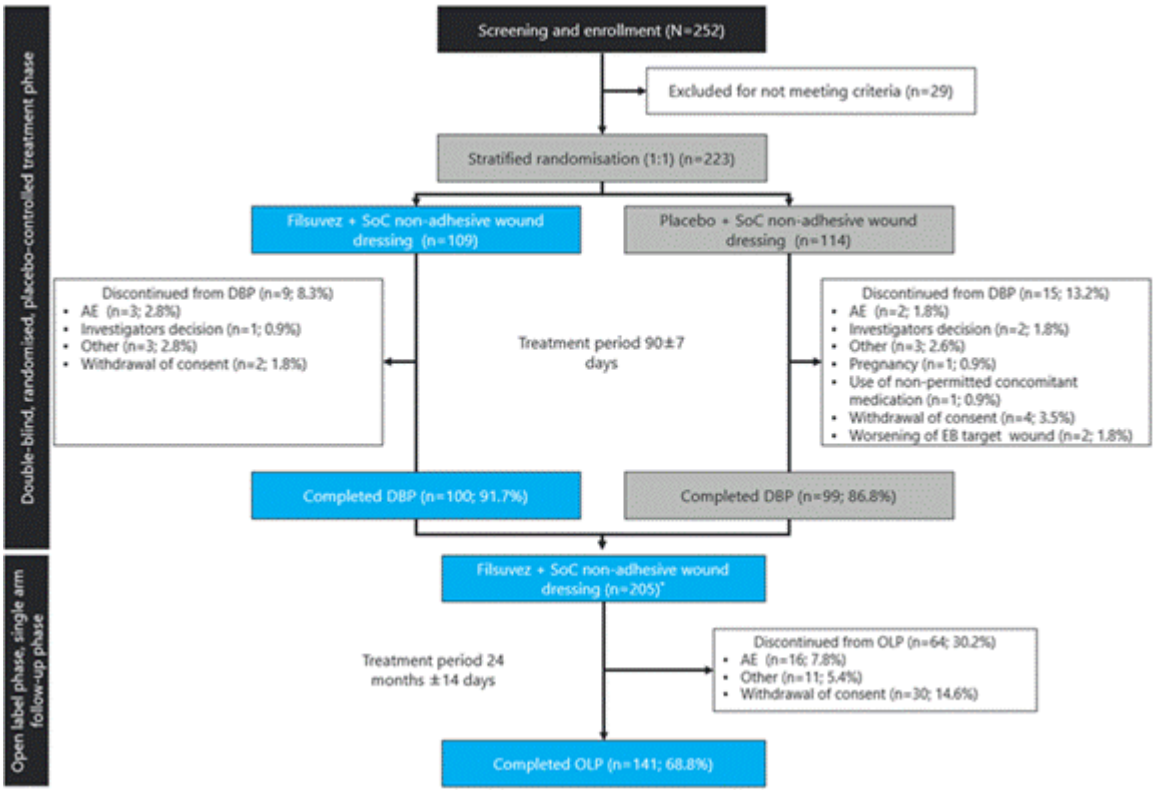
cm2 – square centimetres; DEB – dystrophic epidermolysis bullosa; EB – epidermolysis bullosa; JEB – junctional epidermolysis bullosa
Source: EASE CSR 2022 (data on file 2022)

EASE Study results

Among 223 patients enrolled in the EASE study, 199 (89.2%) completed the DBP and 141 (68.8%) completed the OLP (Kern 2023). The mean duration of treatment in the OLP up to the final database lock was 584.7 days (SD: 246.1) (Chiesi, data on file 2024). In the DBP, a total of 24 patients discontinued (9 in the Filsuvez arm vs 15 in the control-arm [Kern 2023]) and in the OLP the corresponding number was [redacted] (Chiesi, data on file 2024).

The baseline characteristics between the two trial arms were similar (Kern 2019). Based on EB subtype, the majority of patients had RDEB (n=175; 78.5%), while none of the patients had KEB. Based on age, the majority of patients were <18 years (n=156; 69.9%). Most patients changed their dressings daily (43.1% and 45.6% for Filsuvez and control-gel, respectively) or every 2 days (41.3% and 34.2% for Filsuvez and control-gel, respectively).

Figure 7: Participation flow in the EASE study



*6 patients, all control-gel, discontinued from DBP and entered OLP prematurely.
AE – adverse event; DBP – double-blind phase; OLP - open-label phase; SoC – standard of care
Placebo gel refers to the control-gel.
1. EASE CSR 2022 (data on file 2022)

Table 11 Baseline characteristics in EASE

	Filsuvez (n=109)	control-gel (n=114)	Total (N=223)
Age, Median (95 % CI), years	13.0 (14.2, 19.5)	12.0 (13.8, 19.2)	12.0 (14.8, 18.5)
Age group, n (%)			
0 to <4 years	7 (6.4)	10 (8.8)	17 (7.6)
4 to <12 years	42 (38.5)	43 (37.7)	85 (38.1)
12 to <18 years	25 (22.9)	29 (25.4)	54 (24.2)
≥18 years	35 (32.1)	32 (28.1)	67 (30.0)
Female, n (%)	41 (37.6)	48 (42.1)	89 (39.9)
BMI, n (%)			
Underweight	56 (51.4)	59 (51.8)	115 (51.6)
Normal	45 (41.3)	41 (36.0)	86 (38.6)
Overweight	5 (4.6)	6 (5.3)	11 (4.9)
Obese	3 (2.8)	8 (7.0)	11 (4.9)
EB subtype, n (%)			
RDEB	91 (83.5)	84 (73.7)	175 (78.5)

Generalised severe	62 (56.9)	62 (54.4)	124 (55.6)
Generalised intermediate	23 (21.1)	16 (14.0)	39 (17.5)
Localised/other	6 (5.5)	6 (5.3)	12 (5.4)
DDEB	6 (5.5)	14 (12.3)	20 (9.0)
JEB	11 (10.1)	15 (13.2)	26 (11.7)
Generalised severe	0	2 (1.8)	2 (0.9)
Generalised intermediate	8 (7.3)	9 (7.9)	17 (7.6)
Localised/other	3 (2.8)	4 83.5)	7 (3.1)
EB simplex	1 (0.9)	1 (0.9)	2 (0.9)
Target wound size, n (%)			
10 to <20 cm2	69 (63.3)	75 (65.8)	144 (64.6)
20 to <30 cm2	23 (21.1)	24 (21.1)	47 (21.1)
30 to <50 cm2	17 (15.6)	15 (13.2)	32 (14.3)
Target wound age, median (95% CI), days	39.0 (62.1, 186.5)	32.0 (40.6, 212.1)	35.5 (72.5, 178.2)
EBDASI skin activity score, mean (SD)	19.6 (11.3)	19.6 (12.6)	19.6 (11.9)

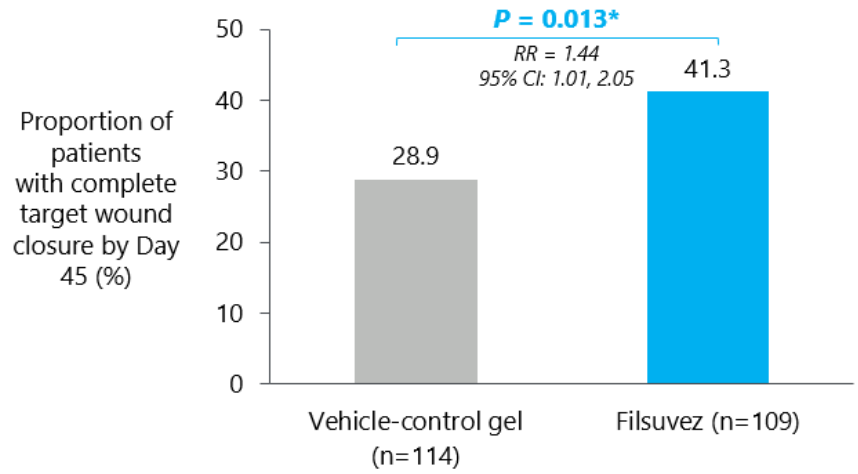
BMI – body mass index; CI – confidence interval; cm2 – square centimetres; DDEB – dominant dystrophic epidermolysis bullosa; EB – epidermolysis bullosa; EBDASI - epidermolysis bullosa disease activity and scarring index; JEB – junctional epidermolysis bullosa; RDEB – recessive dystrophic epidermolysis bullosa; SD – standard deviation

Source: Kern (2023)

Primary outcome

The EASE study met its primary efficacy endpoint; the proportion of patients with first complete closure of the EB target wound by Day 45. Complete target wound closure occurred in 41.3% of target wounds treated with Filsuvez and in 28.9% of target wounds treated with control-gel, resulting in a 44% higher likelihood of achieving wound closure with Filsuvez compared with control-gel (relative risk [RR]: 1.44; 95% CI: 1.01, 2.05; P=0.013) (Kern 2023).

Figure 8: The proportion of patients with first complete target wound closure by Day 45 in the EASE trial DBP, ITT population



*Prespecified adjustment to account for IDMC interim sample size re-estimation
CI – confidence interval; DBP – double-blind phase; IDMC - Independent Data Monitoring Committee; ITT – intention-to-treat; RR – relative risk
Source: Kern (2023)

Secondary outcomes

A number of key secondary efficacy endpoints were defined for analysis based on their importance with respect to demonstration of meaningful clinical benefit to patients with EB. A hierarchical testing approach to control for the impact of multiple comparisons on the significance level was prespecified for the DBP. The first key secondary endpoint to be tested in the DBP, time to first complete closure of the EB target wound within 90 days (DBP), did not demonstrate a statistically significant treatment effect. Therefore, subsequent statistical testing of the remaining secondary endpoints provides nominal, not inferential, P-values and is exploratory in nature (Chiesi data on file 2024).

The secondary endpoints in the following section first present the results of the DBP and then the OLP per outcome.

Time to first complete closure of EB target wound within 90 (±7) days

The mean time to first complete closure of the target wound within 90 days (for the wounds which closed) was numerically faster for patients randomised to Filsuvez than control-gel. Despite not reaching statistical significance (P=0.302), patients in the Filsuvez arm achieved first complete wound closure 6.8 days faster than the control-gel arm (37.7 days vs 44.5 days, respectively).

Table 12: Time to first complete closure of EB target wound up to Day 90 for the DBP population

	Filsuvez (n=109)	Control-gel (n=114)
Mean time to first complete closure, days ±SD	37.7±21.7	44.5±26.2

p-value	0.302	
Median time to first closure, days	33.0	39.0
Median time to first complete closure, days (95% CI)	92.0 (50.0, NE)	94.0 (89.0, NE)

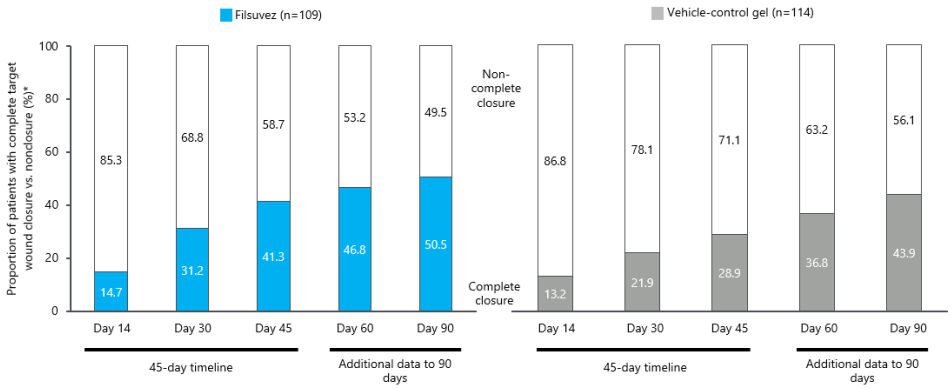
CI – confidence interval; DDEB – dominant dystrophic epidermolysis bullosa; JEB junctional epidermolysis bullosa; NE - not estimable; RDEB – recessive dystrophic epidermolysis bullosa; SD – standard deviation
Source: Kern (2023)4.1.3.2 Proportion of patients with first target wound closure within 90 (±7) days

Proportion of patients with first complete closure within day 90

A numerically higher percentage of patients randomised to Filsuvez achieved first complete closure of the target wound at Day 14, Day 30, Day 45, Day 60, and Day 90 compared with those randomised to control-gel. At Day 90 first complete closure of the target wound was achieved by 50.5% of patients randomised to Filsuvez and 43.9% of patients randomised to control-gel (relative risk [RR]: 1.16; 95% CI: 0.88, 1.52; P=0.296; 95% confidence interval [CI] for treatment difference: −6.2, 20.0).

Moreover, the table below stratifies the proportion of patients with first complete closure into wound size related subgroups) (Kern 2023).

Figure 9: Proportion of patients with first complete closure of EB target wound for the DBP population



*Complete closure of the target wound refers to appearance of complete reepithelialisation without drainage.
Source: Kern (2023)

Table 13: Proportion of patients with first complete closure of EB target wound by EB subtype and wound size up to Day 90 for the DBP population*

	Filsuvez (n=109) n (closure, non-closure)	Control-gel (n=114) n (closure, non-closure)
All patients	109 (55, 54)	114 (50, 64)
EB subtypes		
DEB 10 to <20 cm²	62 (38, 24)	66 (36, 30)
DEB 20 to <30 cm²	22 (10, 12)	21 (8, 13)
DEB 30 to 50 cm²	14 (5, 9)	12 (1,11)

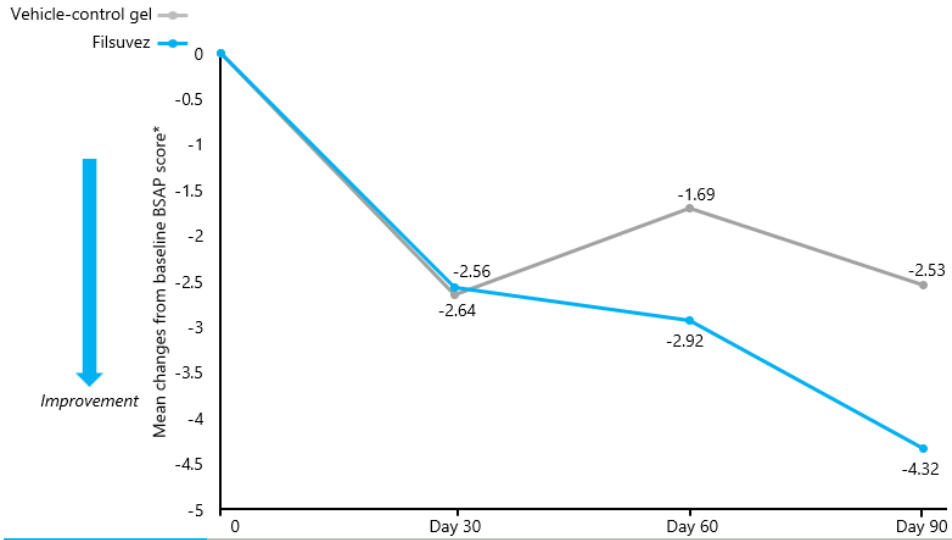
JEB 10 to <20 cm²	7 (1, 6)	9 (4, 5)
JEB 20 to <30 cm²	1 (0, 1)	3 (1, 2)
JEB 30 to 50 cm²	3 (1, 2)	3 (0, 3)

*The data will be subject to changes due to further investigation.
** Cochran-Mantel-Haenszel statistical test stratified by EB subtype and target wound size class. Odds ratio >1 represents a favourable outcome for Filsuvez gel treatment.
CI – confidence interval; DEB – dystrophic epidermolysis bullosa; EB epidermolysis bullosa; JEB junctional epidermolysis bullosa
Source: Kern (2023)

Change from baseline in body surface area percentage (BSAP) at Day 90

The accelerated wound healing observed with Filsuvez gel, as indicated by the primary endpoint, was accompanied by reductions in the change from baseline in body surface area percentage (BSAP) affected with partial thickness wounds. At Day 90, the mean reduction from baseline in total BSAP was -4.32% for Filsuvez, versus -2.53% in the control-gel group (Kern 2023).

Figure 10: Change in BSAP by Day 90 for the DBP population



Filsuvez, n	109	98	92	86
Vehicle-control gel, n	113	98	96	85

*At all timepoints, comparison between Filsuvez gel vs. control-gel was not significant
BSAP – body surface area percentage; DBP – double-blind phase

BSAP in the open-label phase

The mean BSAP score was continually evaluated for the duration of the OLP and both treatment groups demonstrated continued improvement across 24 months. Overall, the mean BSAP at entry to DPB (Day 0) was [redacted] % and [redacted] in the Filsuvez (n=109) and control (n=114) arms respectively (mean [redacted]). The BSAP improved and was reduced to mean [redacted] % for all patients (total n= 129) by month 24 of the OLP. This group thus contains both those starting DPB with Filsuvez ([redacted]) and those starting DPB with control ([redacted]) (Chiesi, data on file 2024). The means at months 3 and 12 of the OLP phase were [redacted], respectively. The total mean reduction in BSAP from baseline (Day 0 of DPB) to end

of study (months 24 OLP) was [redacted], which is used in the economic analysis below.

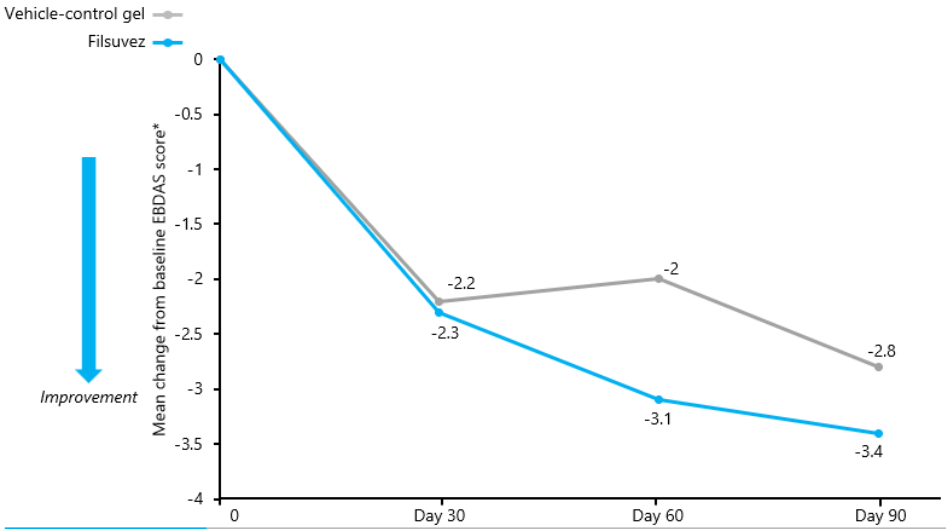
[redacted]

BSAP – body surface area percentage; ITT – intention-to-treat; OLP – open-label phase
Sources. EASE CSR 2022 (Chiesi, data on file 2024)

Change from baseline in total body wound burden (TBWB) using the skin activity component of the EB disease activity and scarring index (EBDASI) at Day 90

Accelerated wound healing with Filsuvez gel (demonstrated by the primary endpoint) was accompanied by a change from baseline in disease activity as measured by section I (assessment of the skin except for the anogenital region) of the EB disease activity and scarring index (EBDASI). At Day 90 the EBDASI score for patients treated with Filsuvez was -3.4, while the score for the control-gel group was -2.8 (Kern 2023).

Figure 11: Change in TBWB using EBDASI skin activity score by Day 90 for the DBP population



Filsuvez, n	108	99	91	84
Vehicle-control gel, n	113	99	96	85

*At all timepoints, comparison between Filsuvez gel vs. control-gel was not significant
DBP – Double-blind phase; EBDASI – Epidermolysis Bullosa Disease Activity and Scarring Index; TBWB – total body wound burden
Source: Kern 2023

Total wound burden measured by EBDASI in the open label phase

Both treatment groups demonstrated continued improvement across 24 months. The mean EBDASI skin activity score at the start of OLP was [redacted] and by conclusion of the OLP, this score had improved to [redacted] from the former Filsuvez group and [redacted] from the former control-gel group. Overall, a clinically meaningful [redacted] point reduction mean EBDASI activity score was observed at Month 24 (Chiesi, data on file 2024).

[redacted]

*Assessments recorded within OLP visit windows were lower than expected largely due to COVID-19. Therefore, a post-hoc analysis was produced without visit windows in the OLP; **A 3-point reduction is considered clinically meaningful Jain (2017)
EBDASI - epidermolysis bullosa disease activity and scarring index; ITT – intention-to-treat; OLP – open-label phase
Sources: EASE CSR 2022 (data on file 2022)

Incidence of wound infection and severity of infection in target wound in DBP

A lower incidence and severity of infections was observed with Filsuvez in the DBP. There were six patients with target wound infections during the DBP, one (0.9%) in the Filsuvez arm compared with five (4.4%) on control gel (Kern 2023). In the control-gel arm there were three infections of moderate severity, one was life-threatening. One wound in each arm was not graded for severity.

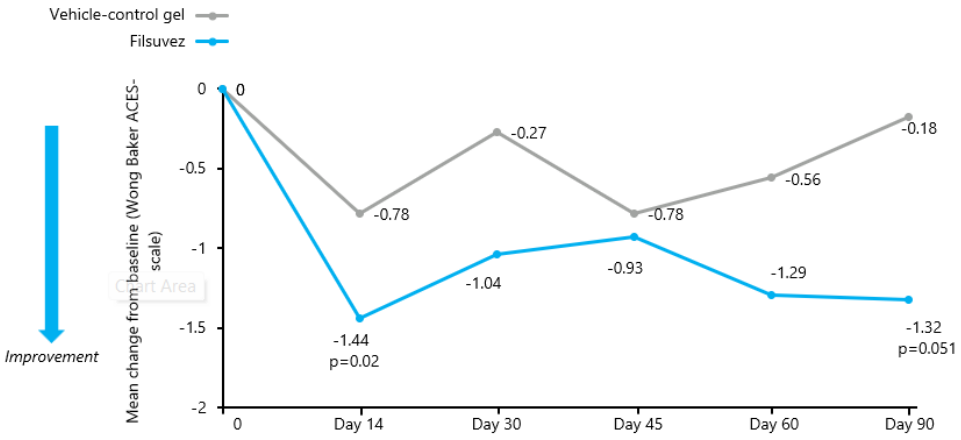
Wound infection and severity of infection in the OLP

Target wound infections occurred in very few subjects with only [redacted] subjects experiencing an infection of the target wound in the OLP. The maximum severity of target wound infections occurring in the OLP (between OLP Day 0 and Month [redacted]) was mild (n=[redacted]) and severe (n=[redacted]) in the former Filsuvez group, and all target wound infections in former control gel group were moderate (n=[redacted] The incidence and severity of additional and other wound infections were very similar between the DBP and OLP through Month 24 (Chiesi, data on file 2024).

Change from baseline in procedural pain after wound dressing changes

Favourable trends were observed for Filsuvez gel compared with control gel when looking at change in procedural pain (pain resulting from dressing changes) at Day 90, measured using Wong-Baker FACES for participants aged ≥4 years and Faces, legs, activity, cry, consolability (FLACC) for those aged <4 years. In patients aged <4 years (FLACC scale), comparable reductions in procedural pain were seen with Filsuvez and control gel that were maintained between Day 14 and Day 90, with a trend favouring Filsuvez compared with control gel at Day 90 (-2.57 vs -1.17, respectively). In patients aged ≥4 years (Wong-Baker FACES scale), reductions in procedural pain were seen with Filsuvez compared with control gel at Day 14 and Day 90. From baseline to Day 90, a reduction in procedural pain was demonstrated, with a score of -1.32 (38%) with Filsuvez gel compared to -0.18 with the control-gel (Kern 2023).

Figure 12: Change from baseline in procedural pain using the Wong-Baker FACES scale for the DBP population (≥4 years)



Filsuvez, n	98	90	90	85	84	76
Vehicle-control gel, n	100	95	90	85	86	78

DBP – double-blind phase
Source: Kern (2023)

Procedural pain in the OLP

Overall, the effects on procedural pain achieved in the DBP for patients ≥4 years (using the Wong-Baker FACES) were generally maintained at Month 3 of the OLP for the former Filsuvez group. Complete resolution of pain, particularly when there is a chronic requirement for dressing changes, is unrealistic; however, maintaining lower severity of pain is and has been demonstrated.

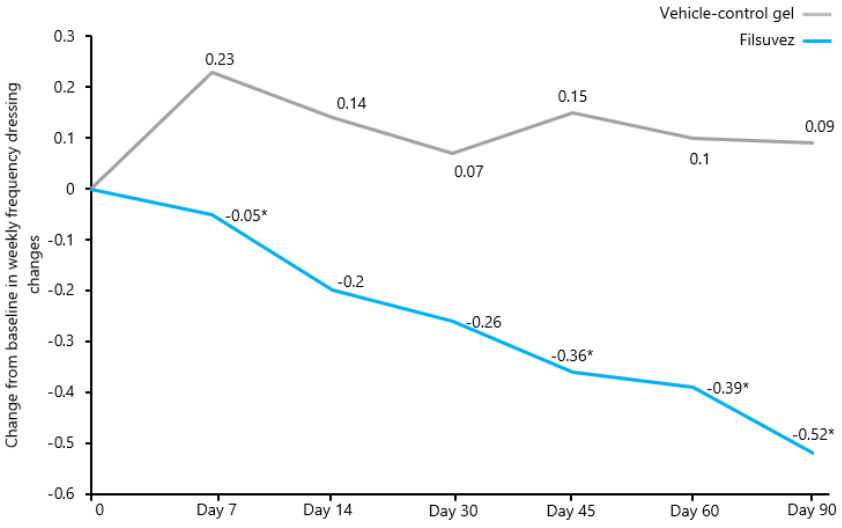
The sample size of the patient group <4 years using the FLACC scale was too small, so no data is presented for this group (Chiesi, data on file 2024).

Change from baseline in weekly frequency of dressing changes

In a post-hoc analysis, patients treated with Filsuvez had a reduced requirement for daily dressing changes compared with patients treated with control-gel. At Day 90, Filsuvez-treated patients required one fewer dressing change every two weeks compared with the control-gel group (P=0.001) (Kern 2023).

In a subpopulation of patients who initially changed their dressings daily (n=99), a significantly higher percentage of patients treated with Filsuvez no longer required daily dressing changes compared with patients treated with control gel at Day 45 (33% vs 10%, respectively; P=0.005), Day 60 (34% vs 13%; P=0.009), and Day 90 (36% vs 11%; P=0.005). This translated to almost three fewer dressing changes every two weeks for Filsuvez-treated patients. In this subpopulation of patients who changed their dressings daily at baseline (n=99), time saved on dressing changes for patients and caregivers equated to 10.9 hours for those randomised to Filsuvez and 4.0 hours for those randomised to control-gel.

Figure 13: Change from baseline in weekly frequency of dressing changes



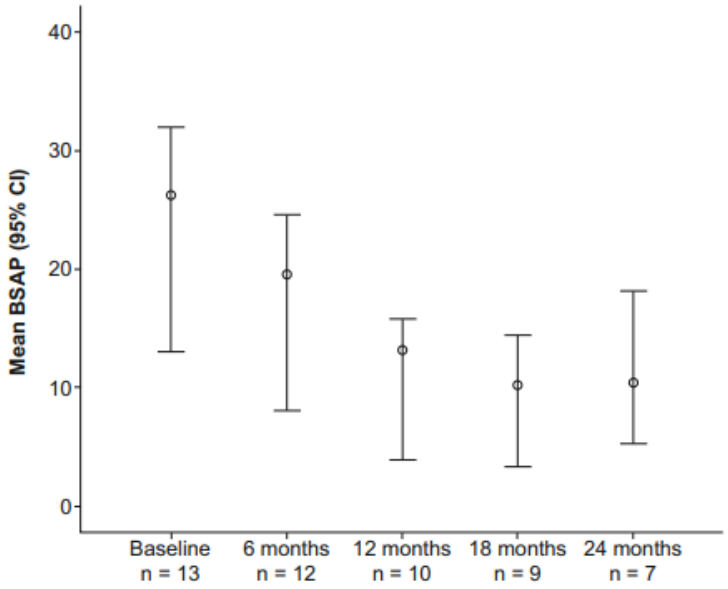
Filsuvez, n	108	105	105	100	101	99	99
Vehicle-control gel, n	113	108	103	103	100	97	97

*Analysis of covariance (ANCOVA) was conducted and a statistically significant difference between Filsuvez and control-gel was observed at Day 7 (P=0.037), Day 45 (P=0.003), Day 60 (P=0.005), and Day 90 (P=0.001).
1. Kern (2023)

6.1.5 Efficacy – results per Torres Pradilla et al

The results showed a reduction in percentage of BSA affected, from a mean of 27.3% at baseline to 10.4% at 24-month follow-up, despite treatment interruptions. A reduction in EBDASI skin activity score of - 16.2 (24 months) together with a reduced skin damage index score of - 15.4 (18 months) was also observed. Physicians, patients, and caregivers perceived faster wound closure. Adherence with therapy by patients was good, and patients expressed satisfaction with treatment and reported improvements in self-esteem, productivity, and social interaction. Oleogel-S10 was well tolerated; however, two patients reported worsening wounds related to gauze adherence.

Figure 14: Mean BSAP over 24 months with Oleogel-S10 (Torres Pradilla 2024)



7. Comparative analyses of efficacy

N/A. only direct trial data used

7.1.1 Differences in definitions of outcomes between studies

N/A. only direct trial data used

7.1.2 Method of synthesis

N/A. only direct trial data used

7.1.3 Results from the comparative analysis

N/A. only direct trial data used

Table 14 Results from the comparative analysis of [intervention] vs. [comparator] for [patient population]

Outcome measure	[Intervention] (N=x)	[Comparator] (N=x)	Result
N/A. only direct trial data used			

7.1.4 Efficacy – results per [outcome measure]

N/A. only direct trial data used

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

The population baseline characteristics are captured from the EASE trial and are presented below. The population of interest is assumed to be relevant and representative of the Danish population.

Table 15. Patients' population and baseline age

Population	Baseline age
Baseline age	Six months (0.5 years)
Share of women	39.9%

The relevant clinical endpoints used to establish the effectiveness of Filsuvez have been sourced and supported by data from the literature, a real-world study (Torre Pradilla 2024) and the EASE clinical trial (Kern 2023). The most relevant input regarding the effectiveness of Filsuvez and CCM used in the model and economic analysis was BSAP score and the patients' quality of life (QoL). Other effectiveness inputs of Filsuvez are changes in dressing frequency and probability of sepsis.

8.1.1 Extrapolation of efficacy data

8.1.1.1 Extrapolation of BSAP

The efficacy in terms of BSAP achieved at the end the clinical trial is assumed to be maintained at that level. This is supported by the time-trend of patient outcomes, e.g. in body surface area percentage (BSAP), seen in long-term trial follow-up as well as real-world data (Kern 2023), Torres Pradilla 2024).

Table 16 Summary of assumptions associated with extrapolation of BSAP

Method/approach	Description/assumption
Data input	EASE trial (Kern 2023) and real-world study (Torres Pradilla 2024)
Model	No modelling of BSAP used
Assumption of proportional hazards between intervention and comparator	Not applicable
Function with best AIC fit	Not applicable
Function with best BIC fit	Not applicable
Function with best visual fit	Not applicable
Function with best fit according to evaluation of smoothed hazard assumptions	Not applicable
Validation of selected extrapolated curves (external evidence)	Not applicable
Function with the best fit according to external evidence	Not applicable
Selected parametric function in base case analysis	Not applicable
Adjustment of background mortality with data from Statistics Denmark	Yes, in general for mortality estimation, but not for BSAP estimation
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

8.1.2 Calculation of transition probabilities

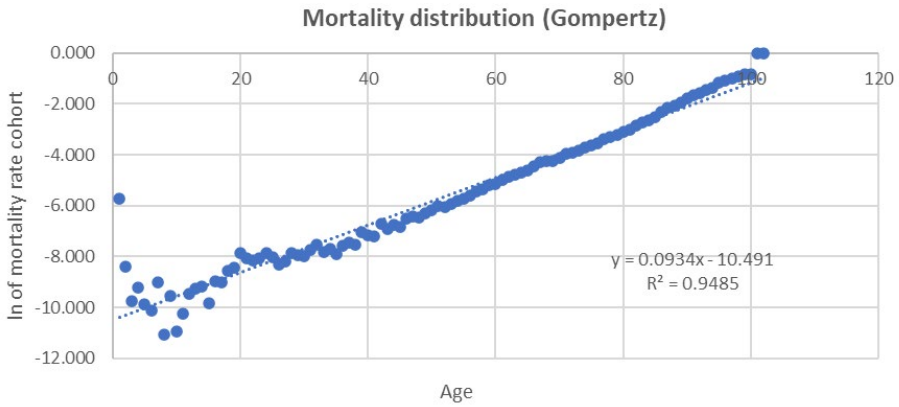
Mortality

To model survival, the probability of mortality stratified by the patient's age was introduced in each model cycle. The probabilities were calculated by adjusting the all-cause mortality probabilities in Denmark with a disease-specific standardised mortality ratio (SMR).

The life expectancy of the general population was estimated from the Danish national life table (Denmark Statistics 2024). From the mortality rate by age and gender, the probability of death of the cohort stratified by age was calculated and weighted by sex. The probabilities were converted to rates by assuming a constant mortality rate each year.

The method described by Haybittle was used to estimate the SMR for EB (Haybittle 1998). A Gompertz distribution of survival was assumed for the general population, and the mortality rate was plotted on the log scale as shown below.

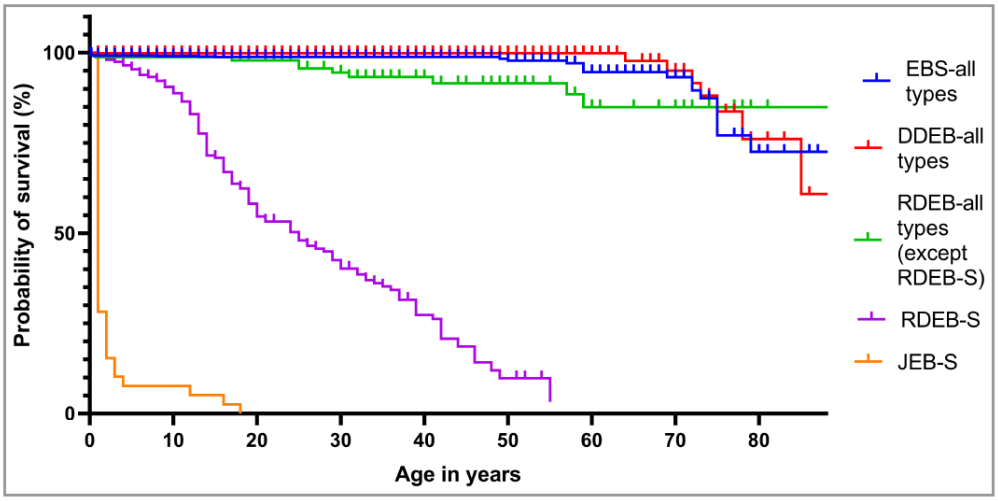
Figure 15. Mortality distribution stratified by age



The SMR was estimated by applying the formula $e^{(-k*\Delta x)}$, corresponding to a Gompertz mortality distribution where k is the slope of the curve (0.0934) and Δx the difference between the expected mean survival for patients with EB and the weighted average life expectancy of the Danish general population (81.12 years) (Denmark Statistics 2024).

Mortality varies between the four major EB subtypes and with severity within the subtypes. Petrof and colleagues demonstrated this by estimating survival for different subtypes of EB in England and Wales (Petrof 2022).

Figure 16. Kaplan-Meier estimators for overall survival in EB



Source: [15], EBS: Epidermolysis bullosa simplex, DDEB: Dominant dystrophic epidermolysis bullosa, RDEB(-S): Recessive dystrophic epidermolysis bullosa (-severe), JEB-S: Junctional epidermolysis bullosa-severe

The mean survival for JEB-S was estimated to be only 8.4 months but nearly 28 years for severe RDEB (calculated from the area under the curve in figure above). The different subtypes of EB in EASE are presented below.

Table 17. Epidermolysis bullosa subtypes in EASE, double-blind phase

EB Subtype n (%)	All subjects (N=223)
RDEB - all	**175 (78.5)**
RDEB, generalized severe	124 (55.6)
RDEB, generalized intermediate	16 (14.0)
RDEB, localized	4 (3.5)
RDEB, other	2 (1.8)
DDEB	14 (12.3)
JEB - all	**15 (13.2)**
JEB, generalized severe	2 (1.8)
JEB, generalized intermediate	9 (7.9)
JEB, localized	0
JEB, other	4 (3.5)
EBS	2 (0.9)

Calculating the expected survival of the mix included in EASE is challenging. However, the largest proportion of patients in EASE had RDEB (78.5%), with 55.6% of those patients having RDEB-S, the most severe. The expected survival of RDEB has been reported to be 40 years old (Soro 2015). This was used in the base case with alternative assumptions

tested in scenario analyses (20 years and 81.12 years, i.e., the same life expectancy as the general population in Denmark).

A life expectancy of 40 years yielded a disease-specific SMR of 49.92. This SMR was then applied (multiplied) to the previously calculated cohort mortality rates stratified by age. Finally, these rates were converted into probabilities by applying the formula p = 1-EXP(-rt), where p is the probability, r is the rate, and t is time (1). This resulted in disease-specific probabilities of mortality stratified by age.

Sepsis and related mortality

Several studies have identified sepsis following wound infection as one of the main causes of death in children with EB (Fine 2008, Maseda 2021). The EASE trial reported fewer infections in patients treated with Filsuvez compared to CCM; the mortality in the Filsuvez arm has been adjusted to account for the lower risk of sepsis.

Maseda et al. 2021 present a retrospective study including all cases with a clinical and molecular diagnosis of EB managed in the Hospital Universitario La Paz in Madrid, Spain, from January 2, 2000, to February 28, 2021 (Maseda 2021). Over the study period of 21 years, 26 of 214 patients (12.1%) had sepsis, and 10 of these died from the sepsis. This means that of those having sepsis, 10/26 ≈ 38.5% died.

With the probability of having sepsis at some point in time over 21 years being 26/214, the probability of having sepsis over one year is 1-(1-26/214)^(1/21) ≈ 0.61%. The annual probability of *dying* from sepsis is then 0.61%*38.5% ≈ 0.24%. The sepsis related mortality is assumed to be included in the mortality risk of the control arm. The mortality data for EB patients used in the model includes patients who died from sepsis, and it is adjusted in the Filsuvez arm in line with clinical trial data reporting fewer infections.

In the EASE trial, 0.9% of the patients treated with Filsuvez had infections compared to 4.4% of the patients in the control arm (Kern 2023), meaning that the incidence of infections was 4.9 times higher in the control arm than in the Filsuvez arm. Assuming the same probability of sepsis in the case of infection in the two arms, the probability of sepsis in the Filsuvez arm is therefore estimated to be 0.24% divided by 4.9 ≈ 0.048%. The absolute difference between Filsuvez and the control arm is then 0.24% - 0.048% ≈ 0.19%. This has been removed from the annual mortality in the Filsuvez arm until patients are 40 years old, representing the mean age of death for the population. After that age, no difference in mortality is assumed between the arms.

In summary, in base case analysis an absolute mortality reduction of 0.19% per year was applied in the model in the Filsuvez arm, until patients reach the age of 40.

Treatment discontinuation

A certain percentage of patients annually are assumed to discontinue treatment. In the base case, this number is 8% during the first year, based on the double-blind phase of the EASE clinical trial. In the open-label phase on EASE 30.2% discontinued but the primary reason for discontinuation was withdrawal of consent for half of these (Kern 2023). We therefore applied an 8% discontinuation also in the second year, followed by

an annual 4% discontinuation is applied, because it is assumed that most patients who do not respond or benefit from treatment will discontinue during the first 2 years.

Table 18 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Filsuvez+CCM	Death	General mortality in Denmark, adjusted for increased EB mortality and a reduced infections-related mortality from Filsuvez treatment	Calculated from Danish statistics and literature (Denmark statistics, Kern 2023, Haybittle 1998, Maseda 2021)
CCM	Death	General mortality in Denmark, adjusted for increased EB mortality	Calculated from Danish statistics and literature (Denmark statistics, Kern 2023, Haybittle 1998, Maseda 2021)
Filsuvez+CCM	CCM	Assumed annual discontinuation rate	From EASE trial (Kern 2023) and assumption

8.2 Presentation of efficacy data from Torres Pradilla

The results from the real-world usage study by Torres Pradilla et al assessed the reduction in percentage of BSA affected and found a reduction from a mean of 27.3% at baseline to 10.4% at 24-month follow-up (Torres Pradilla 2024). The reduction in BSA affected after FIlsuvez treatment from Torres Pradilla is larger than the modelled base case, which uses data from EASE trial, but assumptions assuming larger reduction in BSA affected are tested as well, as described below.

8.3 Modelling effects of subsequent treatments

N/A. no subsequent treatments included

8.4 Other assumptions regarding efficacy in the model

N/A. no other assumptions included

8.5 Overview of modelled average treatment length and time in model health state

Predicted survival is presented below.

Table 19 Estimates in the model

	Modelled average life-years (Markov model sheet in Excel)	Modelled median life-years (Markov model sheet in Excel)	Observed median from relevant study
Filsuvez+CCM	35.9 years	41 years	N/A, not available from studies
CCM	34.4 years	39 years	N/A, not available from studies

The table below presents modelled average treatment length and time in model health state, derived from assumed drop-out and mortality rates.

Table 20 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [months]	CCM Health state [months]	Dead Health state [months]
Filsuvez+CCM	189.2	247.6	763.2
CCM	N/A	419.0	781.0

9. Safety

9.1 Safety data from the clinical documentation

Safety outcomes – Double-blind phase

Of the 223 patients who entered the DBP, 181 (81.2%) reported at least one adverse event (AE), which is not unexpected in a population with such complex needs. The incidence of events was similar between the trial arms: 81.7% in the Filsuvez group and 80.7% in the control gel group.

The most frequently reported treatment-related AEs (TRAE) were wound complications, with similar incidence between Filsuvez and control gel treatment groups (24.8% and 22.8%, respectively). Changes in wound size from visit to visit are expected in patients

with EB who have fragile skin. The patients treated with control gel had more events of increase from baseline with respect to wound size. A higher proportion of patients treated with Filsuvez had healed wounds or decreased wound size, and therefore in these patients the increase in size was either relative to the previous visit or reopening of previously closed wounds. As the Medical Dictionary for Regulatory Activities term of 'wound complication' did not reflect these differences in changes of wound size, the subcategories of wound complication were specific to this study (Kern 2023).

Seven patients (6.4%) in the Filsuvez group and six patients (5.3%) in the control gel group experienced serious adverse events (SAEs). Only one SAE (wound haemorrhage) was considered to be related to study treatment in a patient randomised to Filsuvez. AE-related study withdrawal occurred in three (2.8%) Filsuvez patients and in two (1.8%) control-gel patients. In the Filsuvez group, withdrawals were due to procedural pain, wound haemorrhage and SCC (n=1 for each); the SCC case was not attributed to treatment as Filsuvez was not applied to the lesion. In the control-gel group, withdrawals were due to allergic dermatitis (n=1) and increased wound size compared to baseline (n=1). The majority of AEs in both treatment groups were of mild or moderate severity, and no clinically meaningful differences in reported AEs were observed between the groups (Kern 2023).

Table 21: Overview of safety events. During double-blind (90 day) phase

	Filsuvez, n (%) (n=109) (Kern 2023)	Control-gel, n (%)(n=114) (Kern 2023)	Difference, % (95 % CI)
Number of adverse events, n	Not available	Not available	Not available
Number and proportion of patients with ≥1 adverse events, n (%)	89 (81.7)	92 (80.7)	Not estimated
Number of serious adverse events, n	Not available	Not available	
Number and proportion of patients with ≥ 1 serious adverse events, n (%)	7 (6.4)	6 (5.3)	Not estimated
Number of CTCAE grade ≥ 3 events, n	Not available	Not available	
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events[§], n (%)	Not available	Not available	
Number of adverse reactions, n			

Number and proportion of patients with ≥ 1 adverse reactions, n (%)	Not available	Not available	
Number and proportion of patients who had a dose reduction, n (%)	Not available	Not available	
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	9 (8.3)	15 (13.2)	Not estimated
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	3 (2.8)	2 (1.8)	Not estimated

AE – adverse event; DBP – double-blind phase; SAE – serious adverse event; TRAE – treatment-related adverse event
Source: EASE CSR 2022 (Chiesi, data on file 2024)

Safety outcomes – Open-label phase

Safety outcomes were also continually evaluated for the entire course of the OLP. Overall, the OLP had a very similar AE profile as the DBP, with the reported AEs considered consistent with the expected natural progression of the disease. The rate of reported SAEs was higher in both the group treated with Filsuvez and the group treated with the control-gel in the DBP. Nine deaths occurred during the OLP, however, only two SAEs were attributed to the investigational product and none of the deaths were considered related to the study treatment (Chiesi, data on file 2024).

Of the 205 patients who received Filsuvez during the OLP, [redacted] %) reported at least one AE. Overall, the most frequently reported AEs were [redacted]; however, these conditions were deemed consistent with the natural progression of the disease. A total of [redacted] patients withdrew from the OLP due to AEs; [redacted] patients experienced treatment-related AEs (administration site pain, staphylococcal wound infection and SAE of rash [n=1 for each]) (Chiesi, data on file 2024).

Throughout the OLP, [redacted] patients ([redacted]%) experienced ≥[redacted]; with two cases attributed to the investigational product, involving one case each of rash and wound infection (Chiesi, data on file 2024).

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Table 22 Serious adverse events (During 24 months open-label phase)

Adverse events	Filsuvez, n (%) (n=205) (Kern 2023)		Comparator (Not available)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Subjects with at least one SAE	50 (24.2)	NA	NA	NA
Injury, poisoning and procedural complications	96 (46.8)	NA	NA	NA
Infections and infestations	80 (39.0)	NA	NA	NA
Gastrointestinal disorders	51 (24.9)	NA	NA	NA
Blood and lymphatic system disorders	40 (19.5)	NA	NA	NA
General disorders and administration site conditions	33 (16.1)	NA	NA	NA
Skin and subcutaneous tissue disorders	31 (15.1)	NA	NA	NA
Metabolism and nutrition disorders	25 (12.2)	NA	NA	NA
Eye disorders	17 (8.3)	NA	NA	NA
Congenital, familial and genetic disorders	8 (3.9)	NA	NA	NA
Hepatobiliary disorders	6 (2.9)	NA	NA	NA

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

The model does not consider adverse events (AEs). The safety and tolerability data from EASE demonstrate that Filsuvez is well tolerated in DEB and JEB patients with rates similar to control group, and most AEs reported were mild or moderate and associated with the EB condition rather than treatment. Consequences of adverse events were therefore not included in the health economic model.

Table 23 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Not applicable, AE not included in model				

9.2 Safety data from external literature applied in the health economic model

N/A, not included

Table 24 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
N/A, not included								

10. Documentation of health-related quality of life (HRQoL)

Health-related quality of life (HRQoL) data was collected in the EASE open-label phase (OLP) only using Instrument for Scoring Clinical Outcomes of Research for Epidermolysis Bullosa (iscorEB) (patient completed section), Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) and the EuroQol 5-domain (EQ-5D) generic preference-based measure to assess quality of life across five domains (pain, usual activities, mobility, anxiety/depression, and self-care). The iscorEB and EQ-5D patient-reported outcome (PRO) assessments/endpoints were added in Protocol Version 6.0, approximately 2.5 years after the study was initiated.

Table 25 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
Scoring Clinical Outcomes of Research for Epidermolysis Bullosa (iscorEB)	EASE	Not utilized for utility estimation
Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI)	EASE	Not utilized for utility estimation
EuroQol 5-domain (EQ-5D)	EASE	Estimate link between utility and BSAP

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

Of these measures, the EQ-5D is DMC's preferred measure of health-related quality of life in adults.

As EQ-5D was not collected throughout the EASE trial, a link between other endpoints and health utility score was needed. As described above, to assess the benefit of treatment on quality of life, the body surface area percentage (BSAP) affected outcome was deemed as the most relevant and the best endpoint to reflect the quality of life impact.

The primary endpoint of the EASE RCT focused on the rate of healing in a single target wound. A wound-level rather than patient/body-level measure is well suited to studying clinical effectiveness, as it is less sensitive than secondary study endpoints to the influence of extraneous factors such as the incidence of new wounds that occur as part of the natural history of EB. To assess cost-effectiveness modelling purposes, it is necessary to consider a broader perspective by examining outcomes at the patient level, to understand the overall effects of treatment on patient pathways, resource use, costs and quality of life.

Aside from BSAP, other clinical endpoints available from EASE that measure disease severity at a patient level were iscorEB and EBDASI, both EB-specific severity measures. Neither was collected in full across the DBP of that study, limiting their suitability as a basis for defining model health states to capture treatment effects. Total BSAP, expressed as the weighted sum of wound coverage was considered the best overall proxy for EB wound burden (and validated as a suitable proxy for disease severity by clinicians and patient groups) and was used to derive a utility gain (Chiesi data on file 2024). Although there are individual variations in utility impact depending on the body area affected, the correlation between BSAP and utility shows an average impact of BSAP on utility across different locations. Since there is no evidence that Filsuvez would change the distribution of wound location across the body, using average data on BSAP and its link to utility gives a valid estimate of what the average utility benefit in a patient group would be. Analysis also demonstrated that there was a clear link between BSAP and health utility in the open label phase on the EASE trial, and similar measurement of percentage of body impact are commonly used in other skin diseases to measure impact on quality of life (e.g. Psoriasis Area and Severity Index (PASI) score).

10.1.2 Data collection

HRQoL data in EASE was obtained using the EQ-5D-5L for adults in the EASE open-label phase (OLP), while the youth version (EQ-5D-Y), recommended for use in children aged 8-15 years, was used for child respondents aged 15 and below. Responses for patients younger than four years were proxied by the parent or carer. The EQ-5D instruments were introduced as a protocol amendment in the OLP. There were missing observations for the EQ-5D measurement and the analysis and application of the EQ-5D data is not based on changes over time for individual patients or comparison between groups, instead the EQ-5D data is matched with the BSAP measurement to derive a relationship between these. Therefore, the missing data is not believed to bias that analysis. In total, 144 EQ-5D observations/data points from the OLP were available for analysis.

Table 26 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	205 starting OLP	Not reported	205	144 EQ-5D observations in total available

10.1.3 HRQoL results

The mean utility from the trial EQ-5D data was [redacted] across the 144 observations. Details of the EQ-5D utility data and results are presented in the table below.

Table 27 EQ-5D utility results from EASE trial

Patient group /visit	Population (N)	Utility results			
		Mean	*SD*	*Min*	*Max*
All patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Males	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Females	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Double-Blind Phase - Day 60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of Double-Blind Phase - Day 90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Open-Label Follow-up Phase - Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
End of Open-Label Follow-up Phase - Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The effect of Filsuvez on quality of life was estimated using a regression analysis of the EQ-5D values from EASE OLP, regressing the body surface area percentage (BSAP) affected by chronic EB wounds, a surrogate used for disease severity (Kern 2023, Chiesi data on file 2024).

Generalised linear model (GLM) regressions were used to estimate patient utilities using the EASE 24-month EQ-5D data. Output from the GLM is shown alongside individual EQ-5D observations below.

[redacted]

Source: Chiesi data on file

Detailed result of the regression is presented in the table below. Given that the baseline utility in EASE is unknown and only the average EQ5D index score from EASE OLP is known, a calculation of the utility increase associated with treatment with Filsuvez had to be made. The relationship between BSAP and utility is not fully linear and a weighted average of the utility impact per % reduction in BSAP was therefore calculated, based on the distribution of BSAP at baseline of EASE. This led to an average utility increase per % reduction in BSAP of [redacted].

Table 28. EQ-5D index score per body surface area percentage (BSAP) affected by chronic wounds

BSAP group	EQ-5D index score from regression analysis	Calculated utility increase per % BSAP improvement**	Patient population distribution in EASE trial
≤4% (midpoint 2)	[redacted]	[redacted]	[redacted]
5-7% (midpoint 6)	[redacted]	[redacted]	[redacted]
8-10% (midpoint 9)	[redacted]	[redacted]	[redacted]
11-18% (midpoint 14.5)	[redacted]	[redacted]	[redacted]
19-24% (midpoint 21.5)	[redacted]	[redacted]	[redacted]
≥25% (midpoint 27.5 (assumed))	[redacted]	[redacted]	[redacted]

*Assumed same as from 5-7% to <4%

[redacted]

Data on reduction in BSAP from Filsuvez treatment is available from the EASE trial and the real-world study. These are illustrated in the figure below.

[redacted]*

[redacted]

*Study data adapted with linear extrapolations of point estimates reported in studies

The clinical data demonstrate that the treatment benefits are increasing over time and the short double-blind phase of the EASE trial does therefore not provide appropriate data to estimate the long-term patient benefits. Data from the long-term extension period of the trial and a real-world study are therefore used as basis for estimating the patient benefits of Filsuvez treatment. Although the extension trial phase and the real-world study did not contain a randomised comparator, the differences observed in the extension phase of the trial vs baseline are deemed to be a reliable estimate of the treatment benefits. Also, this removes the uncertain benefits of the active trial comparator arm and is therefore also more reflective of the expected benefits versus current clinical practice (where the trial comparator is not available).

In base case analysis, we apply the reduction from baseline to months 24 in EASE trial, which is [redacted] This may seem conservative in relation to the real-world data and other assumption about BSAP increase is tested as well.

A [redacted] reduction in BSAP corresponds to a utility increase of [redacted] and a [redacted] reduction in BSAP corresponds to a utility increase of [redacted], using the regression analysis described above.

Table 29 HRQoL EQ-5D summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	Compartive data not available				

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

Given that the baseline utility in EASE is unknown and only the average EQ5D index score from EASE OLP is known, a calculation of the utility increase associated with treatment with Filsuvez had to be made. An average utility increase per % reduction in BSAP of [redacted] was applied, as described above.

10.2.1.1 Mapping

To obtain utility scores, adult EQ-5D-5L domain scores collected in EASE were mapped to the EQ-5D-3L using Hernandez Alava et al. (2023) mapping algorithm (Hernandez Alava 2022). For HRQoL data collected among children and adolescents (using the EQ-5D-Y),

the adult EQ-5D-3L tariff was applied directly without a validated value set specific to the youth version. This limitation is considered the best valuation approach that could be adopted. A UK value set was used, as individual data to perform an analysis using Danish value set was not available.

10.2.2 Disutility calculation

Not applicable, disutility from adverse events were not included in model.

10.2.3 HSUV results

As described above, the health utilities for the base case analysis have been sourced from the EASE clinical trial and supported by a real-world study. In the base case analysis, all patients start with the utility of an untreated patient (0.456) based on Angelis et al. 2022 (Angelis 2022). If the patient is being treated with Filsuvez, the utility value increases to [redacted] in base case analysis over one year and to [redacted] in a scenario analysis. The health state utilities are presented below.

Table 30. Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Filsuvez (base case)	[redacted]	EQ-5D-5L	UK	
CCM only	0.456 [not available]	EQ-5D-5L	UK	

CCM: Current clinical management

Age adjustment

The model implemented age adjustment in line with the Danish DMC guidelines. The Danish general population utilities were stratified by age groups to calculate the age-dependent multipliers. The age-dependent multipliers were then used to adjust the individual's undiscounted utility levels each cycle according to their age. Table 31 table below shows the Danish general population utility values stratified by age groups and the table further belowTable 32 shows the matrix with the age-dependent multipliers used in the model. This age adjustment was used in the base case.

Table 31. Danish general population utility values stratified by age groups

Age groups	Values
0-17	1
18-29	0.871
30-39	0.848
40-49	0.834
50-69	0.818

70-79	0.813
80+	0.721

Table 32. The matrix containing the age-dependent multipliers used in the Danish setting

Age group and age-dependent multipliers	0	18	30	40	50	70	80
0	1	0.87	0.85	0.83	0.82	0.81	0.72
18		1.00	0.97	0.96	0.94	0.93	0.83
30			1.00	0.98	0.96	0.96	0.85
40				1.00	0.98	0.97	0.86
50					1.00	0.99	0.88
70						1.00	0.89
80							1.00

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

N/A, no other data than those described are used.

10.3.1 Study design

N/A, no other data than those described are used.

10.3.2 Data collection

N/A, no other data than those described are used.

10.3.3 HRQoL Results

N/A, no other data than those described are used.

10.3.4 HSUV and disutility results

N/A, no other data than those described are used.

Table 33 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A, no other data than those described are used.				

Table 34 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A, no other data than those described are used.				

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

Table 35 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Filsuvez + CCM	Applied to the wound surface at a thickness of approximately 1 mm	NA	As needed	No
CCM alone	NA	NA	As needed	No

Filsuvez treatment cost

The relevant treatment costs for Filsuvez were sourced from Medicinpriser.dk, which listed the drug available in packages of 30 tubes, each tube containing 23.4 g of gel. The price per pack (AIP) is DKK 68,298.61. Study data shows that the dose of drug used decreases over time, possibly due to the decreasing size of body wounds and that patients gets more familiar with Filsuvez use.

The assumption of drug use is based on the number of tubes used per month from the EASE trial. During the initial 3-month double-blind phase, the median use was [redacted] and mean use was [redacted] in the Filsuvez arm. Mean use was however influenced by a few patients with very high use, maximum use was [redacted] tubes per month. This may be a

consequence of the trial setting and it may be likely that patients in real-life will use the treatment differently. The median dose may therefore better reflect future dosing, but mean numbers are used in base case analysis as requested by DMC.

Information from other countries and from clinical expert expectation in Sweden indicate that is likely that patients in clinical praxis more often will share tubes across multiple dressings. This will lead to a lower number of tubes used. Therefore, a lower number of tubes than what was observed in EASE trial is more likely to represent real-world dosing. It is not possible to know with certainty before the introduction of a treatment what the real-world use would be, but for the base case analysis we reduce the number of tubes by [redacted] to reflect the real-world use ad tube sharing.

The number of tubes used was reduced over time and the median during the open-label phase was [redacted] while mean was [redacted], again influenced by some patients with very high use (maximum use during this phase was [redacted] tubes per month). The OLP tube-use was based on an average treatment duration of 20.4 months. The mean values correspond to a reduction in monthly tubes used of [redacted] tubes per month, if a linear decline is assumed. This is reasonable as the percentage of the body affected by wounds is reduced over time, and it is therefore likely that the amount of gel needed to cover the wounds also is reduced by a similar magnitude. The EASE trial and the real-world study shows that the BSAP was reduced by 54-62% over the 2-year follow-up. A reduction of [redacted] tubes per month from the initial in EASE trial would only correspond to approximately [redacted] reduction over 24 months and may therefore be conservative considering that the amount of drug use likely is related to the size of wound affected and consequently treated with the gel.

In a scenario 1 analysis, [redacted] tubes per month are applied during year 1, which is based on the mean use reported in the 3-month double-blind phase ([redacted]) combined with a reduction of [redacted] tubes per month and then reduced by [redacted] % to reflect real-word use as described above. Applying a further reduction of [redacted] tubes per month leads to an estimated [redacted] tubes used per month during year 2. No further reduction beyond two years is assumed and for year 3+, we apply a value of [redacted] tubes per month, which reflects the estimated use at the end of year 2.

In a scenario 2, we exclude the outliers with very high number of tubes used in EASE trial, as this may not reflect future clinical practice. The three patients with the highest number of tubes are excluded. This leads to new restricted means of [redacted] tubes per month during double-blind phase and [redacted] tubes per month during open-label phase. Using same approach as above, it leads to a reduction of [redacted] tubes per month.

The estimated number of tubes used in the model are presented below.

Table 36. Number of tubes used per month in analysis

Time frame	Number of tubes per month

	[redacted]	[redacted]
Year 1	[redacted]	[redacted]
Year 2	[redacted]	[redacted]
Year 3+	[redacted]	[redacted]

As described above, an annual drop-out/discontinuation rate of 8% was assumed during the first two years, based on EASE clinical trial (Kern 2023), followed by an annual 4% discontinuation.

11.2 Medicines– co-administration

N/A, no other medicines than those described

11.3 Administration costs

N/A, no administration costs beyond what is described as wound handling

Table 37 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
N/A, no administration costs beyond what is described as wound handling				

11.4 Disease management costs

Cost of dressing-related disease management

Reduced number of dressing changes

The EASE trial showed a reduction in the frequency of dressing changes for patients in the Filsuvez arm and a slight increase in dressing frequency in the control arm. Supplementary data to Kern et al. 2023 show the distribution of dressing frequency as reflected in the tables below. The average number of dressings per day was calculated assuming that "other" means 4 times per week.

Table 38. Dressing frequency with Filsuvez at baseline and day 90 of the EASE trial

Study day	Frequency of dressing change	Oleogel-S10: number of patients (n=109)	Oleogel-S10: percentage of patients	Oleogel-S10 average dressings per day

0	Daily	47	43.1%	0.700
	Every 2 days	45	41.3%	
	Every 3 days	7	6.4%	
	Every 4 days	4	3.7%	
	2 times per week	0	0.0%	
	3 times per week	0	0.0%	
	Other	6	5.5%	
90	Daily	33	32.0%	0.631
	Every 2 days	45	43.7%	
	Every 3 days	14	13.6%	
	Every 4 days	4	3.9%	
	2 times per week	0	0.0%	
	3 times per week	1	1.0%	
	Other	6	5.8%	
		Difference in no. of dressings per day		-0.068

Table 39. Dressing frequency with the control gel at baseline and day 90 of the EASE trial

Study day	Frequency of dressing change	Control gel: number of patients (n=114)	Control gel: percentage of patients (%)	Control gel average
0	Daily	52	45.6%	0.713
	Every 2 days	39	34.2%	
	Every 3 days	7	6.1%	
	Every 4 days	4	3.5%	
	2 times per week	1	0.9%	
	3 times per week	1	0.9%	
	Other	10	8.8%	
90	Daily	55	50.9%	0.730
	Every 2 days	29	26.9%	
	Every 3 days	9	8.3%	
	Every 4 days	6	5.6%	
	2 times per week	0	0.0%	
	3 times per week	2	1.9%	
	Other	7	6.5%	
		Difference in no. of dressings per day		0.017

A decrease in 0.068 dressings per day means a decrease of 0.48 dressings per week for Filsuvez, and an increase of 0.017 dressings per day means an increase of 0.12 dressings per week for the control arm. The relative difference is a decrease of 0.48 + 0.12 = 0.60 weekly dressings. In the model, 5.11 dressings per week is assumed for control arm (control gel average at Day 90 of EASE trial) and 4.51 for Filsuvez (control gel frequency – 0.60 dressings per week).

Cost of dressings changes

Direct costs of dressing changes were estimated by the use of the DRG cost of dressing of DKK 2,334 (Anlæggelse af skinne, individuelt fremstillet bandage) (Sundhedsdatastyrelsen 2024). The weekly reduction of 0.6 dressings was multiplied by the direct cost of DKK 2,334 per dressing to get an annual saving of DKK 73,000 applied in the model for the fIlsuvez arm.

As discussed above, this estimate is likely conservative as it is based on data on reduction in dressing from day 90 in the EASE trial, while data shows that the benefit of Filsuvez treatment continues to increase beyond day 90 (Kern 2023, Torres Pradilla 2024). Also, EASE clinical trial comparator included a control gel which is not available in clinical practice, but this gel included excipients which, individually, are known to have a potential beneficial effect on wound healing. Therefore, comparing with the control gel likely underestimates the benefit versus current clinical practice and available treatments.

Table 40 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Dressing	Reduction of 0.6 per week	2334	08PR01	Sundhedsdatastyrelsen DRG 2024

Cost of non-dressing-related disease management

Cost and resource use data not related to dressing changes and relevant to the decision problem and appropriate for use in the economic model were identified from the updated version of the multinational, bottom-up costing study (Angelis 2022, Angelis 2016). These are assumed to occur for all the patients in the model.

No Danish data on cost of EB was identified and the study by Angelis was deemed the most recent and relevant study and provides estimates from multiple European countries where the treatment of EB may be expected to be similar. As a validation, Landspatientregistret in Denmark report 279 hospital stays for 39 patients with epidermiolysis bullosa dystrophica between 2021 and 2023. This means 2.4 hospital stays per year per patient. The costs for these stays likely vary, there are for example DRG codes 09MA06 (Kroniske sår i huden) with cost of 59483 DKK and DRG code 09MA03 (Lettere eller moderat hudsygdom, u. kompl. Bidiag) with a cost of 21118 DKK. The cost for these 2.4 stays would with these cost lead to an annual cost between 50,000 and 142,000 DKK. This is higher than the hospital cost of EB assumed in the analysis.

The annual costs expressed in 2020 euros have been converted into current DKK, using the latest six months' average exchange rate of 7.46 (Danmarks Nationalbank 2020) and accounting for inflation between the years 2020 and 2024 (Denmark Statistics 2024).

The costs occurred for the CCM in the adult and paediatric populations are listed in tables below. Each cost category covered several sub-categories, such as drugs, tests, and healthcare visits for direct medical costs, social health services, professional and informal care for the non-direct medical cost category.

Angelis and coworkers point out that bandaging costs were not captured as part of direct medical costs. Therefore, the present analysis assumes that costs presented in that study do not include costs associated with bandaging. This approach allows for the estimation of savings associated with fewer dressings described above separately.

Table 41. Average annual costs per patient, adult patients

Cost category	Costs (2020 €)	Costs (2024 DKK)*	Source
Drugs	1151	9 918	Angelis 2022, Danmarks Nationalbank 2020, Denmark Statistics 2024
Tests	254	2 189	
Visits	2157	18 587	
Hospitals	3083	26 567	
Material	1250	10 772	
HC transport	34	293	
Social health service	1335	11 504	
Professional carer	936	8 066	
Direct medical costs	**10 200**	**87 896**	
Non-HC transport	96	827	
Main informal carer	11 450	98 667	
Other informal carer	5 200	44 809	
Direct non-medical	**16 746**	**144 304**	

*Exchange rate used of 7.46 inflation rate of 1.155

Table 42. Average annual costs per patient, paediatric patients

Cost category	Costs (2020 €)	Costs (2024 DKK)*	Source
Drugs	864	7 445	Angelis 2022, Danmarks Nationalbank 2020, Denmark Statistics 2024
Tests	139	1 198	
Visits	2777	23 930	
Hospitals	2835	24 430	
Material	864	7 445	
HC transport	105	905	
Social health service	1737	14 968	

Professional carer	71	612
Direct medical costs	**9 392**	**80 933**
Non-HC transport	153	1 318
Main informal carer	45 768	394 392
Other informal carer	14 246	122 761
Direct non-medical	**60 167**	**518 471**

* Exchange rate used of 7.46 inflation rate of 1.155

The reduction in number of dressings is also assumed to reflect a lower use of medical resources in general. The relative decrease in the number of dressings between baseline and day 90 was 0.631/0.700 ≈ 90% for Filsuvez and 0.730/0.713 ≈ 102% for the control arm (i.e., an increase in the comparator arm). This was assumed to be reflected in the use of other direct medical costs as well.

It should again be noted that these assumptions on reduction in medical resource use likely also are conservative as they are based on data from day 90 in the EASE trial. This trial and also a real-world study (Torres Pradilla 2024) show that the benefit of Filsuvez treatment continues to increase beyond day 90.

11.5 Costs associated with management of adverse events

N/A, no adverse events included

Table 43 Cost associated with management of adverse events

DRG code	Unit cost/DRG tariff
N/A, no adverse events included	

11.6 Subsequent treatment costs

N/A, no subsequent treatments included

Table 44 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
N/A, no subsequent treatments included				

11.7 Patient costs

On top of the direct costs associated with the bandage and the CCM, patient time costs derived from the time spent by caregivers and adult patients were calculated in the model.

Bruckner et al. present a survey of 156 respondents in the United States aged ≥ 18 years either with a confirmed EB diagnosis or caring for a patient with a confirmed EB diagnosis (Bruckner 2020). The survey covers the time required for whole-body wound care, including preparation and clean-up. The respondents were categorised according to type of EB (simplex, junctional, dominant dystrophic, and recessive dystrophic) and as either patients or caregivers. The table below is adapted the publication by Bruckner et al., which looks only at caregiver-reposted responses and omits EB of simplex type as this is not included in the Filsuvez indication.

Table 45. Caregiver-reported time required for dressing adapted from Bruckner et al

Time required	Junctional EB (n=7)	Dominant dystrophic EB (n=17)	Recessive dystrophic EB (n=34)	Total (n=58)
< 2 h	4	14	12	30
2 – 4 h	1	3	16	20
>4 h	2	0	6	8

When conservatively assuming that <2h is 1h, 2-4h is 2h and >4h is 4h, the weighted average time for dressing is 1.8h. For the paediatric population, an average number of two caregivers was assumed, with an average time per dressing assumed to be 1.8 hours, according to the above result.

Using a carer hourly rate of DKK 188 (DMC 2024), a total informal cost of DKK 677 per dressing change was evaluated for patients under the age of 18, corresponding to a yearly cost-saving associated with Filsuvez of DKK 21,000, which is applied in the model in the Filsuvez arm up to the age of 18 years.

Table 46 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Dressing	1.8 hours x 2 per dressing for patients < 18 years

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

N/A, no other costs than those described above included

12. Results

12.1 Base case overview

An overview of the base case is presented below.

Table 47 Base case overview

Feature	Description
Comparator	Current standard of care (CCM)
Type of model	Markov model
Time horizon	100 years (life time)
Measurement and valuation of health effects	Treatment impact on BSAP linked to utility increased, based on trial data on relationship between BSAP and utility
Costs included	Medicine costs and disease-related costs Patient costs
Dosage of medicine	Based on pivotal trial data
Inclusion of waste	Yes

12.1.1 Base case results

The base case results of the cost-effectiveness analysis are shown below. In base case scenario 1, the discounted incremental costs are [redacted] In dose scenario 2, the discounted incremental costs are [redacted]

Filsuvez is a new treatment for a severe and rare disease. There are uncertainties in long-term outcome and the transfer of clinical trial findings to real-world setting. For Filsuvez, there is a real-world study available at time of launch in Denmark, which is unusual. This study shows that the benefit seen during the first 3 months of the clinical trial, continues to build up over a longer time period. This new real-world study therefore provides

important insight to the expected costs and benefits in future real-world usage in Denmark.

Table 48. Base case results, discounted estimates

	Filsuvez	CCM	Difference
[redacted]			
Drug costs	[redacted]	[redacted]	[redacted]
Regional health care costs	[redacted]	[redacted]	[redacted]
Municipality and carer costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Benefits	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs - Patient	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER (QALY)	[redacted]	[redacted]	[redacted]
ICER (LYGs)	[redacted]	[redacted]	[redacted]
[redacted]			
Drug costs	[redacted]	[redacted]	[redacted]
Regional health care costs	[redacted]	[redacted]	[redacted]
Municipality and carer costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Benefits	[redacted]	[redacted]	[redacted]
Life years	[redacted]	[redacted]	[redacted]
QALYs - Patient	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER (QALY)	[redacted]	[redacted]	[redacted]
ICER (LYGs)	[redacted]	[redacted]	[redacted]

CCM: Current clinical management; ICER: Incremental cost-effectiveness ratio; LYG: Life-years gained; QALYs: Quality-adjusted life years.

As mentioned above, there are uncertainties about future dosing in real-world. In base case, we reduced the number of tubes used by 20% to reflect real-world use, e.g due to an increased tube sharing across wound dressings. Results of analysis not including a 20% reduction of mean number of tubes from EASE trial leads to [redacted] for scenario 1 and [redacted] in scenario 2. Analysis using median doses lead to a discounted incremental cost of [redacted].

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

One-way sensitivity analyses were performed, and the results obtained from are presented below. Results for scenario 1 are only presented, since the influence of model parameters is the same for both scenarios. The results show stable results within the ranges tested. Analysis perspective, utility gain of Filsuvez and start age were most influential of the analysis done.

Table 49 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

It may be noticed that the ICER is reduced when no mortality benefit of Filsuvez treatment is assumed. This may be considered unreasonable and is a consequence of the high disease cost and that prolonging life adds these disease costs also during the extra survival time. If no mortality benefit is assumed, the cost difference becomes [redacted] (dose scenario 1). Applying the same [redacted] QALY gained then leads to an ICER of about [redacted].

It should also be noted that that analysis without age correction may be the most reasonable analysis to use, since the mean utility at baseline assumed is based on a general/average patient population of patients at various ages. This value may therefore be seen as already age adjusted and further age-adjusting this value over time therefore gives a lower population utility than what data shows.

A selection of the one-way sensitivity analyses is plotted in a tornado diagram.

[redacted]

[redacted]

Scenario analyses

A few additional analyses were conducted as scenario analyses and are presented below. Again, only results for scenario 1 are only presented, since the influence of model parameters is the same for both scenarios. Three key assumptions were tested:

- The price of Filsuvez, to see how results are influenced by price
- The % BSAP improvement, to assess how a larger improvement as seen in the real-world study would impact results
- The reduction in number of dressings, to reflect a potential increasing benefit beyond day 90.

The results shows that Filsuves price, as expected, has a large influence on results The % BSAP improvement and reduction in dressings also have a fairly large impact on the results and it may be argued that the base case analysis applied conservative assumptions for the variable, in light of the EASE trial open-label phase and the real-world study (Kern 2023, Torres Pradilla 2024).

Table 50. Result of scenario analyses

Parameter	Value	Incremental cost (DKK)	Incremental QALYs	ICER (DKK/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

12.2.2 Probabilistic sensitivity analyses

A probabilistic sensitivity analysis (PSA) analysis was performed to explore joint parameter uncertainty by defining a selection variables as stochastic variables with probability distributions. Again, only results for scenario 1 are only presented, since the influence of model parameters is the same for both scenarios

The figures below show a scatter plot of the result from 1,000 iterations, a cost-effectiveness acceptability curve (CEAC) and a convergence plot of the ICER. The PSA analysis, based on assumed parameter distributions, shows a scatter plot with most iterations close to the base case mean value. The CEAC shows about [redacted] probability

of being cost-effective at willingness to pay of 2 MDKK. The convergence plot shows that results are stable already at 100 iterations and 1,000 iterations therefore is sufficient for the analysis.

The PSA is based on uncertain parameter distribution as there is a lack of data on the probability distributions. This is not uncommon with rare diseases because there often is a paucity of data available. A selection of the key variables with uncertainty that influence the results were included in the PSA. Since data on probability distributions were missing, assumptions about the distributions were applied. Details of the assumed distributions are presented in Appendix G. Normal distributions were selected for all variables except those which are expected to be within the range 0-1, where beta distributions were used.

[redacted]

[redacted]

[redacted]

13. Budget impact analysis

It estimated that there currently may be 50 patients in Denmark with DEB and JEB eligible for treatment, with about 2 newly diagnosed patients per year. The uptake of Filsuvez is expected to be distributed over a few years and the number of new patients expected to be treated with Filsuvez is presented in the table below. The number of new patients per year is therefore not two patients per year, as it is expected that part of the prevalent pool of about 50 patients will start Filsuvez-treatment over the first few years. The number of "new" patients in the table below and the budget impact analyses therefore reflect the number of existing patients that may be candidates for starting Filsuvez treatment.

Total budget impact at year 5 is estimated at about [redacted]. The analysis is based on dosing scenario 1, as this leads to higher and most conservative budget impact estimate.

Number of patients (including assumptions of market share)

Table 51 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Filsuvez + CCM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CCM alone	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Filsuvez + CCM	0	0	0	0	0
CCM alone	20	20	10	5	2

Budget impact

Table 52 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

Clinical expert consulted:

15. References

Angelis, A., et al., *Social/economic costs and health-related quality of life in patients with epidermolysis bullosa in Europe.* Eur J Health Econ, 2016. **17 Suppl 1**: p. 31-42.

Angelis, A., Mellerio, J.E. and Kanavos, P. (2022) 'Understanding the socioeconomic costs of dystrophic epidermolysis bullosa in Europe: a costing and health-related quality of life study', Orphanet Journal of Rare Diseases, 17, p. 346. Available at: https://doi.org/10.1186/s13023-022-02419-1.

Bardhan, A. et al. (2020) 'Epidermolysis bullosa', Nature Reviews Disease Primers, 6(1), pp. 1–27. Available at: https://doi.org/10.1038/s41572-020-0210-0.

Bruckner, A.L. et al. (2020) 'The challenges of living with and managing epidermolysis bullosa: insights from patients and caregivers', Orphanet Journal of Rare Diseases, 15(1), p. 1. Available at: https://doi.org/10.1186/s13023-019-1279-y.

Chiesi, Data on file, 2024.

Cianfarani, F. et al. (2017) 'Pathomechanisms of Altered Wound Healing in Recessive Dystrophic Epidermolysis Bullosa', The American Journal of Pathology, 187(7), pp. 1445–1453. Available at: https://doi.org/10.1016/j.ajpath.2017.03.003.

Condorelli, A.G. et al. (2019) 'Epidermolysis Bullosa-Associated Squamous Cell Carcinoma: From Pathogenesis to Therapeutic Perspectives', International Journal of Molecular Sciences, 20(22), p. 5707. Available at: https://doi.org/10.3390/ijms20225707.

Danmarks Nationalbank, *Exchange rate EUR to DKK*. 2024.

DEBRA International (2020a) What is EB?, DEBRA International. Available at: https://www.debra-international.org/what-is-eb (Accessed: 21 March 2024).

Denmark Statistics, Consumer price index. 2024.

Denmark Statistics, *HISB8: Life table (2 years tables) by sex, age and life table*. 2024.

Denyer, J., Pillay, E. and Clapham, J. (2017) 'Best practice guidelines for skin and wound care in epidermolysis bullosa. An international consensus.' Wounds International. https://woundsinternational.com/best-practice-statements/best-practice-guidelines-skin-and-wound-care-in-epidermolysis-bullosa/

DMC The Danish Medicines Council methods guide for assessing new pharmaceuticals, 2024

El Hachem, M. et al. (2014) 'Multicentre consensus recommendations for skin care in inherited epidermolysis bullosa', Orphanet Journal of Rare Diseases, 9, p. 76. Available at: https://doi.org/10.1186/1750-1172-9-76.

EMA Filsuvez Gel - Summary of Product Characteristics (SmPC)..

Eng, V.A. et al. (2021) 'Patient-reported outcomes and quality of life in recessive dystrophic epidermolysis bullosa: A global cross-sectional survey', Journal of the

American Academy of Dermatology, 85(5), pp. 1161–1167. Available at: https://doi.org/10.1016/j.jaad.2020.03.028.

Fine JD, Johnson LB, Weiner M, Suchindran C. Assessment of mobility, activities and pain in different subtypes of epidermolysis bullosa. Clin Exp Dermatol. 2004 Mar;29(2):122-7. doi: 10.1111/j.1365-2230.2004.01428.x. PMID: 14987264.

Fine JD, Johnson LB, Weiner M, Suchindran C. Cause-specific risks of childhood death in inherited epidermolysis bullosa. J Pediatr. 2008 Feb;152(2):276-80. doi: 10.1016/j.jpeds.2007.06.039. Epub 2007 Oct 22. PMID: 18206702.

Fine, J.-D. (2010) 'Inherited epidermolysis bullosa', Orphanet Journal of Rare Diseases, 5(1), p. 12. Available at: https://doi.org/10.1186/1750-1172-5-12.

Goldschneider, K.R. et al. (2014) 'Pain care for patients with epidermolysis bullosa: best care practice guidelines', BMC medicine, 12, p. 178. Available at: https://doi.org/10.1186/s12916-014-0178-2.

Has C, Bauer JW, Bodemer C, Bolling MC, Bruckner-Tuderman L, Diem A, Fine JD, Heagerty A, Hovnanian A, Marinkovich MP, Martinez AE, McGrath JA, Moss C, Murrell DF, Palisson F, Schwieger-Briel A, Sprecher E, Tamai K, Uitto J, Woodley DT, Zambruno G, Mellerio JE. Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. Br J Dermatol. 2020 Oct;183(4):614-627.

Haybittle, J.L., *The use of the Gompertz function to relate changes in life expectancy to the standardized mortality ratio.* Int J Epidemiol, 1998. **27**(5): p. 885-9.

Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results from a UK Population Study. Pharmacoeconomics. 2023 Feb;41(2):199-207. doi: 10.1007/s40273-022-01218-7. Epub 2022 Nov 30. PMID: 36449173; PMCID: PMC9883358.

Jain, S.V. et al. (2017) 'The Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI): grading disease severity and assessing responsiveness to clinical change in epidermolysis bullosa', Journal of the European Academy of Dermatology and Venereology, 31(4), pp. 692–698. Available at: https://doi.org/10.1111/jdv.13953.

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.5 (updated August 2024). Cochrane, 2024. Available from www.training.cochrane.org/handbook.

Kern, J.S. et al. (2019) 'Oleogel-S10 Phase 3 study "EASE" for epidermolysis bullosa: study design and rationale', Trials, 20, p. 350. Available at: https://doi.org/10.1186/s13063-019-3362-z.

Kern, J.S. et al. (2023) 'Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: results from the phase III randomized double-blind phase of the EASE study', The British Journal of Dermatology, 188(1), pp. 12–21. Available at: https://doi.org/10.1093/bjd/ljac001.

Kristensen MH, Schmidt SAJ, Kibsgaard L, Mogensen M, Sommerlund M, Koppelhus U. Validity of first-time diagnoses of congenital epidermolysis bullosa in the Danish National Patient Registry and the Danish Pathology Registry. Clin Epidemiol. 2019 Jan 17;11:115-124. doi: 10.2147/CLEP.S184742. PMID: 30697082; PMCID: PMC6340365.

Maseda Pedrero, R., et al., *Epidermolysis Bullosa in Spain: Observational Study of a Cohort of Patients Treated in a National Referral Center.* Actas Dermosifiliogr (Engl Ed), 2021.

Mellerio, J.E. et al. (2023) 'Mapping the burden of severe forms of epidermolysis bullosa - Implications for patient management', JAAD international, 11, pp. 224–232. Available at: https://doi.org/10.1016/j.jdin.2023.02.016.

Molinier L, Bauvin E, Combescure C, et al. Methodological Considerations in Cost of Prostate Cancer Studies: A Systematic Review. Value in Health. 2008/09/01 2008;11(5):878-885. doi:https://doi.org/10.1111/j.1524-4733.2008.00327.x.

Morgan, G., Back, E. and Doug, R. (ISPOR EU 2022, to be published) 'Utility Elicitation in Epidermolysis Bullosa: Cross-Sectional Survey (HCD Economics)'. data on file.

Petrof, G., et al., *The epidemiology of epidermolysis bullosa in England and Wales: data from the national epidermolysis bullosa database.* Br J Dermatol, 2022. **186**(5): p. 843-848.

Picot J, Copley V, Colquitt JL, Kalita N, Hartwell D, Bryant J. The INTRABEAM(R) Photon Radiotherapy System for the adjuvant treatment of early breast cancer: a systematic review and economic evaluation. Health technology assessment (Winchester, England). Aug 2015;19(69):1-190. doi:10.3310/hta19690.

Reed, C. et al. (2017) 'How useful is the EQ-5D in assessing the impact of caring for people with Alzheimer's disease?', Health and Quality of Life Outcomes, 15, p. 16. Available at: https://doi.org/10.1186/s12955-017-0591-2.

Schwieger-Briel, A. et al. (2015) 'Instrument for scoring clinical outcome of research for epidermolysis bullosa: a consensus-generated clinical research tool', Pediatric Dermatology, 32(1), pp. 41–52. Available at: https://doi.org/10.1111/pde.12317.

Schwieger-Briel, A. et al. (2019) 'Mechanism of Oleogel-S10: A triterpene preparation for the treatment of epidermolysis bullosa', Dermatologic Therapy, 32(4), p. e12983. Available at: https://doi.org/10.1111/dth.12983.

Simon, N.J., et al., *Health utilities and parental quality of life effects for three rare conditions tested in newborns.* J Patient Rep Outcomes, 2019. **3**(1): p. 4.

Soro, L., C. Bartus, and S. Purcell, *Recessive dystrophic epidermolysis bullosa: a review of disease pathogenesis and update on future therapies.* J Clin Aesthet Dermatol, 2015. **8**(5): p. 41-6.

Sundhedsdatastyrelsen. DRG-takster 2024. Available from: https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2024.

Tang, J.Y. et al. (2021) 'A systematic literature review of the disease burden in patients with recessive dystrophic epidermolysis bullosa', Orphanet Journal of Rare Diseases, 16(1), p. 175. Available at: https://doi.org/10.1186/s13023-021-01811-7.

Torres Pradilla M, Álvarez E, Novoa M, Lozano I, Trujillo M. Oleogel-S10 in Dystrophic Epidermolysis Bullosa: A Case Series Evaluating the Impact on Wound Burden Over Two Years. Adv Ther. 2024 Feb;41(2):867-877. doi: 10.1007/s12325-023-02749-x. Epub 2024 Jan 3. PMID: 38170434; PMCID: PMC10838820.

Vahidnezhad, H. et al. (2019) ‘Phenotypic Spectrum of Epidermolysis Bullosa: The Paradigm of Syndromic versus Non-Syndromic Skin Fragility Disorders’, The Journal of Investigative Dermatology, 139(3), pp. 522–527. Available at: https://doi.org/10.1016/j.jid.2018.10.017.

von Bischhoffshausen, S. et al. (2017) ‘Recessive dystrophic epidermolysis bullosa results in painful small fibre neuropathy’, Brain, 140(5), pp. 1238–1251. Available at: https://doi.org/10.1093/brain/awx069.

Appendix A. Main characteristics of studies included

Table 53 Main characteristic of studies included, EASE

Trial name: EASE	NCT number: 03068780
Objective	EASE was a double-blind, randomized, vehicle-controlled, phase III study to determine the efficacy and safety of the topical gel Oleogel-S10 (birch triterpenes) in EB.
Publications – title, author, journal, year	Kern JS, Sprecher E, Fernandez MF, Schauer F, Bodemer C, Cunningham T, Löwe S, Davis C, Sumeray M, Bruckner AL, Murrell DF; EASE investigators. Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: results from the phase III randomized double-blind phase of the EASE study. Br J Dermatol. 2023 Jan 23;188(1):12-21. doi: 10.1093/bjd/ljac001. PMID: 36689495. Kern JS, Schwieger-Briel A, Löwe S, Sumeray M, Davis C, Martinez AE. Oleogel-S10 Phase 3 study "EASE" for epidermolysis bullosa: study design and rationale. Trials. 2019 Jun 11;20(1):350. doi: 10.1186/s13063-019-3362-z. PMID: 31186047; PMCID: PMC6560757.
Study type and design	Double-blind, randomized, vehicle-controlled, phase III study. patients were randomized 1:1 to Oleogel-S10 or control gel using a blind-maintained numerical assignation system, with stratification for EB subtypes and according to the size of the selected target partial thickness wound (PTW)
Sample size (n)	223
Main inclusion criteria	• Male and female patients with the following subtypes of inherited EB: junctional EB (JEB), dystrophic EB (DEB), and Kindler EB aged ≥21 days • Patients with an EB target wound (i.e., EB partial thickness wound of 10 cm^2 to 50 cm^2 in size aged ≥21 days and <9 months) • Patient and/or his/her legal representative has/have been informed, has/have read and understood the patient information/informed consent form, and has/have given written informed consent • Patient and/or his/her legal representative must be able and willing to follow study procedures and instructions
Main exclusion criteria	• Patient has EB simplex • EB target wound that is ≥9 months old or has clinical signs of local infection

Trial name: EASE	NCT number: 03068780

- Use of systemic antibiotics for wound-related infections within 7 days prior to enrolment
- Administration of systemic or topical steroids (except for inhaled, ophthalmic or topical applications, such as budesonide suspension for oesophageal strictures [e.g., Pulmicort respules 0.25 mg/2 mL or 0.5 mg/2 mL]) within 30 days before enrolment
- Immunosuppressive therapy or cytotoxic chemotherapy within 60 days prior to enrolment
- Patient has undergone stem cell transplant or gene therapy for the treatment of inherited EB
- Current and/or former malignancy including basal cell carcinomas and squamous cell carcinomas
- Enrolment in any interventional study or treated with any investigational drug for any disease within 4 weeks prior to study entry
- Factors present in the patient and/or his/her legal representative that could interfere with study compliance such as inability to attend scheduled study visits or compliance with home dressing changes
- Pregnant or nursing women and women of childbearing potential including postmenarchal female adolescents not willing to use an effective form of birth control with failure rates <1% per year (e.g., implant, injectable, combined oral contraceptive, intrauterine contraceptive device, sexual abstinence, vasectomised partner) during participation in the study (and at least 3 months thereafter)
- Patient is a member of the investigational team or his/her immediate family
- Patient lives in the same household as a study participant

Intervention	Drug: Oleogel-S10 (10% birch bark extract in 90% sunflower oil. Oleogel-S10 gel or corresponding placebo will be administered topically to all wound areas on the body in a layer of approximately 1-mm thickness and will be covered with a non-adhesive wound dressing.
Comparator(s)	Control Gel
Follow-up time	Double-blind study phase of 90 days, open-lable phase 24 months
Is the study used in the health economic model?	Yes

Trial name: EASE	NCT number: 03068780
Primary, secondary and exploratory endpoints	**DBP** Primary: • Proportion of patients with first complete target wound closure within 45±7 days determined by clinical assessment. Wound closure was defined as skin re-epithelisation without drainage and was confirmed by a second observation after 7±2 days. Secondary: • Time to first wound closure up to 90±7 days of treatment • Incidence of first complete wound closure of EB target wound within 90 (±7) days • Incidence of wound infection within 90 (±7) days • Maximum severity of wound infection between baseline and 90 (±7) days • Change from baseline in total body wound burden as measured through (EBDASI, Section I: Skin, Activity (not Damage), only) Other secondary endpoints included: • Change from baseline in TBWB through BSAP Change from baseline in weekly dressing changes (post-hoc analysis) **OLP** Primary: • N/A, no primary endpoint defined Secondary: • Incidence of Target Wound Infection in the OLP • Maximum Severity of Wound Infection in the OLP (between baseline and Month-24) • Change from baseline in Total Body Wound Burden in the OLP (EBDASI, Section I: Skin, Activity (not Damage), only; Months 3, 12, 24) • Change from baseline in BSAP affected by partial-thickness wounds by Visit (Months 3, 12, 24) • Change from baseline in patients' quality of life as assessed by the EQ-5D (Months 12, 24) **Endpoints included in this application:** [E.g.: The primary endpoint was progression-free survival as assessed by the investigator, according to RECIST version 1.1. Secondary endpoints were overall survival, confirmed objective response

Trial name: EASE	NCT number: 03068780
	according to RECIST version 1.1, response duration, progression-free survival assessed by an independent review facility, health-related quality of life (HRQoL) as assessed by QLQ-C30, and safety. **Other endpoints:** NA
Method of analysis	Statistical analysis of the primary efficacy endpoint was conducted on the full analysis set using a Cochran–Mantel– Haenszel (CMH) test, stratified by EB subtype and target wound size class.
Subgroup analyses	RDEB, DDEB, JEB
Other relevant information	

Table 54 Main characteristic of studies included, Torres Pradilla 2024

Trial name: NA	NCT number: NA
Objective	To explore real-world clinical outcomes of Oleogel-S10
Publications – title, author, journal, year	Torres Pradilla M, Álvarez E, Novoa M, Lozano I, Trujillo M. Oleogel-S10 in Dystrophic Epidermolysis Bullosa: A Case Series Evaluating the Impact on Wound Burden Over Two Years. Adv Ther. 2024 Feb;41(2):867-877. doi: 10.1007/s12325-023-02749-x. Epub 2024 Jan 3. PMID: 38170434; PMCID: PMC10838820.
Study type and design	Observational retrospective medical records review study
Sample size (n)	13
Main inclusion criteria	• Patients with EB treated with Oleogel-S10 through an early access programme in Colombia
Main exclusion criteria	• N/A. no exclusion criteria applied
Intervention	Oleogel-S10 (10% birch bark extract in 90% sunflower oil.
Comparator(s)	Baseline
Follow-up time	24 months

Trial name: NA	NCT number: NA
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Body surface area percentage (BSAP) and the skin component of EB disease and activity and scoring index (EBDASI)
Method of analysis	Qualitative variables were described as absolute and relative frequencies, while quantitative variables were expressed through measures of central tendency
Subgroup analyses	N/A, no subgroups assessed
Other relevant information	

Appendix B. Efficacy results per study

Results per study

Table 55 Results per study, EASE

Results of EASE, NCT03068780											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Primary endpoint: Proportion of patients with first complete closure of EB target wound by day 45	Oleogel-S10	109	41.3%	N/A, not reported	N/A, not reported	N/A, not reported	RR 1.44	1.01-2.05	0.013	Statistical analysis of the primary efficacy endpoint was conducted on the full analysis set using a Cochran–Mantel–Haenszel (CMH) test	Kern 2023
	Control	114	28.9%								
	Baseline	223	12.1-12.2%	[redacted]						Descriptive statistics	

Results of EASE, NCT03068780												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Enpoint used in economic analysis: Total body surface area (BSAP) at end of open-label follow-up	End of follow-up		[redacted] %		N/A, not reported	N/A, not reported	N/A, not reported	N/A, not reported	N/A, not reported		Kern 2023, Chiesi, data on file 2022

Table 56 Results per study, Torres Pradilla 2024

Results of Torres Pradilla 2024											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Body surface area percentage (BSAP)	Oleogel-S10	13	10.4%	-16.9%	N/A, not reported	N/A, not reported	N/A, not reported	N/A, not reported	N/A, not reported	Descriptiv statistics	Pradilla 2024
	Baseline	13	27.3%								

Appendix C. Comparative analysis of efficacy

N/A, not comparative analyses done

Table 57 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		

N/A, not comparative analyses done

Appendix D. Extrapolation

N/A, no extrapolation analysis done

D.1 Extrapolation of [effect measure 1]

N/A, no extrapolation analysis done

D.1.1 Data input

N/A, no extrapolation analysis done

D.1.2 Model

N/A, no extrapolation analysis done

D.1.3 Proportional hazards

N/A, no extrapolation analysis done

D.1.4 Evaluation of statistical fit (AIC and BIC)

D.1.5 N/A, no extrapolation analysis doneEvaluation of visual fit

D.1.6 Evaluation of hazard functions

N/A, no extrapolation analysis done

D.1.7 Validation and discussion of extrapolated curves

N/A, no extrapolation analysis done

D.1.8 Adjustment of background mortality

N/A, no extrapolation analysis done

D.1.9 Adjustment for treatment switching/cross-over

N/A, no extrapolation analysis done

D.1.10 Waning effect

N/A, no extrapolation analysis done

D.1.11 Cure-point

N/A, no extrapolation analysis done

Appendix E. Serious adverse events

[redacted]

Appendix F. Health-related quality of life

N/A, no specific domains or similar from the quality of life assessment to be highlighted besides what is reported above

Appendix G. Probabilistic sensitivity analyses

The table below shows the data/assumptions used in the probabilistic analysis.

Table 58. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Expected mean survival (EB patients)	[redacted]	[redacted]	[redacted]	Normal
Annual mortality reduction - Patients treated with filsuvez	[redacted]	[redacted]	[redacted]	Normal
Carers hourly rate (DKK)	[redacted]	[redacted]	[redacted]	Normal
Utility gain (Filsuvez)	[redacted]	[redacted]	[redacted]	Beta
Annual drop out - Year 1	[redacted]	[redacted]	[redacted]	Beta
Annual drop out - Year 2	[redacted]	[redacted]	[redacted]	Beta
Annual drop out - Year 3+	[redacted]	[redacted]	[redacted]	Beta
Number of tubes per month - Year 1	[redacted]	[redacted]	[redacted]	Normal
Number of tubes per month - Year 2	[redacted]	[redacted]	[redacted]	Normal
Filsuvez - Relative decrease in the number of dressings between baseline and day 90	[redacted]	[redacted]	[redacted]	Beta
BSC - Relative increase in the number of dressings between baseline and day 90	[redacted]	[redacted]	[redacted]	Normal

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

This review aimed to identify evidence relating to the efficacy, safety, and tolerability of Filsuvez gel (birch bark extract [previously Oleogel-S10 (birch triterpenes) during development]) and established clinical management, for the treatment of partial thickness wounds associated with dystrophic epidermolysis bullosa (DEB) and junctional epidermolysis bullosa (JEB). DEB and JEB are severe forms of EB, a group of birth-onset, genetic, skin fragility disorders characterised by blistering, wounds and erosion of the skin as a result of minor trauma. Filsuvez gel (birch bark extract) has marketing authorisation in Great Britain and the European Union for the treatment of partial thickness wounds associated with DEB and JEB, in patients 6 months and older.

Searches were originally conducted on the 7th - 8th of June 2022 and were updated firstly on the 11th - 12th of September 2023, and secondly on the 30th of April - 1st of May 2024. Overall, 5,024 records were identified across the three searches. Following deduplication, 2,658 were primary screened with 423 taken forward to secondary screening. Thirty-five records were included at secondary screening, plus nine additional records identified from other sources, totalling 44 records eligible for inclusion. These were representative of one interventional trial (the phase III EASE trial of Filsuvez gel (birch bark extract) *versus* a control gel), plus two systematic reviews and one guidelines record, which were included for reference checking.

The pivotal phase III EASE trial represents the largest global phase III trial conducted in participants with EB, to date. EASE has a two-phase study design comprising of a 90-day randomised, placebo-controlled, DBP, followed by a 24 months single-arm open-label phase (OLP). EASE provides direct head-to-head evidence of the safety and efficacy of Filsuvez gel (birch bark extract) compared to a control gel arm, which is considered as a proxy for established clinical management in the absence of any other trial evidence of key wound healing endpoints in DEB and JEB patients.

In summary, this review identified evidence of the efficacy, safety, and tolerability of Filsuvez gel (birch bark extract) from the EASE randomised controlled trial (RCT), which also represented the only trial evidence of an intervention arm that could be considered as proxy for established clinical management. As the first licensed intervention for the treatment of partial thickness wounds associated with DEB (DDEB and RDEB), and JEB, Filsuvez gel (birch bark extract) has the potential to redefine wound care in a small population of patients with high unmet need associated with a debilitating wound burden which significantly compromises HRQL for both patients and their carers.

Table 59 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Ovid interface	No limit	30 April – 1 May 2024
Medline	Ovid interface - MEDALL	No limit	30 April – 1 May 2024
Cochrane CENTRAL and database of systematic reviews	Tolley Health Economics Ltd	No limit	30 April – 1 May 2024
AMED	Ovid interface	No limit	30 April – 1 May 2024
CINAHL	EBSCO host	No limit	30 April – 1 May 2024
The international HTA database	https://database.inahta.org/	No limit	30 April – 1 May 2024
The CRD HTA database	https://www.crd.york.ac.uk/CRDWeb/HomePage.asp	No limit	30 April – 1 May 2024
PubMed	limited to e-publications	No limit	30 April – 1 May 2024
Science Citation Index Expanded (SCI-EXPANDED)	Web of Science interface, Clarivate Analytics	No limit	30 April – 1 May 2024
The Retraction Watch Database	http://retractiondatabase.org/RetractionSearch.aspx	No limit	30 April – 1 May 2024

Abbreviations:

Table 60 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Ct.gov	https://www.clinicaltrials.gov/ct2/results/refine?show_xprt=Y	("epidermolysis bullosa" OR "dystrophic bullosa" OR "junctional bullosa" OR "butterfly skin" OR (partial AND thickness AND wounds))	30 April – 1 May 2024
ICTRP	https://trialsearch.who.int/Default.aspx	("epidermolysis bullosa" OR "dystrophic bullosa" OR "junctional bullosa" OR "butterfly skin" OR (partial AND thickness AND wounds))	30 April – 1 May 2024
EUCTR	https://www.clinicaltrialsregister.eu/ctr-search/search	("epidermolysis bullosa" OR "dystrophic bullosa" OR "junctional bullosa" OR "butterfly skin" OR (partial AND thickness AND wounds))	30 April – 1 May 2024

Abbreviations:

Table 61 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
EBClinNET: 2020 Global Congress in Epidermolysis Bullosa (EB2020);	Conference proceedings	Manual search	Manual search	30 April – 1 May 2024
Society for Investigative Dermatology (SID);	Conference proceedings e	Manual search	Manual search	30 April – 1 May 2024
British Association of Dermatologists (BAD);	Conference proceedings	Manual search	Manual search le	30 April – 1 May 2024
European Society for Pediatric Dermatology (ESPD);	Conference proceedings	Manual search	Manual search	30 April – 1 May 2024

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
World Congress on Rare Skin Diseases (WCRSD).	Conference proceedings	Manual search	Manual search	30 April – 1 May 2024

H.1.1 Search strategies

Table 62 of search strategy table for Medline

No	Query	Results
1	Epidermolysis Bullosa/	3112
2	((epidermolysis or dystrophic or junctional) adj5 bullosa*).ti,ab,ot,kf,kw.	6410
3	((EB or DEB or DDEB or RDEB or JEB or "RDEB-GI" or "RDEB-I" or "RDEB-GS" or "RDEB-S" or "JEB-GI" or "JEB-GS") and (wound* or thick* or skin* or bullosa*)).ti,ab,kw,kf,ot.	2486
4	"butterfly skin".ti,ab,kw,kf,ot.	1
5	(partial* adj3 thick* adj3 wound*).ti,ab,ot,kf.	653
6	1 or 2 or 3 or 4 or 5	8331
7	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	707894
8	Randomized Controlled Trial/	612147
9	exp Randomized Controlled Trials as Topic/	173486
10	"Randomized Controlled Trial (topic)"/	0
11	Controlled Clinical Trial/	95536
12	exp Controlled Clinical Trials as Topic/	179279

13	"Controlled Clinical Trial (topic)"/	0
14	Randomization/	107125
15	Random Allocation/	107125
16	Double-Blind Method/	178244
17	Double Blind Procedure/	0
18	Double-Blind Studies/	178244
19	Single-Blind Method/	33428
20	Single Blind Procedure/	0
21	Single-Blind Studies/	33428
22	Placebos/	35941
23	Placebo/	0
24	Control Groups/	2132
25	Control Group/	2132
26	(random* or sham or placebo*).ti,ab,hw,kf,kw.	1903245
27	((singl* or doubl*) adj (blind* or dumm* or mask* or arm or arms)).ti,ab,hw,kf,kw.	290081
28	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	1813
29	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	1294671
30	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	57813

31	allocated.ti,ab,hw.	88820
32	((open label or open-label) adj5 (study or studies or trial* or extension)).ti,ab,hw,kf,kw.	48472
33	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	13322
34	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	652
35	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	8404
36	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	13676
37	("Phase 3*" or "phase3*" or "phase III*" or P3* or "PIII*" or "Phase 2*" or "phase2*" or "phase II*" or P2* or "PII*" or "Phase 1-2" or "Phase 2-3").ti,ab,kw,kf.	408398
38	(trial or trail).ti,ab,kw,kf.	835772
39	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38	3312170
40	6 and 39	619
41	(2023* or 2024*).dt,dp,ed,ep,yr.	2348784
42	40 and 41	63

Table 63 of search strategy table for Embase

No	Query	Results
1	exp *Epidermolysis Bullosa/	6600

2	((epidermolysis or dystrophic or junctional) adj5 bullosa*).ti,ab,ot,kf,kw.	8654
3	((EB or DEB or DDEB or RDEB or JEB or "RDEB-GI" or "RDEB-I" or "RDEB-GS" or "RDEB-S" or "JEB-GI" or "JEB-GS") and (wound* or thick* or skin* or bullosa*)).ti,ab,kw,kf,ot.	4144
4	"butterfly skin".ti,ab,kw,kf,ot.	3
5	(partial* adj3 thick* adj3 wound*).ti,ab,ot,kf.	852
6	1 or 2 or 3 or 4 or 5	10876
7	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	0
8	Randomized Controlled Trial/	818975
9	exp Randomized Controlled Trials as Topic/	273132
10	"Randomized Controlled Trial (topic)"/	273005
11	Controlled Clinical Trial/	473299
12	exp Controlled Clinical Trials as Topic/	282529
13	"Controlled Clinical Trial (topic)"/	13469
14	Randomization/	99217
15	Random Allocation/	94033
16	Double-Blind Method/	193411
17	Double Blind Procedure/	218371
18	Double-Blind Studies/	175830

19	Single-Blind Method/	52425
20	Single Blind Procedure/	54491
21	Single-Blind Studies/	54491
22	Placebos/	355196
23	Placebo/	412073
24	Control Groups/	110770
25	Control Group/	110770
26	(random* or sham or placebo*).ti,ab,hw,kf,kw.	2662812
27	((singl* or doubl*) adj (blind* or dumm* or mask* or arm or arms)).ti,ab,hw,kf,kw.	405010
28	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	2353
29	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	1802115
30	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	73568
31	allocated.ti,ab,hw.	114521
32	((open label or open-label) adj5 (study or studies or trial* or extension)).ti,ab,hw,kf,kw.	94117
33	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	19753
34	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	1006
35	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	9437

36	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	21356
37	("Phase 3*" or "phase3*" or "phase III*" or P3* or "PIII*" or "Phase 2*" or "phase2*" or "phase II*" or P2* or "PII*" or "Phase 1-2" or "Phase 2-3").ti,ab,kw,kf.	642517
38	(trial or trail).ti,ab,kw,kf.	1218798
39	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38	4729158
40	6 and 39	1068
41	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.	5904020
42	40 not 41	671
43	(2023* or 2024*).yr.	2463136
44	42 and 43	58

Table 64 of search strategy table for Central

No	Query	Results
1	MeSH descriptor: [Epidermolysis Bullosa] explode all trees	86
2	((epidermolysis or dystrophic or junctional) NEAR/5 bullosa*):ti,ab,kw	218
3	((EB or DEB or DDEB or RDEB or JEB or "RDEB-GI" or "RDEB-I" or "RDEB-GS" or "RDEB-S" or "JEB-GI" or "JEB-GS") and (wound* or thick* or skin* or bullosa*)):ti,ab,kw	194

4	"butterfly skin":ti,ab,kw	0
5	partial* and thick* and wound*):ti,ab,kw	534
6	#1 or #2 or #3 or #4 or #5	799

Table 65 of search strategy table for Amed

No	Query	Results
1	((epidermolysis or dystrophic or junctional) adj5 bullosa*).ti,ab.	10
2	((EB or DEB or DDEB or RDEB or JEB or "RDEB-GI" or "RDEB-I" or "RDEB-GS" or "RDEB-S" or "JEB-GI" or "JEB-GS") and (wound* or thick* or skin* or bullosa*)).ti,ab.	7
3	"butterfly skin".ti,ab.	0
4	(partial* adj3 thick* adj3 wound*).ti,ab.	6
5	1 or 2 or 3 or 4	20
6	(2023* or 2024*).yr.	1314
7	5 and 6	0

Table 66 of search strategy table for CINAHL

No	Query	Limiters/Expanders	Results
S10	S5 AND S8	Limiters - Published Date: 20220101-20231231 Search modes - Boolean/Phrase	5
S9	S5 AND S8	Search modes - Boolean/Phrase	5
S8	S6 OR S7	Search modes - Boolean/Phrase	1,252, 623

S7	TI (((single N3 arm) or (open N3 Label N3 exten*))) OR AB (((single N3 arm) or (open N3 Label N3 exten*)))	Search modes - Boolean/Phrase	6,671
S6	(((MH "Experimental Studies+") OR (MH "Multicenter Studies") OR (MH "Random Sample+") OR (MH "Placebos") OR (MH "Control (Research)+") OR (MH "Crossover Design") OR ((TI random* OR AB random*) OR (TI sham OR AB sham) OR (TI placebo* OR AB placebo*)) OR (((TI singl* OR AB singl*) OR (TI doubl* OR AB doubl*)) W1 ((TI blind* OR AB blind*) OR (TI dumm* OR AB dumm*) OR (TI mask* OR AB mask*))) OR (((TI tripl* OR AB tripl*) OR (TI trebl* OR AB trebl*)) W1 ((TI blind* OR AB blind*) OR (TI dumm* OR AB dumm*) OR (TI mask* OR AB mask*))) OR ((TI control* OR AB control*) N3 ((TI study OR AB study) OR (TI studies OR AB studies) OR (TI trial* OR AB trial*) OR (TI group* OR AB group*))) OR ((TI clinical OR AB clinical) N3 ((TI study OR AB study) OR (TI studies OR AB studies) OR (TI trial* OR AB trial*))) OR ((TI Nonrandom* OR AB Nonrandom*) OR (TI "non random*" OR AB "non random*") OR (TI "non-random*" OR AB "non-random*") OR (TI "quasi-random*" OR AB "quasi-random*") OR (TI quasirandom* OR AB quasirandom*)) OR ((TI phase OR AB phase) N3 ((TI study OR AB study) OR (TI studies OR AB studies) OR (TI trial* OR AB trial*))) OR (((TI crossover OR AB crossover) OR (TI "cross-over" OR AB "cross-over")) N3 ((TI study OR AB study) OR (TI studies OR AB studies) OR (TI trial* OR AB trial*))) OR (((TI multicent* OR AB multicent*) OR (TI "multi-cent*" OR AB "multi-cent*")) N3 ((TI study OR AB study) OR (TI studies OR AB studies) OR (TI trial* OR AB trial*))) OR (TI allocated OR AB allocated) OR (((TI "open label" OR AB "open label") OR (TI "open-label" OR AB "open-label")) N5 ((TI study OR AB study) OR (TI studies OR AB studies) OR (TI trial* OR AB trial*))) OR (((TI equivalence OR AB equivalence) OR (TI superiority OR AB superiority) OR (TI "non-inferiority" OR AB "non-	Search modes - Boolean/Phrase	1,252, 803

	inferiority") OR (TI noninferiority OR AB noninferiority)) N3 ((TI study OR AB study) OR (TI studies OR AB studies) OR (TI trial* OR AB trial*))) OR ((TI "pragmatic study" OR AB "pragmatic study") OR (TI "pragmatic studies" OR AB "pragmatic studies")) OR (((TI pragmatic OR AB pragmatic) OR (TI practical OR AB practical)) N3 (TI trial* OR AB trial*)) OR (((TI quasiexperimental OR AB quasiexperimental) OR (TI "quasi-experimental" OR AB "quasi-experimental")) N3 ((TI study OR AB study) OR (TI studies OR AB studies) OR (TI trial* OR AB trial*))) OR TI trial)		
S5	S1 OR S4	Search modes - Boolean/Phrase	1,049
S4	TI (partial* N2 thick* N2 wound*) OR AB (partial* N2 thick* N2 wound*)	Search modes - Boolean/Phrase	253
S3	TI "butterfly skin" OR AB "butterfly skin"	Search modes - Boolean/Phrase	0
S2	TI ((EB or DEB or DDEB or RDEB or JEB or "RDEB-GI" or "RDEB-I" or "RDEB-GS" or "RDEB-S" or "JEB-GI" or "JEB-GS")) OR AB ((EB or DEB or DDEB or RDEB or JEB or "RDEB-GI" or "RDEB-I" or "RDEB-GS" or "RDEB-S" or "JEB-GI" or "JEB-GS"))	Search modes - Boolean/Phrase	0
S1	TI (((epidermolysis or dystrophic or junctional) N4 bullosa*)) OR AB (((epidermolysis or dystrophic or junctional) N4 bullosa*))	Search modes - Boolean/Phrase	799

Table 67 of search strategy table for INAHTA

No	Query	Results
1	Epidermolysis Bullosa	1
2	((EB or DEB or DDEB or RDEB or JEB or "RDEB-GI" or "RDEB-I" or "RDEB-GS" or "RDEB-S" or "JEB-GI" or "JEB-GS") and (wound* or thick* or skin* or bullosa*))	0

3	"butterfly skin"	0
4	(partial* and thick* and wound*)	1
5	(oleogel or Filsuvez)	1

Table 68 of search strategy table for SCI-expanded

No	Query	Results
1	” Epidermolysis Bullosa" (Topic) and (random* or trial*) (Topic)	Not available

Table 69 of search strategy table for PubMed

No	Query	Results
1	((((((((((pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb])))))))))) AND (Epidermolysis Bullosa)) AND ((random* or trial))	Not available

Table 70 of search strategy table for Retraction Watch

No	Query	Results
1	Epidermolysis Bullosa n=0 (searched in title field).	Not available

H.1.2 Systematic selection of studies

Primary screening

Titles and abstracts of identified records were assessed to select those addressing the SLR eligibility criteria. This assessment was undertaken by two reviewers independently (CW and EP or JNL), using the Covidence online screening tool. If there was uncertainty about the relevance of a record based on the abstract, it was included, and a full copy of the publication was obtained.

Secondary screening

Electronic or paper copies of potentially relevant full papers meeting the SLR inclusion criteria were obtained. They were then assessed in detail for relevance to the eligibility

criteria by two reviewers independently (CW and JNL), and final selection of studies was made to inform the SLR. Where researchers disagreed regarding the inclusion or exclusion of a record, they discussed reasons for disagreement until a consensus was reached. If consensus was not reached, then a third researcher (AS) would have been involved to aid decision, however this was not necessary.

Table 71 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Adults or children (from birth) with DEB (RDEB or DDEB) or JEB	Other subtypes of EB not listed (e.g., EB simplex and EB acquisita)	N/A, no changes done
Intervention	• Oleogel-S10 (as referred to by any terminology relating to the product and active ingredients)	Any other interventions not listed	N/A, no changes done
Comparators	• Established clinical EB wound management including any other active clinical therapy/ wound care practice deemed part of current UK clinical practice in relation to the care of partial thickness wounds associated with DEB and JEB • Placebo, and control interventions	Any other interventions not listed	N/A, no changes done
Outcomes	Any wound-related clinical effectiveness, safety and tolerability, and PRO outcomes (e.g. EQ-5D, iscorEB) will be eligible for inclusion.	Any other outcomes not listed e.g., epidemiology, resource utilisation, pharmacokinetics, genetic diagnosis studies.	N/A, no changes done

Study design/publication type	• RCTs • Non-randomised comparative studies • Non-comparative, single-arm experimental studies • Open-label extension trials • SLRs/ NMAs Guidelines	• Phase I studies • Natural history studies • In vitro and animal studies • Pharmacodynamics • Non-systematic reviews • Opinion pieces • Editorials • Letters • Commentaries • Press releases • Prospective and retrospective observational cohort studies Case studies/ reports/ series	N/A, no changes done
Language restrictions	No date or language limits applied, with the exception of conference proceedings (2020-present, only).		

PICOS refinement

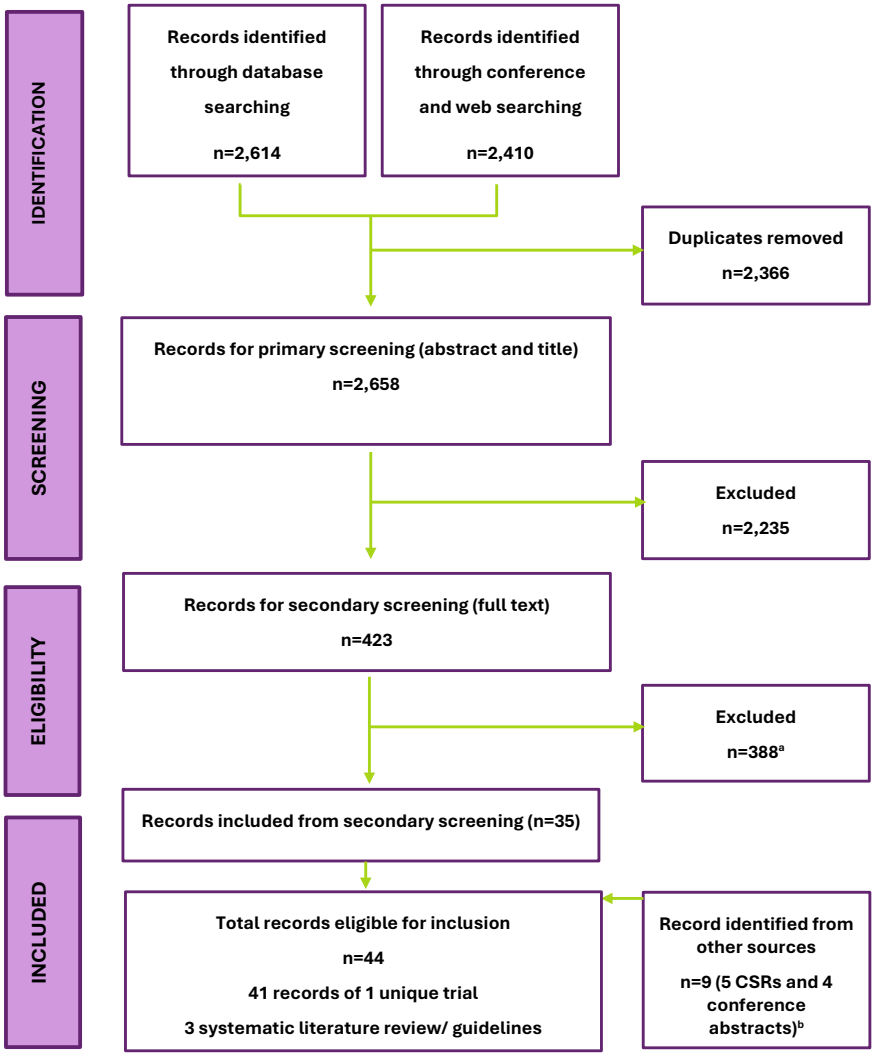
As detailed in the protocol, the review considered that established clinical wound management could include any other active clinical therapy or wound care practice deemed part of clinical practice in relation to the care of partial thickness wounds associated with DEB and JEB. The search strategy and PICOS were kept broad, and primary screening was conducted to this end.

Additional input from clinicians confirmed that while the standard of care for EB partial thickness wounds is heterogenous, it commonly consists of the use of a variety of non-adhesive dressings and bandages, topical antimicrobials, topical steroids, and a variety of topical agents, none of which are licensed for use in the management of EB wounds. Hygiene advice is often also provided; bathing is often tolerated more than showering, and can be used to cleanse, reduce the trauma of dressing changes, and allow supplemental antibacterial cleaning by using diluted acetic acid or bleach. Additional recommendations for management of cutaneous manifestations may include: lancing and draining of intact blisters since EB blisters are not self-limiting, action to address colonisation and infection of wounds such as the use of antiseptics and topical/ systemic antimicrobials mentioned above, efforts to treat intense pruritus, and protection from further cutaneous trauma. Pain management, including pharmacological and non-pharmacological interventions, is also key to tackle both background pain and procedural pain experienced during wound management practices such as bathing, dressing changes and blister lancing, and other clinical procedures.

During secondary screening it became apparent that the majority of active interventions within otherwise eligible trial records could not be considered part of this current

established clinical management, mainly because they included investigational agents or techniques, those unlicensed in EB, that could not be considered established in relation to the care of partial thickness wounds associated with DEB and JEB. Therefore, PICOS refinement was not necessary and PICOS criteria were applied as per the protocol, throughout.

Figure 17. PRISMA diagram of the overall study selection process



[a] *Exclusion reasons: abstract with insufficient information n=20; EB type not specified n=4; eligible patients not reported separately n=3; ineligible intervention n=115; ineligible patient population n=17; ineligible publication type n=41; ineligible study design n=91; no eligible outcomes reported n=6; studies with no published results n=79; unable to locate full record n=12.*

[b] Six of the eight conference abstracts identified through grey literature searching in the original PRISMA were found through the 2023 updated database searches and therefore only two of these abstracts are reported as being identified through grey literature, in addition to another found during the 2023 update and one found during the 2024 update

Only one trial was identified as providing evidence relevant to the decision problem to be addressed in the health technology assessment of Oleogel-S10 based on screening

against the predefined PICOS criteria. EASE is a phase III RCT providing direct head-to-head evidence of the safety and efficacy of Oleogel-S10 compared to a control gel arm, which is considered as a proxy for standard of care/ established clinical management in the absence of any other trial evidence of key wound healing endpoints in DEB and JEB patients.

Table 72 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
EASE	Determine the efficacy and safety of the topical gel Oleogel-S10 (birch triterpenes) in EB	Double-blind, randomized, vehicle-controlled, phase III study t	Patients with dystrophic EB, junctional EB or Kindler EB	Oleogel-S10 or control gel	Complete target wound closure within 45 days	Key endpoints (additional endpoints above in document): • Time to wound closure up to 90 ± 7 days of treatment (key secondary endpoint) • Incidence of first complete wound closure of EB target wound at different time points • Change from baseline in EB target wound size • Change in total body wound burden over time • Change in percentage

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						s of TBSA affected by EB partial thickness wounds

H.1.3 Excluded fulltext references

Table Excluded references

Excluded records
Abstract only with insufficient information (n=19)
Bruckner, A.; Tang, J.; Chung, W.; Morel, K.; Chen, M.; Woodley, D.; Keene, D.; Peoples, K.; Barriga, M.; Carroll, J.; Levin, L.; Ravindran, S.; Mangone, M.; Ramsdell, D.; Landy, H. 295 Collagen 7 (C7) protein replacement therapy (PTR-01) durably reduces wound size and symptoms in patients with recessive dystrophic epidermolysis bullosa (RDEB). SID. 2022.
De Graaf, P. Psychosocial guidelines. Acta Dermato-Venereologica. 2020. 100; SUPPL 220: 27.
De Rosa, L. Hologene projects. Acta Dermato-Venereologica. 2020. 100; SUPPL 220: 12.
Gorell, E.; Eichstadt, S.; Barriga, M.; Ponakala, A.; Teng, C.; Nguyen, N.; Siprashvili, Z.; Nazaroff, J.; Chiou, A.; Taylor, L.; Khuu, P.; Keene, D.; Rieger, K.; Khosla, R.; Lorenz, H. P.; Furukawa, L.; Marinkovich, M. P.; Tang, J. Y. Phase 1/2a clinical trial of gene-corrected autologous cell therapy for recessive dystrophic epidermolysis bullosa. Acta Dermato-Venereologica. 2020. 100: 75-75.
Hao, M.; Antaya, R.; Cogan, J.; Hamilton, C.; Hou, Y.; Kwong, A.; Woodley, D.; Chen, M. Intravenous gentamicin therapy for junctional epidermolysis bullosa patients harboring nonsense mutations. Journal of Investigative Dermatology. 2020. 140; 7: S112-S112.
Hovnanian, A. Ebgraft and advances in skin grafting using improved vectors. Acta Dermato-Venereologica. 2020. 100; SUPPL 220: 12.
Kyrova, J.; Kopeckova, L.; Fajkusova, L.; Rotschein, P.; Pinkova, B.; Gaillyova, R.; Hlavackova, E.; Buckova, H. P030 EB Centre Czech Republic and DEBRA Czech Republic - 23 years of collaboration and experience. 2024.
Marinkovich, M. P.; Lane, A.; Sridhar, K.; Keene, D.; Malyala, A.; Spellman, M.; Maslowski, J. A phase 1/2 study of genetically corrected, collagen VII expressing autologous human dermal fibroblasts injected into the skin of patients with recessive dystrophic epidermolysis bullosa (RDEB). Acta Dermato-Venereologica. 2020. 100; SUPPL 220: 75.
Marinkovich, M.P. Research update (gene and protein). Acta Dermato-Venereologica. 2020. 100; SUPPL 220: 23-24.
Marinkovich, M. P.; Sridhar, K.; Karkala, V.; Yenamandra, V. K.; Gurevitch, I.; Dolorito, J.; Bagci, I. S.; O'Mara, C.; Ramsdell, D.; Landy, H. Topical QR-313, an Antisense Oligonucleotide, in the Treatment of Dystrophic Epidermolysis Bullosa. Journal of Investigative Dermatology. 2020. 140; 7: S37-S37.

Excluded records

Okata-Karigane, U.; Gorell, E.; Sum, K.; Yekrang, K.; Phung, M.; Barriga, M.; Udrizar, P.; Bailey, I.; Li, S.; Tang, J.; Chiou, A. 280 A phase 2 randomized clinical trial of serlopitant, a neurokinin-1 receptor antagonist for the treatment of chronic itch in patients with epidermolysis bullosa. SID. 2022.

Okata-Karigane, U.; Pathmarajah, P.; Li, S.; Lu, Y.; Tang, J. Y.; Chiou, A. S. 592 Patient-reported outcome measures for chronic itch in epidermolysis bullosa: an exploratory analysis of a randomized controlled trial. Journal of investigative dermatology. 2023. 143; 5: S101.

Shakouri, R.; Abdollahimajd, F.; Samsavar, S.; Youssefian, L.; Vahidnezhad, H.; Uitto, J.; Shokri, B. The efficacy and safety of cold atmospheric pressure plasma versus low level laser for the treatment of wounds in epidermolysis bullosa patients. Acta Dermato-Venereologica. 2020. 100; SUPPL 220: 66.

Sumeray, M. Development of two topical approaches to wound healing in EB an update on progress with oleogel-S10 and AP103. Acta Dermato-Venereologica. 2020. 100; SUPPL 220: 22.

Tamai, K. Development of hmgb1 peptide drug for regenerating epidermal stem cell niehces in rdeb skin. Acta Dermato-Venereologica. 2020. 100; SUPPL 220: 11.

Tang, J.; Bruckner, A.; Chen, M.; Woodley, D. T.; Keene, D.; Barriga, M.; Peoples, K.; Johnson, R.; Ramsdell, D.; Landy, H. 438 A phase 1/2 trial of PTR-01, a collagen 7 (C7) protein replacement therapy, in patients with recessive dystrophic epidermolysis bullosa (RDEB). Journal of investigative dermatology. 2021. 141; 5: S76.

Tang, J.; Bruckner, A.; Chen, M.; Woodley, D. T.; Keene, D.; Barriga, M.; Peoples, K.; Johnson, R.; Ramsdell, D.; Landy, H. A phase 1/2 trial of PTR-01, a collagen 7 (C7) protein replacement therapy, in patients with recessive dystrophic epidermolysis bullosa (RDEB). Journal of Investigative Dermatology. 2021. 141; 5: S76-S76.

Tang, J. Large rdeb wounds: An update on natural history data and EB101. Acta Dermato-Venereologica. 2020. 100; SUPPL 220: 14.

Virginie, J.; Serge, B. Using urgotul dressing for the management of epidermolysis bullosa skin lesions. Journal of Wound Care. 2020. 29; SUPPL 7B: 281.

Woodley, D. T. Read-through therapeutics: Drug repurposing for rdeb. Acta Dermato-Venereologica. 2020. 100; SUPPL 220: 9.

EB type not specified (n=4)

EUCTR2021-000103-20-NL A study on the effect of Transvamix on pain in adults with epidermolysis bullosa.. An explorative randomized, placebo-controlled and double-blind intervention crossover study: Transvamix (100mg/mL THC / 50mg/mL CBD) to treat chronic pain in Epidermolysis Bullosa. 2021.

NCT02654483 Neurokinin-1 Receptor Antagonist for the Treatment of Itch in EB Patients. 2016.

NCT00311766 A Phase 2 Study on Effect of Thymosin Beta 4 on Wound Healing in Patients With Epidermolysis Bullosa. A Randomized, Double-Blind, Placebo-Controlled, Dose-Response Study of the Safety and Efficacy of Thymosin Beta 4 in the Treatment of Patients With Epidermolysis Bullosa. 2006.

NCT00951964 Treatment of Epidermolysis Bullosa Dystrophica by Polyphenon E (Epigallocatechin 3 Gallate). Treatment of Epidermolysis Bullosa Dystrophica by Polyphenon E (Epigallocatechin 3 Gallate). 2009.

Eligible patients not reported separately (n=3)

Blanchet-Bardon, C.; Bohbot, S. Using Urgotul dressing for the management of epidermolysis bullosa skin lesions. Journal of wound care. 2005. 14; 10: 490-496.

Dwiyana, R. F.; Yogya, Y.; Gondokaryono, S. P.; Diana, I. A.; Suwarsa, O.; Ramali, L. M.; Sutedja, E. K.; Rahardja, J. I.; Gunawan, H. Clinical efficacy of biocellulose, carboxymethyl cellulose and normal saline dressing in epidermolysis bullosa. Journal of Wound Care. 2019. 28; Supplement 10: S4-S9.

Excluded records

Huang, C. H.; Lee, J. Y.; Hsu, H. L.; Liao, Y. H.; Hsu, C. K.; Yang, C. C.; Tu, W. T.; Hsieh, Y. J.; Lu, W. S.; Lin, I. Y.; Chan, Y. M.; Chen, C. K. Diacerein 1% ointment for epidermolysis bullosa in a randomized controlled pilot study. Acta Dermato-Venereologica. 2020. 100: 32-32.

Ineligible intervention (n=102)

2005-002329-30 Ensayo Clinico Comparativo, Abierto, Multicentrico, Para Evaluar La Eficacia Y Seguridad De Una Nueva Terapia Con Piel QuimÃ‰rica Cultivada Para El Tratamiento De Las Lesiones CutÃneas De Los Pacien.

2014-002288-14 A Phase 3, Multi-center, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of SD-101 Cream in Patients with Epidermolysis Bullosa.

2018-001009-98 An interventional, multicenter, single arm, phase I/IIa clinical trial to investigate the efficacy and safety of allo-APZ2-EB on epidermolysis bullosa (EB).

A Long-term Treatment With B-VEC for Dystrophic Epidermolysis Bullosa.

A Phase I/II Study of KB103, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB). 2023.

A Study of FCX-007 for Recessive Dystrophic Epidermolysis Bullosa (RDEB).

ACTRN Investigation of cell therapy for recessive dystrophic epidermolysis bullosa (RDEB) in Australia through intradermal injection of allogeneic fibroblasts. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12610000760077. 2010.

ACTRN Investigation of micro-needling skin therapy for recessive dystrophic epidermolysis bullosa (RDEB) in Australia. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12611000668909. 2011.

Allogeneic ABCB5-positive Stem Cells for Treatment of Epidermolysis Bullosa.

Bauer, E. A.; Cooper, T. W.; Tucker, D. R.; Esterly, N. B. Phenytoin therapy of recessive dystrophic epidermolysis bullosa. Clinical trial and proposed mechanism of action on collagenase. New England Journal of Medicine. 1980. 303; 14: 776-781.

Caldwell-Brown, D.; Stern, R. S.; Lin, A. N.; Carter, D. M. Lack of efficacy of phenytoin in recessive dystrophic epidermolysis bullosa. New England Journal of Medicine. 1992. 327; 3: 163-167.

Chen, H.; Marinkovich, M.P.; Gonzalez, M.E.; Guide, S.V.; Bagci, I.S.; Chitra, S.; Agostini, B.; Feeney, G.; Kapadia, B.; Krishnan, S. 0013 GEM-3: Phase 3 study of beremagene geperpavec, an investigational, topical gene therapy, for the treatment of dystrophic Epidermolysis Bullosa. 2021.

Chen, H.; Marinkovich, M. P.; Gonzalez, M. E.; Guide, S. V.; Bagci, I. S.; Chitra, S.; Agostini, B.; Feeney, G.; Kapadia, B.; Krishnan, S. GEM-3: phase 3 study of beremagene geperpavec, an investigational, topical gene therapy, for the treatment of dystrophic Epidermolysis Bullosa. Pediatric dermatology. 2022. 39; SUPPL 1: 9-10.

Dieter, K. ABCB5+ mesenchymal stem cells for the treatment of rdeb from bench to bedside. Acta Dermato-Venereologica. 2020. 100; SUPPL 220: 15.

Dieter, K.; Niebergall-Roth, E.; Daniele, C.; Fluhr, S.; Frank, N. Y.; Ganss, C.; Kiritsi, D.; McGrath, J. A.; Tolar, J.; Frank, M. H.; Kluth, M. A. ABCB5+mesenchymal stromal cells facilitate complete and durable wound closure in recessive dystrophic epidermolysis bullosa. Cytotherapy. 2023. 25; 7: 782-788.

Eldarouti, M.; Nada, H.; El-Komy, M.; Abdelhady, M.; Saadi, D.; Doss, S.; El Sayed, H.; Mostafa, P. Efficacy of combined use of mycophenolate mofetil and granulocyte-colony-stimulating factor in the treatment of patients with dystrophic epidermolysis bullosa. Journal of the Egyptian Women's Dermatologic Society. 2022. 19; 3: 181-185.

ESSENCE Study: Efficacy and Safety of SD-101 Cream in Participants With Epidermolysis Bullosa.

Excluded records

EUCTR2014-002288-14-DE. An Investigation into the Efficacy and Safety of SD-101 Cream in Patients with Epidermolysis Bullosa. 2014.

EUCTR2012-001394-87-GB. A prospective phase I/II study to evaluate allogeneic mesenchymal stromal cells for the treatment of skin disease in children with recessive dystrophic epidermolysis bullosa. 2012.

EUCTR2009-012750-21-FR. Traitement des Epidermolyses bulleuses dystrophiques hereditaires par l'epigallocatachine-3-gallate oral (Polyphenon E). 2009.

EUCTR2014-002288-14-GB. An Investigation into the Efficacy and Safety of SD-101 Cream in Patients with Epidermolysis Bullosa. A Phase 3, Multi-center, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of SD-101 Cream in Patients with Epidermolysis Bullosa - Study of Effectiveness and Safety of SD-101 in Subjects with Epidermolysis Bullosa/ESSENCE Stud. 2014.

EUCTR2015-003670-32-DE. Phase I/II trial to establish safety, tolerability and efficacy of losartan in children with epidermolysis bullosa. A dual-center prospective phase I/II trial to establish safety, tolerability and to obtain first data on efficacy of losartan in children with recessive dystrophic epidermolysis bullosa (RDEB) - REFLECT. 2016.

EUCTR2016-001967-35-AT. A study to assess the efficacy of a vitamin D-containing ointment applied on the skin to improve wound healing in "butterfly children". A double-blind, placebo-controlled cross-over study to assess the efficacy of topical calcipotriol (Psorcutana-ointment containing 0.05 µg/g calcipotriol) to improve wound healing in dystrophic epidermolysis bullosa (DEB) - Topical calcipotriol in DEB. 2016.

EUCTR2018-000261-36-IT Gene therapy for patient with junctional epidermolysis bullosa. multicentre, open-label, uncontrolled, pivotal clinical trial to confirm the efficacy and safety of autologous fibrin-cultured epidermal grafts containing epidermal stem cells genetically modified for restoration of epidermis in patients with junctional epidermolysis bullosa. 2020.

EUCTR2018-001009-98-DE. Study to investigate the efficacy and safety of allo-APZ2-EB on wound healing of epidermolysis bullosa (EB). An interventional, multicenter, single arm, phase I/IIa clinical trial to investigate the efficacy and safety of allo-APZ2-EB on epidermolysis bullosa (EB). 2018.

EUCTR2020-002936-55-CZ. Safety and Efficacy of Mesenchymal Stromal Cells Derived from Adipose Tissue of Non-related Donors in Patients with The Butterfly Disease: Clinical Trial Phase I/II. Safety and Efficacy of Allogenic Adipose Tissue-derived Mesenchymal Stromal Cells in Patients with Epidermolysis Bullosa: Clinical Trial Phase I/II - MSC-EB. 2020.

EUCTR2021-000214-42-GR. INM-755 cream for patients with EB. A Randomised, Double-Blind, Vehicle-Controlled Phase 2 Study of Topically Applied INM-755 (cannabinol) Cream in Patients with Epidermolysis Bullosa. 2021.

Guide, S. V.; Gonzalez, M. E.; Bagcl, I. S.; Agostini, B.; Chen, H.; Feeney, G.; Steimer, M.; Kapadia, B.; Sridhar, K.; Quesada Sanchez, L.; Gonzalez, F.; Van Ligten, M.; Parry, T. J.; Chitra, S.; Kammerman, L. A.; Krishnan, S.; Marinkovich, M. P. Trial of Beremagene Geperpavec (B-VEC) for Dystrophic Epidermolysis Bullosa. New England Journal of Medicine. 2022. 387; 24: 2211-2219.

Gurevich, I.; Agarwal, P.; Zhang, P.; Dolorito, J. A.; Oliver, S.; Liu, H.; Reitze, N.; Sarma, N.; Bagci, I. S.; Sridhar, K.; et al. In vivo topical gene therapy for recessive dystrophic epidermolysis bullosa: a phase 1 and 2 trial. Nature medicine. 2022. 28; 4: 780-788.

Guttmann-Gruber, C.; Hofbauer, J. P.; Tockner, B.; Reichl, V.; Hofbauer, P.; Wolkersdorfer, M.; Diem, A.; Ude-Schoder, K.; Hitzl, W.; Lagler, F.; et al. The impact of low-dose calcipotriol ointment on wound healing, pruritus and pain in patients with dystrophic epidermolysis bullosa. Acta dermato-venereologica. 2020. 100; SUPPL 220: 41.

Excluded records

Guttmann-Gruber, C.; Hofbauer, J. P.; Tockner, B.; Reichl, V.; Klausegger, A.; Hofbauer, P.; Wolkersdorfer, M.; Tham, K. C.; Lim, S. S.; Common, J. E.; Diem, A.; Ude-Schoder, K.; Hitzl, W.; Lagler, F.; Reichelt, J.; Bauer, J. W.; Lang, R.; Laimer, M. Impact of low-dose calcipotriol ointment on wound healing, pruritus and pain in patients with dystrophic epidermolysis bullosa: A randomized, double-blind, placebo-controlled trial. Orphanet Journal of Rare Diseases. 2021. 16; 1.

IRCT20150825023753N. The effectiveness of oral Cicaglucal on wound healing and pruritus management in patients with Epidermolysis bullosa. 2024.

IRCT20181222042074N2. Evaluation of the effect of amniotic scaffold and keratinocyte cells on wound healing from butterfly wing disease. Design and evaluation of biological dressing efficiency with tissue engineering structure in wound healing of Epidermolysis bullosa patients: the first stage of phase 2. 2022.

ISRCTN67757229. Allogeneic fibroblast cell therapy for dystrophic epidermolysis bullosa. 2011.

ISRCTN14409785. Mesenchymal stromal cell therapy for children with recessive dystrophic epidermolysis bullosa. Double-blinded placebo-controlled crossover study of Mesenchymal Intravenous Stromal cell Infusions in children with recessive dystrophic Epidermolysis Bullosa. 2021.

ISRCTN67757229. Allogeneic fibroblast cell therapy for dystrophic epidermolysis bullosa. A prospective placebo controlled phase II study to evaluate ICX-RHY-013 for the treatment of skin erosions in dystrophic epidermolysis bullosa patients. 2011.

ISRCTN81030001. Double blind, placebo controlled crossover study of the efficacy and side effects of low dose amitriptyline treatment for chronic pain, disordered sleep and reduced mobility in children with Epidermolysis Bullosa. 2010.

JPRN-jRCT1080224498. A clinical study of CL2020 in patients with epidermolysis bullosa. A clinical study of CL2020 in patients with epidermolysis bullosa. 2018.

JPRN-jRCT2053230075 Open Label Extension Protocol (Japan): Assess the Efficacy and Safety of Beremagene Geperpavec (B-VEC, previously KB103) for the Treatment of Japanese Patients with Dystrophic Epidermolysis Bullosa (DEB). 2023.

JPRN-UMIN000006723. Clinical research of bone marrow-derived mesenchymal stem cell transplantation for the patients with epidermolysis bullosa. 2011.

JPRN-UMIN000020734. Pivotal study of J-TEC-01 from revertant mosaicism for epidermolysis bullosa. 2016.

JPRN-UMIN000026645 A Clinical Study to Evaluate the Efficacy and Safety of JR-031 in Patients with Epidermolysis Bullosa. A Clinical Study to Evaluate the Efficacy and Safety of JR-031 in Patients with Epidermolysis Bullosa - A Clinical Study to Evaluate the Efficacy and Safety of JR-031 in Patients with Epidermolysis Bullosa. 2017.

Kiritsi, D.; Dieter, K.; Niebergall-Roth, E.; Fluhr, S.; Daniele, C.; Esterlechner, J.; Sadeghi, S.; Ballikaya, S.; Erdinger, L.; Schauer, F.; Gewert, S.; Laimer, M.; Bauer, J. W.; Hovnanian, A.; Zambruno, G.; El Hachem, M.; Bourrat, E.; Papanikolaou, M.; Petrof, G.; Kitzmuller, S.; Ebens, C. L.; Frank, M. H.; Frank, N. Y.; Ganss, C.; Martinez, A. E.; McGrath, J. A.; Tolar, J.; Kluth, M. A. Clinical trial of ABCB5+mesenchymal stem cells for recessive dystrophic epidermolysis bullosa. JCI Insight. 2021. 6; 22: e151922.

Lara-Corrales, I.; Parkin, P. C.; Stephens, D.; Hamilton, J.; Koren, G.; Weinstein, M.; Sibbald, R. G.; Pope, E. The efficacy of trimethoprim in wound healing of patients with epidermolysis bullosa: A feasibility trial. Journal of the American Academy of Dermatology. 2012. 66; 2: 264-270.

Marinkovich, M.; Gonzalez, M.; Guide, S.; Bagci, I.S.; Chitra, S.; Agostini, B.; Chen, H.; Parry, T.; Krishnan, S. 465 GEM-3: phase 3 safety and immunogenicity results of beremagene geperpavec (B-VEC), an investigational, topical gene therapy for dystrophic epidermolysis bullosa (DEB). SID. 2022.

Excluded records

Marinkovich, M.; Gonzalez, M.; Guide, S.; Bagci, I.S.; Chitra, S.; Agostini, B.; Chen, H.; Feeney, G.; Kapadia, B.; Steimer, M.; Krishnan, S. WCRSD2200003: GEM-3: A Phase 3 Study of Beremagene Geperpavec (B-VEC), an Investigational, Topical Gene Therapy, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB). WCRSD. 2022.

Marinkovich, M.; Gonzalez, M.; Guide, S.; Bagci, I.S.; Chitra, S.; Agostini, B.; Chen, H.; Parry, T.; Krishnan, S. WCRSD2200004: GEM-3: Phase 3 Safety and Immunogenicity Results of Beremagene Geperpavec (B-VEC), an Investigational, Topical Gene Therapy for Dystrophic Epidermolysis Bullosa (DEB). WCRSD. 2022.

Marinkovich, M. P.; Gonzalez, M.; Guide, S.; Bagci, I. S.; Chitra, S.; Agostini, B.; Chen, H.; Feeney, G.; Kapadia, B.; Steimer, M.; Krishnan, S. GEM-3: A phase 3 study of beremagene geperpavec, an investigational, topical gene therapy, for the treatment of dystrophic epidermolysis bullosa. Pediatric Dermatology. 2023. 40; Supplement 1: 38.

Marinkovich, M. P.; Gonzalez, M.; Guide, S.; Bagci, I. S.; Chitra, S.; Agostini, B.; Chen, H.; Parry, T.; Krishnan, S. GEM-3: phase 3 safety and immunogenicity results of beremagene geperpavec, an investigational, topical gene therapy for dystrophic epidermolysis bullosa. Pediatric dermatology. 2023. 40: 38-39.

Marinkovich, M. P.; Sridhar, K. J.; Bagci, I. S.; Dolorito, J. A. M.; Keene, D. R.; Yonchek, M.; Blumenthal, R. L.; Spellman, M. C. The Treatment of Wounds Associated with Recessive Dystrophic Epidermolysis Bullosa with Local Injections of Gene-Corrected, Collagen VII-Expressing Autologous Human Dermal Fibroblasts. Molecular Therapy. 2022. 30; 4: 376-376.

Marinkovich, M. P.; Sridhar, K.; Kakarla, V.; Yonchek, M.; Blumenthal, R.; Spellman, M. The treatment of wounds associated with recessive dystrophic epidermolysis bullosa with local injections of gene-corrected, collagen VII-expressing autologous human dermal flbroblasts. Journal of Clinical and Aesthetic Dermatology. 2021. 14; 5 SUPPL 1: S30.

Marinkovich, M. P.; Vinzant, S.; Agarwal, P.; Krishna, S. Results from a phase I/II study of a topical gene therapy (bercolagene telserpavec, B-VEC) in patients with recessive dystrophic epidermolysis bullosa (RDEB). Acta dermato-venereologica. 2020. 100; SUPPL 220: 48.

Marinkovich, M. P.; Vinzant, S.; Karkala, V.; Sridhar, K.; Gurevitch, I.; Dolorito, J.; Agarwal, P.; Krishnan, S. 305 In vivo correction of recessive dystrophic epidermolysis bullosa (RDEB) by direct cutaneous COL7A1 gene replacement: results of a phase 1-2 trial. Journal of investigative dermatology. 2020. 140; 7: S37.

Marinkovich, M.; Forte, S.; Oliver, S.; Dolorito, J.; Sridhar, K.; Liu, H.; Reitze, N.; Sarma, N.; Krishnan, S. 155 Assessment of safety in repeat dosing of an in vivo topical gene therapy for the treatment of recessive dystrophic epidermolysis bullosa (RDEB) in a phase I/II trial. Journal of investigative dermatology. 2021. 141; 5: S28.

Marinkovich, M.; Gonzalez, M.; Guide, S.; Bagci, I. S.; Chitra, S.; Agostini, B.; Chen, H.; Parry, T.; Krishnan, S. GEM-3: phase 3 safety and immunogenicity results of beremagene geperpavec (B-VEC), an investigational, topical gene therapy for dystrophic epidermolysis bullosa (DEB). Journal of Investigative Dermatology. 2022. 142; 8: S79-S79.

Mellerio, J. E.; Pillay, E. I.; Ledwaba-Chapman, L.; Bisquera, A.; Robertson, S. J.; Papanikolaou, M.; McGrath, J. A.; Wang, Y. Z.; Martinez, A. E.; Jeffs, E. Itch in recessive dystrophic epidermolysis bullosa: findings of PEBLES, a prospective register study. Orphanet Journal of Rare Diseases. 2023. 18; 1.

Murrell, D. F.; Paller, A. S.; Bodemer, C.; Browning, J.; Nikolic, M.; Barth, J. A.; Lagast, H.; Krusinska, E.; Reha, A. Wound closure in epidermolysis bullosa: data from the vehicle arm of the phase 3 ESSENCE Study. Orphanet Journal of Rare Diseases. 2020. 15; 1: 1435.

NCT03836001 A Neurokinin-1 Receptor Antagonist for the Treatment of Pruritus in Patients With Epidermolysis Bullosa. 2019.

NCT05944250. A Pilot Study to Evaluate a Temporary Skin Substitute (SpincareÂ Matrix) for Wound Healing in RDEB Patients. 2023.

Excluded records

NCT05838092 Allogeneic ABCB5-positive Dermal Mesenchymal Stromal Cells for Treatment of Epidermolysis Bullosa (Phase III). 2023.

NCT02384460 ESSENCE Study: Efficacy and Safety of SD-101 Cream in Patients With Epidermolysis Bullosa. 2015.

NCT02014376 Study of Effectiveness and Safety of SD-101 in Subjects With Epidermolysis Bullosa. 2013.

NCT05529134 Study of PTW-002 in Patients With Dominant or Recessive Dystrophic Epidermolysis Bullosa Due to Mutation(s) in Exon 73 of the COL7A1 Gene. 2022.

NCT00380640 The Efficacy of Trimethoprim in Wound Healing of Patients With Epidermolysis Bullosa. 2006.

NCT04491604 The Objective of This Study is to Compare the Efficacy and Safety of Beremagene Geperpavec (B-VEC) Topical Gel With That of Placebo for the Treatment of Dystrophic Epidermolysis Bullosa (DEB). 2020.

NCT00231517 Randomised Double Blind Placebo Controlled Cross Over Design of the Efficacy of Topical Morphine for Inflammatory Pain in Children With Epidermolysis Bullosa.

NCT00380640 The Efficacy of Trimethoprim in Wound Healing of Patients With Epidermolysis Bullosa. The Efficacy of Trimethoprim in Wound Healing of Patients With Epidermolysis Bullosa: A Randomized, Double Blinded, Placebo Controlled, Cross-over Pilot Study. 2006.

NCT00587223 Safety and Efficacy of Apligraf in Nonhealing Wounds of Subjects With Junctional or Dystrophic Epidermolysis Bullosa (EB). A Prospective, Multicenter, Within Subject Controlled Study to Evaluate the Effect of Apligraf in Nonhealing Wounds of Subjects With Junctional or Dystrophic Epidermolysis Bullosa. 2007.

NCT01749306 A Study of the Efficacy and Safety of ABH001 in the Treatment of Patients With Epidermolysis Bullosa Who Have Wounds That Are Not Healing.

NCT02698735 Gentamicin Therapy for Recessive Dystrophic Epidermolysis Bullosa (RDEB) Nonsense Mutation Patients. 2016.

NCT03468322 A Double-blind, Intra-individual Comparison, POC Trial of AC-203 in EB Patients. A Double-blind, Intra-individual Comparison, Proof-of-concept Trial of Topical AC-203 in Patients With Inherited Epidermolysis Bullosa. 2018.

NCT03490331 Clinical Trial to Assess Safety and Efficacy of Autologous Cultured Epidermal Grafts Containing Epidermal Stem Cells Genetically Modified in Patients With JEB (HOLOGENE17). Prospective, Open-label, Uncontrolled Clinical Trial to Assess the Safety and Efficacy of Autologous Cultured Epidermal Grafts Containing Epidermal Stem Cells Genetically Modified With a Gamma-retroviral (rv) Vector Carrying COL17A1 cDNA for Restoration o. 2018.

NCT03536143 A Phase I/II Study of KB103, a Topical HSV1-COL7, on DEB Patients. A Phase I/II Study of KB103, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB). 2018.

NCT03578029 Evaluation of the Safety and Efficacy Study of RGN-137 Topical Gel for Junctional and Dystrophic Epidermolysis Bullosa. A Randomized,Single-Blind, Placebo-controlled, Self-matched Pairing, Independent Evaluated Study to Evaluate the Efficacy and Safety of RGN-137 Topical Gel in Subjects With Junctional and Dystrophic Epidermolysis Bullosa (CELEB). 2018.

NCT03752905 A Phase 1/2 Trial of PTR-01 in Adult Patients With Recessive Dystrophic Epidermolysis Bullosa (RDEB). A Phase 1/2 Randomized, Saline-Controlled, Single-Blind, Multiple Ascending Dose, Dose-Escalation, Multi-Center Trial of PTR-01 in Adult Patients With Recessive Dystrophic Epidermolysis Bullosa (RDEB). 2018.

Excluded records

NCT03928093 Pregabalin Treatment for RDEB Pain and Itch. A Double-blind, Randomized, Cross-over, Feasibility Trial of Pregabalin for the Treatment of Recessive Dystrophic Epidermolysis Bullosa-associated Neuropathic Pain and Itch. 2019.

NCT04173650 MSC EVs in Dystrophic Epidermolysis Bullosa. A Safety Study of the Administration of Mesenchymal Stem Cell Extracellular Vesicles in the Treatment of Dystrophic Epidermolysis Bullosa Wounds. 2019.

NCT04213261 A Study of FCX-007 for Recessive Dystrophic Epidermolysis Bullosa. A Pivotal Phase 3 Study of FCX-007 (Genetically-Modified Autologous Human Dermal Fibroblasts) for Recessive Dystrophic Epidermolysis Bullosa. 2019.

NCT04491604 Ph 3 Efficacy and Safety of B-VEC for the Treatment of DEB.

NCT04491604 The Objective of This Study is to Compare the Efficacy and Safety of Beremagene Geperpavec (B-VEC) Topical Gel With That of Placebo for the Treatment of Dystrophic Epidermolysis Bullosa (DEB).. A Phase III Double Blinded, Placebo-Controlled, Efficacy and Safety Study of Beremagene Geperpavec (B-VEC, Previously "KB103") for the Treatment of Dystrophic Epidermolysis Bullosa (DEB). 2020.

NCT04613102 The Efficacy and Safety of 3% Cannabidiol (CBD) Cream in Patients With Epidermolysis Bullosa: A Phase II/III Trial. The Efficacy and Safety of 3% Cannabidiol (CBD) Cream in Patients With Epidermolysis Bullosa: A Phase II/III Trial. 2020.

NCT04908215 INM-755 (Cannabinol) Cream for Treatment of Epidermolysis Bullosa. A Randomised, Double-Blind, Vehicle-Controlled Phase 2 Study of Topically Applied INM-755 (Cannabinol) Cream in Patients With Epidermolysis Bullosa. 2021.

NCT05143190 Extension Study to PTR-01-002 (A Study in Recessive Dystrophic Epidermolysis Bullosa (RDEB) Patients Previously Treated With PTR-01). A Phase 2b Open-Label Study of PTR-01 in Recessive Dystrophic Epidermolysis Bullosa (RDEB) Patients Previously Treated With PTR-01 in Study PTR-01-002. 2021.

NCT05464381 Allogeneic ABCB5-positive Dermal Mesenchymal Stromal Cells for Treatment of Epidermolysis Bullosa (Phase III, Cross-over). A Double-blind, Randomized, Placebo-controlled, Interventional, Multicenter, Phase III Clinical Trial to Investigate the Safety and Efficacy of ABCB5-positive Mesenchymal Stromal Cells (ABCB5+ MSCs) on Epidermolysis Bullosa (EB). 2022.

NCT05651607 Evaluation of the Efficacy of CANNABIDIOL on the Pruritus in Children With Hereditary Epidermolysis Bullosa. Evaluation of the Efficacy of CANNABIDIOL on the Pruritus in Children With Hereditary Epidermolysis Bullosa. 2022.

NCT05708677 A Long-Term Extension Study for Participants Previously Treated With EB-101 for the Treatment of RDEB. A Long-Term Extension Study for Participants Previously Treated With EB-101 for the Treatment of Recessive Dystrophic Epidermolysis Bullosa (RDEB). 2023.

NCT05725018 EB-101 Treatment for New and Previously Treated Patients With Recessive Dystrophic Epidermolysis Bullosa (RDEB). A Phase 3b Study for the Treatment of Recessive Dystrophic Epidermolysis Bullosa (RDEB) in New and Previously EB-101 Treated Patients. 2023.

NCT05838092 Allogeneic ABCB5-positive Dermal Mesenchymal Stromal Cells for Treatment of Epidermolysis Bullosa (Phase III).

NCT06007235 CACIPLIQ20 in Wound Healing in Subjects With Epidermolysis Bullosa. A Randomized, Double-Blind, Placebo-Controlled, Crossover, Pilot Stage Clinical Trial Evaluating CACIPLIQ20 in Wound Healing in Subjects With Epidermolysis Bullosa. 2023.

NCT06177353 Study of the Blood and Skin Immunological Profile of Patients With Recessive Dystrophic Epidermolysis Bullosa: in Vivo Analysis and the Impact of Placental Stem Cells in Vitro. 2023.

Excluded records

Niazi, M.; Parvizi, M. M.; Saki, N.; Parvizi, Z.; Mehrbani, M.; Heydari, M. Efficacy of a Topical Formulation of Henna (Lawsonia Inermis Linnaeus) on the Itch and Wound Healing in Patients With Epidermolysis Bullosa: a Pilot Single-arm Clinical Trial. Dermatology Practical & Conceptual. 2022. 12; 3.

NICE [GID-TA10868] Beremagene geperpavec for treating dystrophic epidermolysis bullosa in children, young people and adults [ID3959]. 2022.

NICE [ID3959] Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa.

NL9347 A prospective explorative controlled study on cannabinoids to treat chronic pain in epidermolysis bullosa.. Transvamix (10% THC / 5% CBD) to treat chronic pain in Epidermolysis Bullosa: An explorative randomized, placebo-controlled and double-blind intervention crossover study. 2021.

NL-OMON28210 A prospective explorative controlled study on cannabinoids to treat chronic pain in epidermolysis bullosa.. Transvamix (10% THC / 5% CBD) to treat chronic pain in Epidermolysis Bullosa: An explorative randomized, placebo-controlled and double-blind intervention crossover study. 2021.

NL-OMON41470 Unrelated cord blood transplantation after reduced toxicity conditioning with mesenchymal stromal cell co-infusion in patients with severe epidermolysis bullosa. Unrelated cord blood transplantation after reduced toxicity conditioning with mesenchymal stromal cell co-infusion in patients with severe epidermolysis bullosa - CB+MSCforEB. 2015.

NL-OMON43935 An Open Label Multi-Center Extension Study to Evaluate the Long-term Safety of Zorblisa
(SD-101-6.0) in Patients with Epidermolysis Bullosa
. An Open Label Multi-Center Extension Study to Evaluate the Long-term Safety of Zorblisa
(SD-101-6.0) in Patients with Epidermolysis Bullosa
 - SD-006 Open Label Extension Study. 2016.

NL-OMON46073 A Multi-center Study to Evaluate the Pharmacokinetics of Diacerein and Rhein and the Safety of Diacerein after Maximum Use, Topical Administration of CCP-020 (Diacerein 1% ointment) to Patients with Epidermolysis Bullosa (EB). A Multi-center Study to Evaluate the Pharmacokinetics of Diacerein and Rhein and the Safety of Diacerein after Maximum Use, Topical Administration of CCP-020 (Diacerein 1% ointment) to Patients with Epidermolysis Bullosa (EB) - CCP2101. 2018.

NL-OMON51174 Transvamix (10% THC / 5% CBD) to treat chronic pain in Epidermolysis Bullosa: An explorative randomized, placebo-controlled and double-blind intervention crossover study. Transvamix (10% THC / 5% CBD) to treat chronic pain in Epidermolysis Bullosa: An explorative randomized, placebo-controlled and double-blind intervention crossover study - A study on the effect of Transvamix for pain in adults with EB. 2021.

Okata-Karigane, U.; Pathmarajah, P.; Li, S.; Lu, Y.; Tang, J. Y.; Chiou, A. S. Patient-reported outcome measures for chronic itch in epidermolysis bullosa: An exploratory analysis of a randomized controlled trial. Journal of Investigative Dermatology. 2023. 143; 5: S101-S101.

Paller, A. S.; Browning, J.; Nikolic, M.; Bodemer, C.; Murrell, D. F.; Lenon, W.; Krusinska, E.; Reha, A.; Lagast, H.; Barth, J. A. Efficacy and tolerability of the investigational topical cream SD-101 (6% allantoin) in patients with epidermolysis bullosa: A phase 3, randomized, double-blind, vehicle-controlled trial (ESSENCE study). Orphanet Journal of Rare Diseases. 2020. 15; 1: 158.

Petrof, G.; Martinez-Queipo, M.; Mellerio, J. E.; Kemp, P.; McGrath, J. A. Fibroblast cell therapy enhances initial healing in recessive dystrophic epidermolysis bullosa wounds: Results of a randomized, vehicle-controlled trial. British Journal of Dermatology. 2013. 169; 5: 1025-1033.

Saki, N.; Vahedi, S.; Parvizi, M. M.; Shafie'ei, M.; Hosseini, S. A.; Ahramiyanpour, N. Topical gabapentin 10% in the treatment of epidermolysis bullosa pruritus: A pilot, double-blind, split-site, randomized controlled trial. Dermatologic Therapy. 2022. 35; 10.

Excluded records

Schrader, N. H. B.; Duipmans, J. C.; Renken, R. J.; Soros, P.; Vermeulen, K. M.; Bolling, M. C.; Wolff, A. P. The C4EB study Transvamix (10% THC / 5% CBD) to treat chronic pain in epidermolysis bullosa: a protocol for an explorative randomized, placebo controlled, and double blind intervention crossover study. PloS one. 2022. 17; 45272.

Sharma, A.; Nasi, G.; Zaafouri, S.; Varkhande, S. R.; Klicznik, M. M.; Umundum, K.; Lew, M.; Sophianidis, A.; Schoftner, L. C.; Gerstenberger, A. C.; Hofbauer, J. P.; Guttmann-Gruber, C.; Fortelny, N.; Wallly, V.; Campbell, D. J.; Gratz, I. K. Squamous cell carcinoma in patients with recessive dystrophic epidermolysis bullosa is associated with dysregulated T cell function. Journal of Investigative Dermatology. 2023. 143; (11): S365-S365.

So, J. Y.; Nazaroff, J.; Iwummadu, C. V.; Harris, N.; Gorell, E. S.; Fulchand, S.; Bailey, I.; McCarthy, D.; Siprashvili, Z.; Marinkovich, M. P.; Tang, J. Y.; Chiou, A. S. Long-term safety and efficacy of gene-corrected autologous keratinocyte grafts for recessive dystrophic epidermolysis bullosa. Orphanet Journal of Rare Diseases. 2022. 17; 1.

Spellman, M. A tale of two therapeutic approaches an update on clinical studies in diacerein and FCX-007. Acta dermato-venereologica. 2020. 100; SUPPL 220: 14-15.

Study of Alwextina Cream in Treating Epidermolysis Bullosa.

Study of Effectiveness and Safety of SD-101 in Participants With Epidermolysis Bullosa.

Tang, J. Y.; Marinkovich, M. P.; Wiss, K.; McCarthy, D.; Truesdale, A.; Chiou, A. S.; McIntyre, J. K.; Moore, A.; Grachev, I. 806 Results from VIITAL: a phase 3, randomized, intrapatient-controlled trial of an investigational collagen type VII geneâ€“corrected autologous cell therapy, EB-101, for the treatment of recessive dystrophic epidermolysis bullosa (RDEB). Journal of investigative dermatology. 2023. 143; 5: S138.

Tang, J. Y.; Marinkovich, M. P.; Wiss, K.; McCarthy, D.; Truesdale, A.; Chiou, A. S.; McIntyre, J. K.; Moore, A.; Grachev, I. Results from VIITAL: A phase 3, randomized, intrapatient-controlled trial of an investigational collagen type VII gene-corrected autologous cell therapy, EB-101, for the treatment of recessive dystrophic epidermolysis bullosa (RDEB). Journal of Investigative Dermatology. 2023. 143; (5): S138-S138.

Topical Beremagene Geperpavec (KB103) Gene Therapy to Restore Functional Collagen VII for the Treatment of Dystrophic Epidermolysis Bullosa.

Trial To Assess Efficacy Of A Chimeric Skin In Patients With Epidermolysys Bullosa.

Wang, X. D.; Li, Y. H.; SÃ¡ez, I. L.; Wang, W. X. Non-Viral Gene Editing Therapy for Recessive Dystrophic Epidermolysis Bullosa: CRISPR/Cas9 Mediated COL7A1 Exon 80 Excision. Tissue Engineering Part A. 2023. 29; (13-14).

Woodley, D. T.; Hao, M.; Kwong, A.; Levian, B.; Cogan, J.; Hou, Y.; Mosallaei, D.; Kleinman, E.; Zheng, K.; Chung, C.; Kim, G.; Peng, D.; Chen, M. Intravenous gentamicin therapy induces functional type VII collagen in recessive dystrophic epidermolysis bullosa patients: An open label clinical trial. Br J Dermatol. 2024.

Ineligible outcomes (n=6)

Adams, R. H. A controlled study of vitamin E treatment in epidermolysis bullosa. British journal of dermatology. 1975. 93; Suppl 11: 10.

Jain, S. V.; Harris, A. G.; Su, J. C.; Orchard, D.; Warren, L. J.; McManus, H.; Murrell, D. F. The Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI): grading disease severity and assessing responsiveness to clinical change in epidermolysis bullosa. Journal of the European Academy of Dermatology and Venereology. 2017. 31; 4: 692-698.

Mahajan, R.; Bishnoi, A.; Manjunath, S.; Kumar, A.; Handa, S.; De, D. Application of targeted next-generation sequencing in diagnosing atypical phenotypes and detecting novel genotypes in epidermolysis bullosa. British Journal of Dermatology. 2020. 183: 145-146.

Excluded records

Morisaka, H.; Yoshimi, K.; Okuzaki, Y.; Hotta, A.; Takeda, J.; Mashimo, T.; Sano, S. Possibility of therapeutic application to autosomal dominant dystrophic epidermolysis bullosa using large deletion genome editing with CRISPR-Cas3. Journal of Investigative Dermatology. 2020. 140; 7: S34-S34.

Nihr, Hsric Allantoin (Zorblisa) for lesions associated with epidermolysis bullosa â€“ first line. 2016.

Rennekampff, H.; Fimmers, R.; Metelmann, H.; Schumann, H.e; Tenenhaus, M. Reliability of photographic analysis of wound epithelialization assessed in human skin graft donor sites and epidermolysis bullosa wounds. Trials. 2015. 16: 235.

Ineligible patient population (n=17)

Bolton, L.; McNees, P.; van Rijswijk, L.; de Leon, J.; Lyder, C.; Kobza, L.; Edman, K.; Scheurich, A.; Shannon, R.; Toth, M. Wound-healing outcomes using standardized assessment and care in clinical practice. Journal of wound, ostomy, and continence nursing : official publication of The Wound, Ostomy and Continence Nurses Society / WOCN. 2004. 31; 2: 65-71.

Chiou, A. S.; Choi, S.; Barriga, M.; Dutt-Singkh, Y.; Solis, D. C.; Nazaroff, J.; Bailey-Healy, I.; Li, S.; Shu, K.; Joing, M.; et al. Phase 2 trial of a neurokinin-1 receptor antagonist for the treatment of chronic itch in patients with epidermolysis bullosa: a randomized clinical trial. Journal of the American Academy of Dermatology. 2020. 82; 6: 1415-1421.

Dwiyana, R. F.; Gondokaryono, S. P.; Rahardja, J. I.; Arline Diana, I.; Yogya, Y.; Gunawan, H. Clinical efficacy of dialkylcarbamoylchloride-coated cotton acetate dressing versus combination of normal saline dressing and 2% mupirocin ointment in infected wounds of epidermolysis bullosa. Dermatologic Therapy. 2019. 32; 5: e13047.

Ebens, C. L.; McGrath, J. A.; Riedl, J. A.; Keith, A. R.; Lilja, G.; Rusch, S.; Keene, D. R.; Tufa, S. F.; Riddle, M. J.; Shanley, R.; Van Heest, A. E.; Tolar, J. Immune tolerance of allogeneic haematopoietic cell transplantation supports donor epidermal grafting of recessive dystrophic epidermolysis bullosa chronic wounds*. British Journal of Dermatology. 2021. 184; 6: 1161-1169.

EMA Episalvan. 2022.

EUCTR2020-002358-26-DE. A clinical trial to assess the effect of petrolatum or, respectively, the vehicle for Oleogel-S10 on the skin healing process of healthy volunteers with superficial skin wounds. 2020.

EUCTR2019-002081-12-DE. A clinical trial to assess the effect of Petrolatum, the vehicle for Oleogel-S10 or, respectively, no treatment on the skin healing process of healthy volunteers with superficial skin wounds. 2019.

EUCTR2016-003832-19-AT Clinical Trial to evaluate the efficacy of the drug "Rigosertib" against non-melanoma skin cancer in "Butterfly Children". A Phase II, Open Study to Assess Efficacy and Safety of Rigosertib in Patients with Recessive Dystrophic Epidermolysis bullosa associated Locally Advanced/Metastatic Squamous Cell Carcinoma - Rigosertib for RDEB-SCC. 2017.

ISRCTN60271166. A preliminary single-centre, randomised, comparative study of the Eakin wound dressing in the management of superficial/partial thickness wounds. 2005.

Martini, L.; Reali, U. M.; Borgognoni, L.; Brandani, P.; Andriessen, A. Comparison of two dressings in the management of partial-thickness donor sites. Journal of wound care. 1999. 8; 9: 457-460.

NCT02654483 Neurokinin-1 Receptor Antagonist for the Treatment of Itch in EB Patients. A Phase 2 Trial of Neurokinin-1 Receptor Antagonist for the Treatment of Itch in Epidermolysis Bullosa Patients. 2016.

NCT03836001 A Neurokinin-1 Receptor Antagonist for the Treatment of Pruritus in Patients With Epidermolysis Bullosa. A Neurokinin-1 Receptor Antagonist for the Treatment of Pruritus in Patients With Epidermolysis Bullosa. 2019.

NL8722, INM-755 Cream on Epidermal Wounds. 2020.

Excluded records

Okata-Karigane, U.; Gorell, E.; Sum, K.; Yekrang, K.; Phung, M.; Barriga, M.; Udrizar, P.; Bailey, I.; Li, S.; Tang, J.; Chiou, A. A phase 2 randomized clinical trial of serlopitant, a neurokinin-1 receptor antagonist for the treatment of chronic itch in patients with epidermolysis bullosa. Journal of Investigative Dermatology. 2022. 142; 8: S48-S48.

Rahardja, J. I.; Dwiyana, R. F.; Gondokaryono, S. P.; Diana, I. A. Clinical efficacy of dialkylcarbamoylchloride-coated cotton acetate dressing versus combination of normal saline dressing and 2% mupirocin ointment in infected wounds of epidermolysis bullosa. Journal of the dermatology nurses' association. 2020. 12; 2.

Seo, T.; Natsuga, K.; Takashima, S.; Nohara, T.; Ujiie, H. Clinically revertant skin in epidermolysis bullosa: A single-institute experience. Journal of Investigative Dermatology. 2023. 143; 5: S141-S141.

Yoelin, S. G.; Dhawan, S. S.; Vitarella, D.; Ahmad, W.; Hasan, F.; Abushakra, S. Safety and Efficacy of EB-001, a Novel Type E Botulinum Toxin, in Subjects with Glabellar Frown Lines: results of a Phase 2, Randomized, Placebo-Controlled, Ascending-Dose Study. Plastic and reconstructive surgery. 2018. 142; 6: 847-855e.

Ineligible publication type (n=39)

Abdul-Wahab, A.; Petrof, G.; McGrath, J. A. Bone marrow transplantation in epidermolysis bullosa. Immunotherapy. 2012. 4; 12: 1859-1867.

Alexandroff, A. B.; Harman, K. E. Blistering skin disorders: an evidence-based update. Conference report. British Journal of Dermatology. 2009. 160; 3: 502-504.

Anonymous Clinical trial of Oleogel-S10 (birch bark extract gel) in epidermolysis bullosa. British Journal of Dermatology. 2023. 188; 1: E4.

Ayres Jr, S.; Mihan, R.; Wilson, B. Epidermolysis bullosa: Vitamin E as an effective treatment. Journal of the American Academy of Dermatology. 1981. 4; 4: 482-483.

Bohbot, Serge Management of Epidermolysis Bullosa With a Lipidocolloid Contact Layer. Ostomy Wound Management. 2018. 64; 12: 45207.

Chan, J. M.; Weisman, A.; King, A.; Maksomski, S.; Shotwell, C.; Bailie, C.; Weaver, H.; Bodan, R.; Guerrero, E.; Zmazek, M.; Khuu, P. Occupational therapy for epidermolysis bullosa: Clinical practice guidelines. Orphanet Journal of Rare Diseases. 2019. 14; 1: 129.

Chiaverini, C.; Roger, C.; Fontas, E.; Bourrat, E.; Bourdon-Lanoy, E.; Labreze, C.; Mazereeuw, J.; Vabres, P.; Bodemer, C.; Lacour, J. Oral epigallocatechin-3-gallate for treatment of dystrophic epidermolysis bullosa: a multicentre, randomized, crossover, double-blind, placebo-controlled clinical trial. Orphanet journal of rare diseases. 2016. 11: 31.

De Luca, M.; Aiuti, A.; Cossu, G.; Parmar, M.; Pellegrini, G.; Robey, P. G. Advances in stem cell research and therapeutic development. Nature Cell Biology. 2019. 21; 7: 801-811.

De Rosa, L.; Carulli, S.; Cocchiarella, F.; Quaglino, D.; Enzo, E.; Franchini, E.; Giannetti, A.; De Santis, G.; Recchia, A.; Pellegrini, G.; De Luca, M. Long-term stability and safety of transgenic cultured epidermal stem cells in gene therapy of junctional epidermolysis bullosa. Stem Cell Reports. 2014. 2; 1: 45139.

Dellambra, E.; Pellegrini, G.; Guerra, L.; Ferrari, G.; Zambruno, G.; Mavilio, F.; De Luca, M. Toward epidermal stem cell-mediated ex vivo gene therapy of junctional epidermolysis bullosa. Human Gene Therapy. 2000. 11; 16: 2283-2287.

Dunnill, M. G. S.; Eady, R. A. J. The management of dystrophic epidermolysis-bullosa. Clinical and Experimental Dermatology. 1995. 20; 3: 179-188.

El Hachem, M.; Zambruno, G.; Bourdon-Lanoy, E.; Ciasulli, A.; Buisson, C.; Hadj-Rabia, S.; Diociaiuti, A.; Gouveia, C. F.; Hernandez-Martin, A.; De Lucas Laguna, R.; Dolenc-Voljc, M.; Tadini, G.; Salvatori, G.; De Ranieri, C.; Leclerc-Mercier, S.; Bodemer, C. Multicentre consensus recommendations for skin care in inherited epidermolysis bullosa. Orphanet Journal of Rare Diseases. 2014. 9; 1: 76.

Excluded records

Fujita, Y.; Nohara, T.; Takashima, S.; Natsuga, K.; Adachi, M.; Yoshida, K.; Shinkuma, S.; Takeichi, T.; Nakamura, H.; Wada, O.; Akiyama, M.; Ishiko, A.; Shimizu, H. Intravenous allogeneic multilineage-differentiating stress-enduring cells in adults with dystrophic epidermolysis bullosa: a phase 1/2 open-label study. Journal of the European Academy of Dermatology and Venereology. 2021. 35; 8: e528-e531.

Garcia-Doval, I.; Davila-Seijo, P.; Langan, S. M. Updated systematic review of randomized controlled trials of treatments for inherited forms of epidermolysis bullosa. Clinical and Experimental Dermatology. 2013. 38; 1: 92-94.

Gaucher, S.; Lwin, S. M.; Titeux, M.; Abdul-Wahab, A.; Pironon, N.; Izmiryan, A.; Miskinyte, S.; Ganier, C.; Duchatelet, S.; Mellerio, J. E.; Bourrat, E.; McGrath, J. A.; Hovnanian, A. EBGene trial: patient preselection outcomes for the European GENEGRAFT ex vivo phase I/II gene therapy trial for recessive dystrophic epidermolysis bullosa. British Journal of Dermatology. 2020. 182; 3: 794-797.

Has, C. Molecular therapies for inherited epidermolysis bullosa. Giornale Italiano Di Dermatologia E Venereologia. 2016. 151; 4: 397-402.

Has, C.; South, A.; Uitto, J. Molecular Therapeutics in Development for Epidermolysis Bullosa: Update 2020. Molecular Diagnosis & Therapy. 2020. 24; 3: 299-309.

Hasegawa, T.; Suga, Y.; Mizoguchi, M.; Ikeda, S.; Ogawa, H.; Kubo, K.; Matsui, H.; Kagawa, S.; Kuroyanagi, Y. Clinical trial of allogeneic cultured dermal substitute for the treatment of intractable skin ulcers in 3 patients with recessive dystrophic epidermolysis bullosa [9]. Journal of the American Academy of Dermatology. 2004. 50; 5: 803-804.

Hilton, L. Pipeline progress in epidermolysis bullosa. Dermatology Times. 2020. 41; 6: 47-51.

Ilic, D.; Vicovac, L.; Nikolic, M.; Ilic, E. L. Human amniotic membrane grafts in therapy of chronic non-healing wounds. British Medical Bulletin. 2016. 117; 1: 59-67.

Jarratt, M. Diagnosis and treatment of epidermolysis bullosa. Southern Medical Journal. 1976. 69; 1: 113-117.

Jayarajan, V.; Kounatidou, E.; Qasim, W.; Di, W. L. Ex vivo gene modification therapy for genetic skin diseases-recent advances in gene modification technologies and delivery. Experimental Dermatology. 2021. 30; 7: 887-896.

Khan, A.; Riaz, R.; Ashraf, S.; Akilimali, A. Revolutionary breakthrough: FDA approves Vyjuvek, the first topical gene therapy for dystrophic epidermolysis bullosa. Ann Med Surg (Lond). 2023. 85; (12): 6298-6301.

Keith, A. R.; Twaroski, K.; Ebens, C. L.; Tolar, J. Leading edge: emerging drug, cell, and gene therapies for junctional epidermolysis bullosa. Expert Opinion on Biological Therapy. 2020. 20; 8: 911-923.

Kiuru, M.; Itoh, M.; Cairo, M. S.; Christiano, A. M. Bone marrow stem cell therapy for recessive dystrophic epidermolysis bullosa. Dermatologic Clinics. 2010. 28; 2: 371-382.

Langan, S. M.; Williams, H. C. A systematic review of randomised controlled trials of treatments for inherited forms of epidermolysis bullosa. Journal of Investigative Dermatology. 2006. 126: 106-106.

Li, Y.; Shen, J.; Liang, J.; Zheng, L.; Chen, F.; Yao, Z.; Li, M. Gentamicin induces COL17A1 nonsense mutation readthrough in junctional epidermolysis bullosa. Journal of Dermatology. 2020. 47; 3: e82-e83.

McNamara, S. A.; Hirt, P. A.; Weigelt, M. A.; Nanda, S.; de Bedout, V.; Kirsner, R. S.; Schachner, L. A. Traditional and advanced therapeutic modalities for wounds in the paediatric population: An evidence-based review. Journal of Wound Care. 2020. 29; 6: 321-334.

Naso, G.; Petrova, A. Cellular therapy options for genetic skin disorders with a focus on recessive dystrophic epidermolysis bullosa. British Medical Bulletin. 2020. 136; 1: 30-45.

Nihr, H. S. C. ICX-RHY (Vavelta) for recessive dystrophic epidermolysis bullosa - second line. 2012.

Excluded records

Payne, A. S. Topical Gene Therapy for Epidermolysis Bullosa. New England Journal of Medicine. 2022. 387; 24: 2281-2284.

Petrof, G.; Lwin, S. M.; Martinez-Queipo, M.; Abdul-Wahab, A.; Tso, S.; Mellerio, J. E.; Slaper-Cortenbach, I.; Boelens, J. J.; Tolar, J.; Veys, P.; Ofuya, M.; Peacock, J. L.; Martinez, A. E.; McGrath, J. A. Potential of Systemic Allogeneic Mesenchymal Stromal Cell Therapy for Children with Recessive Dystrophic Epidermolysis Bullosa. Journal of Investigative Dermatology. 2015. 135; 9: 2319-2321.

Phase I/II Ex Vivo Gene Therapy Clinical Trial for Recessive Dystrophic Epidermolysis Bullosa Using Skin Equivalent Grafts Genetically Corrected with a COL7A1-Encoding SIN Retroviral Vector (GENEGRAFT). Human Gene Therapy Clinical Development. 2014. 25; 2: 65-66.

Raoufinia, R.; Rahimi, H. R.; Keyhanvar, N.; Moghbeli, M.; Abdyazdani, N.; Rostami, M.; Naghipoor, K.; Forouzanfar, F.; Foroudi, S.; Saburi, E. Advances in Treatments for Epidermolysis Bullosa (EB): Emphasis on Stem Cell-Based Therapy. Stem Cell Rev Rep. 2024.

Rashidghamat, E.; McGrath, J. A. Novel and emerging therapies in the treatment of recessive dystrophic epidermolysis bullosa. Intractable Rare Dis Res. 2017. 6; 1: 43983.

Schaffer, D. V. The Coming of Age of Topical Gene Therapy for Dystrophic Epidermolysis Bullosa. New England Journal of Medicine. 2022. 387; 24: 2279-2280.

Scheffler, A. The Wound Healing Properties of Betulin from Birch Bark from Bench to Bedside. Planta Medica. 2019. 85; 7: 524-527.

Schwieger-Briel, A.; Ott, H.; Kiritsi, D.; Laszczyk-Lauer, M.; Bodemer, C. Mechanism of Oleogel-S10: A triterpene preparation for the treatment of epidermolysis bullosa. Dermatologic Therapy. 2019. 32; 4: e12983.

Shinkuma, S. Advances in gene therapy and their application to skin diseases: A review. Journal of Dermatological Science. 2021. 103; 1: 45171.

Wang, S.; Yang, Z.; Liu, Y.; Zhao, M. T.; Zhao, J.; Zhang, H.; Liu, Z. Y.; Wang, X. L.; Ma, L.; Yang, Y. H. Application of topical gentamicin-a new era in the treatment of genodermatosis. World Journal of Pediatrics. 2021. 17; 6: 568-575.

Yan, W. F.; Murrell, D. F. Fibroblast-Based Cell Therapy. Strategy for Recessive Dystrophic Epidermolysis Bullosa. Dermatologic Clinics. 2010. 28; 2: 367.

Ineligible study design (n=85)

2014-004500-30 A phase I/II study evaluating allogeneic mesenchymal stromal cells in adults with recessive dystrophic epidermolysis bullosa

2017-000606-37 Safety and preliminary efficacy study of infusing mesenchymal stem cells derived from bone marrow for treating Recessive Dystrophic Epidermolysis Bullosa.

A Follow-up Study to Evaluate the Efficacy and Safety of ALLO-ASC-DFU in ALLO-ASC-EB-101 Clinical Trial.

ACTRN12610000760077 Investigation of cell therapy for recessive dystrophic epidermolysis bullosa (RDEB) in Australia through intradermal injection of allogeneic fibroblasts.. In adult patients with recessive dystrophic epidermolysis bullosa (RDEB), are intradermal allogeneic cultured fibroblast wound injections in transport solution (Plasmalyte and 2% albumex) more effective than a placebo in promoting wound healing and collag. 2010.

Autologous Transplantation of Cultured Fibroblast on Amniotic Membrane in Patients With Epidermolysis Bullosa.

Banky, J. P.; Sheridan, A. T.; Storer, E. L.; Marshman, G. Successful treatment of epidermolysis bullosa pruriginosa with topical tacrolimus. Archives of Dermatology. 2004. 140; 7: 794-796.

Excluded records

Barbier, M. A.; Piaceski, A. D.; Larouche, D.; Ghani, K.; Pope, E.; Caruso, M.; Germain, L. Ex vivo gene therapy of recessive dystrophic epidermolysis bullosa skin cells leads to dermo-epidermal adhesion strength restoration in autologous bilayered self-assembled skin substitutes. Journal of Investigative Dermatology. 2023. 143; 5: S143-S143.

Bellon, N.; Polivka, L.; Hadj-Rabia, S.; Bodemer, C. WCRSD2200078 Experience of dupilumab treatment for pruritic genodermatoses in a French referral center. WCRSD. 2022.

Boulanger, E.; Catteau, B.; Pagniez, D.; Ferrier, M. L.; Roueff, S.; Reade, R.; Bergoend, H.; Dequiedt, P. Recessive dystrophic epidermolysis bullosa and IgA glomerulonephritis. Clinical Nephrology. 1998. 49; 1: 68-68.

Brooks, I.; Zebrowska, P.; Laczmanski, L.; McGrath, J. A.; Jackow, J. Optimising specificity and applicability of base editing for COL7A1 mutations in recessive dystrophic epidermolysis bullosa. Journal of Investigative Dermatology. 2022. 142; 12: S229-S229.

ChiCTR1900021437 Clinical study for omalizumab in the treatment of hereditary bullous epidermolysis. Clinical study for omalizumab in the treatment of hereditary bullous epidermolysis. 2019.

ChiCTR2000036109 Safety and Preliminary Efficacy Study of Engineered Epidermal Autograft in Patients with Recessive Dystrophic Epidermolysis Bullosa (RDEB). Safety and Preliminary Efficacy Study of Engineered Epidermal Autograft in Patients with Recessive Dystrophic Epidermolysis Bullosa (RDEB). 2020.

Cooper, T. W.; Bauer, E. A. Therapeutic efficacy of phenytoin in recessive dystrophic epidermolysis: a comparison of short and long-term treatment. Indian journal of dermatology, venerology and leprology. 1984. 50: 176.

De Brito Caldeira, J.; Lacerda e Costa, M. H. Epidermolysis bullosa hereditaria. Clinical trial with fluocinonide FAPG 0.05 percent in five cases. Acta dermato-venereologica. Supplementum. 1971. 52; 67: 88-90.

Desai, A. D.; Soliman, Y.; Behbahani, S. Epidermolysis bullosa in the pediatric population: Analysis of the KID database. Journal of the American Academy of Dermatology. 2022. 87; 3: AB55-AB55.

Dimitrievska, M.; McGrath, J. A.; Jackow, J. High efficiency and safe base editor correction of recurrent COL7A1 mutations underlying dominant dystrophic epidermolysis bullosa. Journal of Investigative Dermatology. 2022. 142; 12: S231-S231.

Dorfer, S.; Ablinger, M.; Wimmer, M.; Ibrahimpasic, S.; Illmer, J.; Bauer, J. W.; Zauner, R.; Wally, V. Investigating the potential of repurposing diacerein for the treatment of cutaneous wounds in recessive dystrophic epidermolysis bullosa. Journal of Investigative Dermatology. 2023. 143; (11): S363-S363.

DRKS00006565 A Prospective Short-term Study to Evaluate Methodologies for the Assessment of Disease Extent, Impact, and Wound Evolution in Patients With Dystrophic Epidermolysis Bullosa (DEB). A Prospective Short-term Study to Evaluate Methodologies for the Assessment of Disease Extent, Impact, and Wound Evolution in Patients With Dystrophic Epidermolysis Bullosa (DEB). 2014.

DRKS00024070 Defect closure with keratinocytes grafts from revertant mosaicism areals in patients suffering from epidermolysis bullosa. Defect closure with keratinocytes grafts from revertant mosaicism areals in patients suffering from epidermolysis bullosa - REGRAFT EB. 2021.

Eichstadt, S.; Barriga, M.; Ponakala, A.; Teng, C.; Nguyen, N.T.; Siprashvili, Z.; Nazaroff, J.; Gorell, E.S.; Chiou, A. S.; Taylor, L.; Khuu, P.; Keene, D.R.; Rieger, K.; Khosla, R.K.; Furukawa, L.K.; Lorenz, H.P.; Marinkovich, M.P; Tang, J.Y. Phase 1/2a clinical trial of gene-corrected autologous cell therapy for recessive dystrophic epidermolysis bullosa. JCI insight. 2019. 4; 19.

Eisenberg, M. The effect of occlusive dressings on re-epithelializations of wounds in children with epidermolysis bullosa. Journal of Pediatric Surgery. 1986. 21; 10: 892-894.

Excluded records

El-Darouti, M. A.; Fawzy, M. M.; Amin, I. M.; Abdel Hay, R. M.; Hegazy, R. A.; Abdel Halim, D. M. Mycophenolate mofetil: A novel immunosuppressant in the treatment of dystrophic epidermolysis bullosa, a randomized controlled trial. Journal of Dermatological Treatment. 2013. 24; 6: 422-426.

El-Darouti, M.; Fawzy, M.; Amin, I.; Abdel Hay, R.; Hegazy, R.; Gabr, H.; El Maadawi, Z. Treatment of dystrophic epidermolysis bullosa with bone marrow non-hematopoeitic stem cells: A randomized controlled trial. Dermatologic Therapy. 2016. 29; 2: 96-100.

EUCTR2010-019945-24-DE Open, Prospective, Controlled Case series Documentation to Compare Intra-individually the Efficacy and Tolerance of Sericare versus Non-adhesive Wound Dressing alone in Accelerating the Epithelialization of Skin lesions of Patients with Epidermolysis bull. 2010.

EUCTR2014-004884-19-GB Gene Therapy Trial in adults with Inherited Blistering Skin Disease. Phase I study of lentiviral-mediated COL7A1 gene-modified autologous fibroblasts in adults with recessive dystrophic epidermolysis bullosa (RDEB) - LENTICOL-F. 2015.

EUCTR2018-000439-29-GB A Multi-center Study to Evaluate How CCP-020 (Diacerein 1% ointment) is Absorbed in the Blood and Removed from the Body in Patients with Epidermolysis Bullosa (EB). 2018.

Falabella, A. F.; Valencia, I. C.; Eaglstein, W. H.; Schachner, L. A. Tissue-engineered skin (Apligraf) in the healing of patients with epidermolysis bullosa wounds. Archives of Dermatology. 2000. 136; 10: 1225-1230.

Fine, J.; Manes, B.; Frangoul, H. Systemic granulocyte colony-stimulating factor (G-CSF) enhances wound healing in dystrophic epidermolysis bullosa (DEB): Results of a pilot trial. Journal of the American Academy of Dermatology. 2015. 73; 1: 56-61.

Fulchand, S.; Harris, N.; Li, S.; So, J.; Nazaroff, J.; Tang, J. Assessing the natural history of recessive dystrophic epidermolysis bullosa wounds using a home photography app. Journal of Investigative Dermatology. 2022. 142; 8: S131-S131.

Gelmetti, A.; Greppi, N.; Guez, S.; Grassi, F.; Rebulla, P.; Tadini, G. Cord blood platelet gel for the treatment of inherited epidermolysis bullosa. Transfusion and Apheresis Science. 2018. 57; 3: 370-373.

Gorell, E. S.; Leung, T. H.; Khuu, P.; Lane, A. T. Purified type I collagen wound matrix improves chronic wound healing in patients with recessive dystrophic epidermolysis bullosa. Pediatric Dermatology. 2015. 32; 2: 220-225.

Hou, P.; Tu, W.; Wang, H.; Yang, H.; Huang, H.; Lin, C.; McGrath, J. A.; Hsu, C. LB732 Intravenous gentamicin therapy in adult junctional and recessive dystrophic Epidermolysis Bullosa with nonsense mutations does not result in sustained clinical improvement. Journal of Investigative Dermatology. 2021. 141; 9: B8.

Huang, H.; Aala, W. F.; Onoufriadis, A.; Hsu, C.; McGrath, J. A. Methotrexate improves pruritus in patients with recessive dystrophic epidermolysis bullosa. Journal of Investigative Dermatology. 2023. 143; 5: S141-S141.

Ikeda, S.; Manabe, M.; Muramatsu, T.; Takamori, K.; Ogawa, H. Protease inhibitor therapy for recessive dystrophic epidermolysis bullosa. In vitro effect and clinical trial with camostat mesylate. Journal of the American Academy of Dermatology. 1988. 18; 6: 1246-1252.

Izmiryan, A.; Berthault, C.; Gouin, O.; Chen, M.; Woodley, D.; Gaucher, S.; Hovnanian, A. Efficient ex-vivo COL7A1 correction of patient's primary keratinocytes and fibroblasts using RNP-based CRISPR/Cas9 and homology-directed repair to treat recessive dystrophic epidermolysis bullosa. Journal of Investigative Dermatology. 2022. 142; 8: S81-S81.

Jones, E.; Marsh, S.; O'Shaughnessy, R.; Aumailley, M.; McGrath, J. A.; O'Toole, E. A.; Caley, M. P. Junctional Epidermolysis Bullosa:Repairing The Epidermal Skin Barrier. Journal of Investigative Dermatology. 2022. 142; 12: S213-S213.

Kida, M.; Wu, M.; Cole, P.; Falang, V.; Sharov , A.; Alan, R. 816 Dual LSD1/HDAC inhibition accelerates skin wound healing. 2020.

Excluded records

Kwong, A.; Cogan, J.; Hou, Y.; Antaya, R.; Hao, M.; Kim, G.; Lincoln, V.; Chen, Q.; Woodley, D. T.; Chen, M. Gentamicin Induces Laminin 332 and Improves Wound Healing in Junctional Epidermolysis Bullosa Patients with Nonsense Mutations. Molecular Therapy. 2020. 28; 5: 1327-1338.

Lee, S. J.; Kim, K.; Cho, B.; Roh, K.; Kim, S. C.; Lee, S. E. Safety and clinical effects of systemic allogeneic ucb-mscs therapy for patients with RDEB. Acta Dermato-Venereologica. 2020. 100; SUPPL 220: 68.

Lee, S.; Kim, K.; Cho, B.; Roh, K.; Kim, S. 307 Safety and clinical effects of systemic allogeneic UCB-MSCs therapy for patients with RDEB. Journal of Investigative Dermatology. 2020. 140; 7 Supplement: S38.

Lee, S.E.; Lee, S.; Kim, S.; Kim, K.; Cho, B.; Roh, K.; Kim, S. Intravenous allogeneic umbilical cord blood-derived mesenchymal stem cell therapy in recessive dystrophic epidermolysis bullosa patients. JCI insight. 2021. 6; 2.

Levian, B. A.; Mosallaei, D.; Antaya, R.; Woodley, D.; Chen, M. Optimization of intravenous gentamicin to restore functional laminin 332 in junctional epidermolysis bullosa patients harboring nonsense mutations. Journal of Investigative Dermatology. 2022. 142; 8: S147-S147.

Liemberger, B.; Bischof, J.; Kocher, T.; Ablinger, M.; Murauer, E. M.; Nystrom, A.; Wally, V.; Mayr, E.; Koller, U.; Bauer, J. Non-viral COL7A1 editing as therapy approach for dystrophic epidermolysis bullosa. Journal of Investigative Dermatology. 2023. 143; 5: S151-S151.

Liemberger, B.; Bischof, J.; Kocher, T.; Ablinger, M.; Murauer, E.; Nystrom, A.; Wally, V.; Mayr, E.; Bauer, J.; Koller, U. Development of a non-invasive, non-viral RNA therapy approach for dystrophic epidermolysis bullosa. Journal of Investigative Dermatology. 2022. 142; 12: S229-S229.

Malta, M. D.; Fernandes, M. G.; Andre, A.; Martins, P.; Pires, R. A.; Osorio, H.; Guttmann-Gruber, C.; Kocher, T.; Cerqueira, M. T.; Marques, A. P. Biological and mechanical unique extracellular matrix among different subtypes of dystrophic epidermolysis bullosa. Tissue Engineering Part A. 2023. 29; 45271: 383-384.

Marinkovich, M. P.; Sridhar, K.; Karkala, V.; Yenamandra, V. K.; Gurevitch, I.; Dolorito, J.; Bagci, I. S.; O'Mara, C.; Ramsdell, D.; Landy, H. 306 Topical QR-313, an Antisense Oligonucleotide, in the Treatment of Dystrophic Epidermolysis Bullosa. Journal of Investigative Dermatology. 2020. 140; 7: S37.

Martin, K.; Geuens, S.; Asche, J. K.; Bodan, R.; Browne, F.; Downe, A.; Garcia Garcia, N.; Jaega, G.; Kennedy, B.; Mauritz, P. J.; Perez, F.; Soon, K.; Zmazek, V.; Mayre-Chilton, K. M. Psychosocial recommendations for the care of children and adults with epidermolysis bullosa and their family: Evidence based guidelines. Orphanet Journal of Rare Diseases. 2019. 14; 1: 133.

Matsumura, W.; Fujita, Y.; Shinkuma, S.; Suzuki, S.; Yokoshiki, S.; Goto, H.; Hayashi, H.; Ono, K.; Inoie, M.; Takashima, S.; Nakayama, C.; Nomura, T.; Nakamura, H.; Abe, R.; Sato, N.; Shimizu, H. Cultured Epidermal Autografts from Clinically Revertant Skin as a Potential Wound Treatment for Recessive Dystrophic Epidermolysis Bullosa. Journal of Investigative Dermatology. 2019. 139; 10: 2115.

Mondon, G.; Brunel, K.; Vieira-Rodrigues, D.; Turczynski, S.; Garcia, L.; Titeux, M.; Hovnanian, A. Targeted exon skipping using conjugated tricycloDNA antisense oligonucleotides: A therapeutic strategy for recessive dystrophic epidermolysis bullosa. Human Gene Therapy. 2022. 33; 23-24: A187-A187.

Moravvej, H.; Abdollahimajd, F.; Naseh, M. H.; Piravar, Z.; Abolhasani, E.; Mozafari, N.; Niknejad, H. Cultured allogeneic fibroblast injection vs. fibroblasts cultured on amniotic membrane scaffold for dystrophic epidermolysis bullosa treatment. British Journal of Dermatology. 2018. 179; 1: 72-79.

Moravvej, H.; Abdollahimajd, F.; Naseh, M. H.; Piravar, Z.; Abolhasani, E.; Mozaffari, N.; Niknejad, H. Cultured allogeneic fibroblast injection vs. fibroblasts cultured on amniotic membrane scaffold for dystrophic epidermolysis bullosa treatment. Journal of the Dermatology Nurses' Association. 2020. 12; 2.

Excluded records

Mosallaei, D.; Hao, M.; Antaya, R. J.; Levian, B.; Kwong, A.; Cogan, J.; Hamilton, C.; Schwieger-Briel, A.; Tan, C.; Tang, X.; Woodley, D. T.; Chen, M. Molecular and Clinical Outcomes After Intravenous Gentamicin Treatment for Patients With Junctional Epidermolysis Bullosa Caused by Nonsense Variants. JAMA Dermatology. 2022. 158; 4: 366-374.

Natsuga, K.; Sawamura, D.; Goto, M.; Homma, E.; Goto-Ohguchi, Y.; Aoyagi, S.; Akiyama, M.; Kuroyanagi, Y.; Shimizu, H. Response of Intractable Skin Ulcers in Recessive Dystrophic Epidermolysis Bullosa Patients to an Allogeneic Cultured Dermal Substitute. Acta Dermato-Venereologica. 2010. 90; 2: 165-169.

NCT01263379 Gene Transfer for Recessive Dystrophic Epidermolysis Bullosa.

NCT01538862 Efficacy of Granulocyte Colony Stimulating Factor (GCSF) In Patients With Dystrophic Epidermolysis Bullosa.

NCT02698735 Gentamicin Therapy for Recessive Dystrophic Epidermolysis Bullosa (RDEB) Nonsense Mutation Patients.

NCT03012191 Gentamicin for RDEB.

NCT04917887 Long-Term Follow-up Protocol.

Negru, M.; Sandoval, D. M.; He, Z. L.; Li, Y. H.; Saez, I. L.; Wang, W. X. Type vii collagen evaluation in recessive dystrophic epidermolysis bullosa human skin equivalents following non-viral vector gene therapy. Tissue engineering part a. 2023. 29; 45271: 978-979.

NL-OMON34434 Characteristics of Patients with Dystrophic Epidermolysis Bullosa. Characteristics of Patients with Dystrophic Epidermolysis Bullosa - Characteristics of DEB. 2010.

Oleogel-S10 in Wound Healing of Inherited Epidermolysis Bullosa (BEB-10).

Papanikolaou, M.; Pink, A. E.; Smith, C. H.; McGrath, J. A. Success of dupilumab in itchy recessive dystrophic epidermolysis bullosa of non-pruriginosa subtype. Journal of the American Academy of Dermatology. 2023. 89; (3): AB226-AB226.

Parzymies, P.; Jones, E. M.; Mayes, A.; Messenger, D.; O'Toole, E.; Caley, M. Junctional epidermolysis bullosa: repairing the epidermal lipid barrier. British Journal of Dermatology. 2023. 189; 1: E11-E11.

Petkovic, I.; Bischof, J.; Kocher, T.; March, O.; Liemberger, B.; Hainzl, S.; Strunk, D.; Binder, H.; Bauer, J.; Koller, U. Traceless, homology-directed repair-mediated gene editing for junctional epidermolysis bullosa. Journal of Investigative Dermatology. 2022. 142; 12: S229-S229.

Pliszczynski, J.; Nita, M.; Kowalewski, C.; Wozniak, K.; Eljaszewicz, A.; Moniuszko, M.; Kaminski, A.; Sladowski, D.; Zimek, Z.; Majewski, S.; Kosieradzki, M.; Fiedor, P. Transplantation of a New Biological Product in Rare Diseases, Such as Epidermolysis Bullosa: Response and Clinical Outcome. Transplantation Proceedings. 2020. 52; 7: 2239-2243.

Popa, L.; Andreescu, N.; Zimbru, C.; Chirita-Emandi, A.; Farcas, S.; Chilom, D.; Puiu, M. Epidermolysis Bullosa: Literature Review and Three Case Presentation. European Journal of Human Genetics. 2023. 31: 130-131.

Rashidghamat, E.; Kadiyirire, T.; Ayis, S.; Petrof, G.; Liu, L.; Pullabhatla, V.; Ainali, C.; Guy, A.; Aristodemou, S.; McMillan, J. R.; Ozoemena, L.; Mee, J.; Pramanik, R.; Saxena, A.; Nuamah, R.; de Rinaldis, E.; Serrano, S.; Maurin, C.; Martinez-Queipo, M.; Lwin, S. M.; Ilic, D.; Martinez, A.; Dazzi, F.; Slaper-Cortenbach, I.; Westinga, K.; Zeddies, S.; van den Broek, M.; Onoufriadis, A.; Mellerio, J. E.; McGrath, J. A. Phase I/II open-label trial of intravenous allogeneic mesenchymal stromal cell therapy in adults with recessive dystrophic epidermolysis bullosa. Journal of the American Academy of Dermatology. 2020. 83; 2: 447-454.

Sabater, A. L.; Tovar, A.; Gomez, J.; Parry, T.; Chen, H.; Agostini, B.; Krishnan, S. Compassionate use of topical beremagene geperpavec (B-VEC) for the treatment of recurrent cicatrizing conjunctivitis in a patient with dystrophic epidermolysis bullosa. Investigative Ophthalmology & Visual Science. 2023. 64; (8).

Excluded records

Safety and Effectiveness Study of Allogeneic Umbilical Cord Blood-derived Mesenchymal Stem Cell in Patients With RDEB.

Safety, Tolerability, and Pharmacokinetics of Ascending Topical Doses of TCP-25 Applied to Epidermal Suction Blister Wounds, Non-Healing Leg Ulcers and Patients With Dystrophic Epidermolysis Bullosa.

Schwieger-Briel, A.; Kiritsi, D.; Schempp, C.; Has, C.; Schumann, H. Betulin-based oleogel to improve wound healing in dystrophic epidermolysis bullosa: A prospective controlled proof-of-concept study. Dermatology Research and Practice. 2017. 2017: 5068969.

Self-Assembled Skin Substitute for the Treatment of Epidermolysis Bullosa.

Shehadeh, W.; Sarig, O.; Bar, J.; Sprecher, E.; Samuelov, L. Treatment of epidermolysis bullosa pruriginosa-associated pruritus with dupilumab. Acta Dermato-Venereologica. 2020. 100; SUPPL 220: 77-78.

Siprashvili, Z.; Nguyen, N. T.; Gorell, E. S.; Loutit, K.; Khuu, P.; Furukawa, L. K.; Lorenz, H. P.; Leung, T. H.; Keene, D. R.; Rieger, K. E.; et al. Safety andwound outcomes following genetically corrected autologous epidermal grafts in patients with recessive dystrophic epidermolysis bullosa. JAMA - journal of the american medical association. 2016. 316; 17: 1808-1817.

Sivesind, T.E.; Maghfour, J.; Rietcheck, H.; Kamel, K.; Malik, A.S.; Dellavalle, R.P. Cannabinoids for the Treatment of Dermatologic Conditions. JID innovations: skin science from molecules to population health. 2022. 2; 2: 100095.

Smith, E. B.; Michener, W. M. Vitamin E treatment of dermolytic bullous dermatosis: a controlled study. Archives of dermatology. 1973. 108; 2: 254-6.

So, J.; Iwummadu, V.; Nazaroff, J.; Bailey, I.; McCarthy, D.; Mirza, M.; Tang, J.; Chiou, A. 273 Long-term efficacy and safety of investigational autologous gene- corrected skin sheets (EB-101) for recessive dystrophic epidermolysis bullosa (RDEB). SID. 2022.

Study of Cellutome System for Treatment of Individual Lesions in EB Pts.

Study to Evaluate the Safety of ALLO-ASC-DFU in the Subjects With Dystrophic Epidermolysis Bullosa.

Supp, D. M.; Blackstone, B. N.; Hahn, J. M.; Powell, H. M. Rete ridges improve epidermal adhesion in engineered skin substitutes containing recessive dystrophic epidermolysis bullosa (RDEB) keratinocytes and normal or RDEB fibroblasts. Journal of Investigative Dermatology. 2022. 142; 8: S145-S145.

Syed, F.; Georgiadis, C.; Abdul-Wahab, A.; Petrova, A.; Ghani, S.; Thrasher, A.; McGrath, J.; Di, W. L.; Qasim, W. Lentiviral-Mediated COL7A1 Gene Modified Autologous Fibroblast Therapy for Recessive Dystrophic Epidermolysis Bullosa (RDEB): Preparations for Phase-I Clinical Trials. Molecular Therapy. 2014. 22: S283-S283.

Tang, J. Y.; Peter Marinkovich, M.; Barriga, M.; Bailey, I.; Harris, N.; Fulchand, S.; McCarthy, D.; Rudin, D. Long-term healing, pain reduction, and patient-reported outcomes in recessive dystrophic epidermolysis bullosa (RDEB) following EB-101 treatment of large, chronic wounds. Pediatric Dermatology. 2021. 38; 5: 1433.

Tang, J.; Marinkovich, M.; Barriga, M.; Bailey, I.; Harris, N.; Rudin, D. 173 Patient reported outcomes following EB-101 treatment of recessive dystrophic epidermolysis bullosa (rdeb) wounds showed durable wound healing and reduction in disease burden. Journal of Investigative Dermatology. 2021. 141; 5: S31.

To Evaluate the Pharmacokinetic of Diacerein and Rhein After Maximum Use in Patients With Epidermolysis Bullosa (EB).

Treatment of Chronic and Non-Chronic Wounds in Patients With Recessive Dystrophic Epidermolysis Bullosa Using Helicoll Collagen Dressings Versus Standard of Care.

Excluded records

Venugopal, S. S.; Intong, L. R.; Cohn, H. I.; Mather-Hillon, J.; Murrell, D. F. Responsiveness of nonHerlitz Junctional Epidermolysis Bullosa to topical gentian violet. International Journal of Dermatology. 2010. 49; 11: 1282-1285.

Venugopal, S.S.; Yan, W.; Frew, J. W.; Cohn, H. I.; Rhodes, L. M.; Tran, K.; Melbourne, W.; Nelson, J. A.; Sturm, M.; Fogarty, J.; et al. A phase II randomized vehicle-controlled trial of intradermal allogeneic fibroblasts for recessive dystrophic epidermolysis bullosa. Journal of the American Academy of Dermatology. 2013. 69; 6: 898-908.e7.

Wally, V.; Reisenberger, M.; Kitzmuller, S.; Laimer, M. Small molecule drug development for rare genodermatoses - evaluation of the current status in epidermolysis bullosa. Orphanet Journal of Rare Diseases. 2020. 15; 1: 292.

Wang, X. Q.; Li, Y. H.; He, Z. L.; Sandoval, D. M.; Lara-Saez, I.; Wang, W. X. Non-viral gene therapy for recessive dystrophic epidermolysis bullosa: hyper branched aminated polyesters mediated minicircle dna delivery. Tissue Engineering Part A. 2023. 29; 45271: 1296-1296.

Welponer, T.; Prodinger, C.; Pinon-Hofbauer, J.; Hintersteininger, A.; Breitenbach-Koller, H.; Bauer, J. W.; Laimer, M. Clinical Perspectives of Gene-Targeted Therapies for Epidermolysis Bullosa. Dermatology and Therapy. 2021. 11; 4: 1175-1197.

Woodley, D. T.; Cogan, J.; Hou, Y.; Lyu, C.; Marinkovich, M. P.; Keene, D.; Chen, M. Gentamicin induces functional type VII collagen in recessive dystrophic epidermolysis bullosa patients. Journal of Clinical Investigation. 2017. 127; 8: 3028-3038.

Study with no results (n=78)

2015-003670-32 A dual-center prospective phase I/II trial to establish safety, tolerability and to obtain first data on efficacy of losartan in children with recessive dystrophic epidermolysis bullosa (RDEB).

2016-002790-35 Phase I/II ex vivo gene therapy clinical trial for RDEB using autologous skin equivalent grafts genetically corrected with a COL7A1-encoding SIN retroviral vector.

2018-000261-36 Multicentre, Open-Label, Uncontrolled, Pivotal Clinical Trial to Confirm the Efficacy and Safety of Autologous Fibrin-Cultured Epidermal Grafts Containing Epidermal Stem Cells Genetically Modified.

2020-002936-55 Safety and Efficacy of Allogenic Adipose Tissue-derived Mesenchymal Stromal Cells in Patients with Epidermolysis Bullosa: Clinical Trial Phase I/II.

ACTRN12611000668909 Investigation of micro-needling skin therapy for recessive dystrophic epidermolysis bullosa (RDEB) in Australia. Investigation of micro-needling skin therapy for recessive dystrophic epidermolysis bullosa (RDEB) in Australia to assess median healing time of lesions. 2011.

ACTRN12611000677909 An Australian Study assessing the effects of Avene Thermal Water Spray in patients with recessive dystrophic epidermolysis bullosa. An Australian Study assessing the effects of Avene Thermal Water Spray in patients with recessive dystrophic epidermolysis bullosa. 2011.

Bageta, M.; Balboa, P. L.; Glover, R.; Cooper, C.; Papaioannou, D.; Julious, S.; Dimairo, M.; Biggs, K.; Petrof, G.; Martinez, A. E. Mesenchymal stromal cells infusions in children with recessive dystrophic epidermolysis bullosa (MissionEB): a randomised controlled trial. Pediatric dermatology. 2022. 39; SUPPL 1: 35.

Bageta, M. L.; Balboa, P. L.; Glover, R.; Cooper, C.; Papaioannou, D. E.; Julious, S.; Dimairo, M.; Biggs, K.; Petrof, G.; Martinez, A. E. Mesenchymal stromal cells infusions in children with recessive dystrophic epidermolysis bullosa (MissionEB): a randomized controlled trial. British Journal of Dermatology. 2023. 189; (3): E42-E43.

Bageta, M.; Balboa, P. L.; Glover, R.; Cooper, C.; Papaioannou, D.; Julious, S.; Dimairo, M.; Biggs, K.; Petrof, G.; Martinez, A. Mesenchymal stromal cells infusions in children with recessive dystrophic epidermolysis bullosa (MissionEB): a randomised controlled trial. Pediatric dermatology. 2023. 40: 5.

Excluded records

Bageta, M.; Balboa, P.L.; Glover, R.; Cooper, C.; Papaioannou, D.; Julious, S.; Dimairo, M.; Biggs, K.; Petrof, G.; Martinez, A.E. P055 Mesenchymal stromal cells infusions in children with recessive dystrophic epidermolysis bullosa (MissionEB): A randomised controlled trial. 2021.

Biochemical Correction of Severe EB by Allo HSCT and "Off-the-shelf" MSCs.

CTRI/2018/08/015422 Assessing effectiveness of topical gentamicin cream in junctional and dystrophic epidermolysis bullosa. 2018.

CTRI/2021/04/032642 To Assess the efficacy and safety Of Oral Losartan In The Treatment Of Recessive Dystrophic Epidermolysis Bullosa. 2021.

CTRI/2021/04/033024 Effectiveness of topical amlexanox in Dystrophic epidermolysis Bullosa. Pilot single-arm open label study to assess the effectiveness of topical amlexanox in promoting wound healing and collagen 7 expression in patients with Dystrophic Epidermolysis bullosa. 2021.

De Rosa, L.; Enzo, E.; Zardi, G.; Bodemer, C.; Magnoni, C.; Schneider, H.; De Luca, M. Hologene 5: A Phase II/III Clinical Trial of Combined Cell and Gene Therapy of Junctional Epidermolysis Bullosa. Frontiers in Genetics. 2021. 12: 705019.

De Rosa, L.; Enzo, E,; Zardi, G.; Bodemer, C.; Magnoni, C.; Schneider, H,; De Luca, M. WCRSD2200040 Hologene 5: A Phase II/III Clinical Trial of Combined Cell and Gene Therapy of Junctional Epidermolysis Bullosa. WCRSD. 2022.

EUCTR2017-004806-17-FR Study to Evaluate QR-313 in subjects with Recessive Dystrophic Epidermolysis Bullosa (RDEB) due to mutation(s) in exon 73 of the COL7A1 gene. 2018.

EUCTR2009-012750-21-FR Traitement des epidermolyses bulleuses dystrophiques hereditaires par l’epigallocatachine-3-gallate oral (Polyphenon EÂ). 2009.

EUCTR2021-000214-42-GR INM-755 cream for patients with EB. 2021.

EUCTR2021-000103-20-NL A study on the effect of Transvamix on pain in adults with epidermolysis bullosa. 2021.

EUCTR2018-003890-91-PL Treatment of wound in the course of Epidermolysis Bullosa, chronic venous leg ulceration and thermal injury by biological dressing made of mesynchemal stem cells seeded on acellular human skin. 2018.

EUCTR2010-023121-38-GB A prospective placebo controlled phase II study to evaluate the use of allogeneic fibroblasts for the treatment of skin erosions in recessive dystrophic epidermolysis bulllosa. - Fibroblast cell therapy for RDEB - a phase II clinical trial. 2010.

EUCTR2012-000605-72-NL Stem cell transplantation with cord blood and mesenchymal stem cells after reduced intensity conditioning for severe forms of the blistering disease epidermolysis bullosa. Unrelated cord blood transplantation after reduced toxicity conditioning with mesenchymal stromal cell co-infusion in patients with severe epidermolysis bullosa - CB+MSCforEB. 2013.

EUCTR2014-004500-30-GB A prospective phase I/II study to evaluate the use of mesenchymal stromal (stem) cells for the treatment of skin disease in adults with recessive dystrophic epidermolysis bullosa. A phase I/II study evaluating allogeneic mesenchymal stromal cells in adults with recessive dystrophic epidermolysis bullosa - ADSTEM. 2014.

EUCTR2015-004592-74-AT Gene Therapy for patients with Recessive Dystrophic Epidermolysis Bullosa (RDEB). Prospective, open label, uncontrolled clinical trial to assess the safety and efficacy of autologous cultured epidermal grafts containing epidermal stem cells genetically modified with a gamma-retroviral (rv) vector carrying col7a1 cdna for restoration of. 2016.

EUCTR2016-002790-35-FR Phase I/II ex vivo gene therapy clinical trial for RDEB using autologous skin equivalent grafts genetically corrected with a
 COL7A1-encoding SIN retroviral vector - EBGraft. 2018.

Excluded records

EUCTR2020-002337-15-NO Topical gentamicin treatment of patients with epidermolysis bullosa. Topical gentamicin treatment of patients with epidermolysis bullosa due to nonsense mutations (the gentelbull study) - gentelbull. 2020.

Hao, M.; Antaya, R.; Cogan, J.; Hamilton, C.; Hou, Y.; Kwong, A.; Woodley, D.; Chen, M. 861 Intravenous gentamicin therapy for junctional epidermolysis bullosa patients harboring nonsense mutations. 2020.

IRCT20080901001159N Effects of cell therapy in treatment of epidermolysis bullosa. 2018.

IRCT20141007019432N5 Study of the effectiveness of Cord Blood Platelet Gel (CBPG) for treatment of Epidermolysis Bullosa (EB) ulcers. 2018.

IRCT20150825023753N14 Efficacy of topical formulation of Henna in itching sensation and wound healing in patients with epidermolysis bullosa. The pilot study of efficacy of topical formulation of Henna (Lawsonia inermis)1% in itching sensation and wound healing in patients with epidermolysis bullosa: a non randomized open clinical trial. 2019.

IRCT20160320027109N The efficacy of atmospheric pressure plasma versus low-level laser on chronic wounds (including epidermolysis bullosa). 2018.

IRCT20210822052258N Evaluation of the efficacy of topical Gabapentin for the treatment of pruritus in patients with Epidermolysis bullosa. 2021.

ISRCTN81030001 Double blind, placebo controlled crossover study of the efficacy and side effects of low dose amitriptyline treatment for chronic pain, disordered sleep and reduced mobility in children with Epidermolysis Bullosa. 2010.

ISRCTN14409785 Mesenchymal stromal cell therapy for children with recessive dystrophic epidermolysis bullosa. 2021.

ISRCTN46615946 Study to evaluate the use of allogeneic mesenchymal stromal cells for the treatment of skin disease in children with recessive dystrophic epidermolysis bullosa. A prospective phase I/II study to evaluate the use of allogeneic mesenchymal stromal cells for the treatment of skin disease in children with recessive dystrophic epidermolysis bullosa. 2012.

JPRN-UMIN000026645 A Clinical Study to Evaluate the Efficacy and Safety of JR-031 in Patients with Epidermolysis Bullosa. 2017.

JPRN-UMIN000006723 Clinical research of bone marrow-derived mesenchymal stem cell transplantation for the patients with epidermolysis bullosa. 2011.

JPRN-UMIN000020734 Pivotal study about efficiency and safety of JTEC-01 made from revertant mosaicism in epidermolysis bullosa. 2016.

JPRN-JapicCTI-184563 A clinical study of CL2020 in patients with epidermolysis bullosa. A clinical study of CL2020 in patients with epidermolysis bullosa. 2018.

JPRN-JapicCTI-194798 Follow-up study for the KOI2-002 study in epidermolysis bullosa patients. Follow-up study for the KOI2-002 study in epidermolysis bullosa patients. 2019.

JPRN-jRCT2033210128 A confirmatory clinical study of ISN001 in patients with epidermolysis bullosa. A confirmatory clinical study to evaluate efficacy and safety of ISN001 in patients with epidermolysis bullosa. 2021.

JPRN-UMIN000014883 Feasibility study of the treatment of the refractory skin ulcer by the punch graft from the Natural gene therapy area in epidermolysis bullosa. . 2014.

JPRN-UMIN000028366 A clinical study to evaluate efficacy, safety and tolerability of ISN001 in dystrophic epidermolysis bullosa patients. 2017.

Excluded records

JPRN-UMIN000029962 Clinical trial of mesenchymal stem cell mobilization factor KOI2 in epidermolysis bullosa patients. Clinical trial of KOI2 in epidermolysis bullosa patients. 2017.

Kiritsi, D. Losartan for rdeb trial results and international perspectives. Acta Dermato-Venereologica. 2020. 100; SUPPL 220: 7.

NCT00231517 Randomised Double Blind Placebo Controlled Cross Over Design of the Efficacy of Topical Morphine for Inflammatory Pain in Children With Epidermolysis Bullosa. 2005.

NCT00951964 Treatment of Epidermolysis Bullosa Dystrophica by Polyphenon E (Epigallocatechin 3 Gallate). 2009.

NCT01528306 A Pilot Study of HP802-247 in Dystrophic Epidermolysis Bullosa. An Exploratory, Cross-Over Study of the Safety of HP802-247 Applied to Open Wounds of Subjects With Dystrophic Epidermolysis Bullosa. 2012.

NCT02286427 A Comparative Study of the Healing of Chronic Ulcers of Recessive Epidermolysis Bullosa : dressing vs Amniotic Membrane. 2014.

NCT02286427 A Comparative Study of the Healing of Chronic Ulcers of Recessive Epidermolysis Bullosa : Dressing vs Amniotic Membrane. 2014.

NCT02323789 Mesenchymal Stromal Cells in Adults With Recessive Dystrophic Epidermolysis Bullosa.

NCT02582775 MT2015-20: Biochemical Correction of Severe EB by Allo HSCT and Serial Donor MSCs.

NCT03392909 Intravenous Gentamicin Therapy for Recessive Dystrophic Epidermolysis Bullosa (RDEB).

NCT03468322 A Double-blind, Intra-individual Comparison, POC Trial of AC-203 in EB Patients. 2018.

NCT03526159 Gentamicin for Junctional Epidermolysis Bullosa.

NCT03578029 Evaluation of the Safety and Efficacy Study of RGN-137 Topical Gel for Junctional and Dystrophic Epidermolysis Bullosa. 2018.

NCT03640871 HEAL Study: Healing Results, Efficacy and Acceptability of a New Contact Layer.

NCT03730584 Evaluation of the Efficacy of ROPIVACAINE in Children and Young Adults With Hereditary Epidermolysis Bullosa.

NCT03752905 A Phase 1/2 Trial of PTR-01 in Adult Patients With Recessive Dystrophic Epidermolysis Bullosa (RDEB). 2018.

NCT03928093 Pregabalin Treatment for RDEB Pain and Itch. 2019.

NCT04140786 Optimizing IV Gentamicin in JEB.

NCT04153630 Safety Study and Preliminary Efficacy of Infusion Haploidentical Mesenchymal Stem Cells Derived From Bone Marrow for Treating Recessive Dystrophic Epidermolysis Bullosa.

NCT04173650 MSC EVs in Dystrophic Epidermolysis Bullosa. 2019.

NCT04186650 Ex Vivo Gene Therapy Clinical Trial for RDEB Using Genetically Corrected Autologous Skin Equivalent Grafts.

NCT04213261 A Pivotal Phase 3 Study of FCX-007 (Genetically-Modified Autologous Human Dermal Fibroblasts) for Recessive Dystrophic Epidermolysis Bullosa. A Pivotal Phase 3 Study of FCX-007 (Genetically-Modified Autologous Human Dermal Fibroblasts) for Recessive Dystrophic Epidermolysis Bullosa. 2019.

NCT04227106 Phase 3, Open-label Clinical Trial of EB-101 for the Treatment of Recessive Dystrophic Epidermolysis Bullosa (RDEB).

Excluded records

NCT04599881 A Study of PTR-01 in Recessive Dystrophic Epidermolysis Bullosa.

NCT04644627 Topical Gentamicin Nonsense Suppression Therapy of EB.

NCT04908215 INM-755 (Cannabinol) Cream for Treatment of Epidermolysis Bullosa. 2021.

NCT05111600 Open-label, Pivotal Clinical Trial to Confirm Efficacy and Safety of Autologous Grafts Containing Stem Cells Genetically Modified for Epidermis Restoration in Patients With Junctional Epidermolysis Bullosa.

NCT05143190 Extension Study to PTR-01-002.

NCT05157958 Study to Evaluate Safety and Efficacy of ALLO-ASC-SHEET in Subjects With Dystrophic Epidermolysis Bullosa. 2021.

NCT05157958 Study to Evaluate Safety and Efficacy of ALLO-ASC-SHEET in Subjects With Dystrophic Epidermolysis Bullosa. Double Blind, Randomized, Phase II Clinical Study to Evaluate Safety and Efficacy of ALLO-ASC-SHEET Versus Vehicle Control in Dystrophic Epidermolysis Bullosa (DEB) Patients. 2021.

NCT05954416 FARD (RaDiCo Cohort) (RaDiCo-FARD). National Cohort for Evaluation of the Burden of Rare Skin Diseases. 2023.

NIHR, H. S. C. THYMOSIN BETA-4 FOR EPIDERMOLYSIS BULLOSA. 2014.

Nita, M.; Pliszczynski, J.; Wozniak, K.; Majewski, S.; Kowalewski, C.; Kosieradzki, M.; Fiedor, P. New surgical approach to use human allograft as biological dressing in patients with epidermolysis bullosa (EB). Transplant International. 2021. 34; SUPPL 1: 217.

NL9347 A prospective explorative controlled study on cannabinoids to treat chronic pain in epidermolysis bullosa. https://trialsearch.who.int/Trial2.aspx?TrialID=. 2021.

Spellman, M.; Yonchek, M.; Blumenthal, R. A Randomized Trial to Determine the Efficacy and Safety of FCX-007 for the Treatment of Recessive Dystrophic Epidermolysis Bullosa -DEFI-RDEB. Molecular Therapy. 2022. 30; 4: 378-378.

Unable to locate full record (n=12)

Barbier, M. A.; Piaceski, A. D.; Morissette, A.; Larose, A.; Cartier, A.; Villeneuve, S.; Larouche, D.; Ghani, K.; Pope, E.; Caruso, M.; Germain, L. Ex Vivo Gene Therapy Of Skin Cells And Autologous Bilayered Skin Substitutes As A Potential Treatment For Recessive Dystrophic Epidermolysis Bullosa Skin Wounds. Tissue Engineering Part A. 2022. 28: 44987.

CTRI/2018/08/015422 Assessing effectiveness of topical gentamicin cream in junctional and dystrophic epidermolysis bullosa. Pilot study to assess the effectiveness of topical gentamicin in a collagen base versus paraffin guaze dressings in promoting wound healing in patients with Junctional and Dystrophic Epidermolysis bullosa. 2018.

CTRI/2021/09/036619 To check for effectiveness of Losartan in patients with Dystrophic Epidermolysis Bullosa (DEB). Safety and efficacy of Losartan in patients with Dystrophic Epidermolysis Bullosa (DEB): an open labeled controlled trial. 2021.

Epidermolysis bullosa clinical trial recruiting. Ostomy Wound Management. 2015. 61; 8: 46-46.

EUCTR2017-000606-37-ES Safety study of mesenchymal stem cells in the treatment of Recessive Dystrophic Epidermolysis Bullosa.. Safety and preliminary efficacy study of infusing mesenchymal stem cells derived from bone marrow for treating Recessive Dystrophic Epidermolysis Bullosa.. 2017.

Hilton, L. Dystrophic EB: No adverse events in gene therapy trial. Dermatology Times. 2017. 38; 10: 27-27.

Hilton, L. New hope for children with EB. Dermatology Times. 2016. 37; 1: 28-31.

Excluded records
JPRN-jRCT2080224722 Follow-up study for the KOI2-002 study in epidermolysis bullosa patients. Follow-up study for the KOI2-002 study in epidermolysis bullosa patients. 2019.
Mealmaker, C.; Kopacz, M. R.; Rohde, C. B.; Angel, M. Efficient Non-Viral Ablation of COL7A1 Exon 73 Splice Acceptor for the Treatment of Dystrophic Epidermolysis Bullosa (DEB). Molecular Therapy. 2020. 28; 4: 97-98.
Myers, R. B.; Moore, K.; Mulder, G. D.; Pike, R. A.; Kissil, M. T. Report of a multicenter clinical trial of the performance characteristics of two occlusive hydrocolloid dressings in the treatment of noninfected partial-thickness wounds [published erratum appears in J Enterostomal Ther 1988 Sep-Oct;15(5): 209]. Journal of enterostomal therapy. 1988. 15; 4: 158-161.
National Horizon Scanning, Centre Cx501 for cutaneous lesions associated with recessive dystrophic epidermolysis bullosa. 2010.
NCT03632265 Study of EB-101 for the Treatment of Recessive Dystrophic Epidermolysis Bullosa. VITAL: A Pivotal Phase 3 Study of EB-101 for the Treatment of Recessive Dystrophic Epidermolysis Bullosa (RDEB) (GENE TRANSFER). 2018.

H.1.4 Quality assessment

During data extraction, two researchers (CW and JNL) independently conducted quality assessment of each included study using version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) and the CASP or ROBINS-I tools for any non-RCTs, and any experimental cohort studies (e.g. single-arm trials) as appropriate.

Where researchers disagreed, they discussed reasons for disagreement. If consensus could not be reached on the quality of a study, then a third researcher (AS) would have been involved, however this was not necessary.

Quality assessment was used to provide an assessment of the risk of bias for each study and was not used to exclude eligible studies. If missing data or inadequate information to complete the quality assessment tool was identified, study authors would have been contacted for further information, however this was not necessary.

H.1.5 Unpublished data

NA

Appendix I. Literature searches for health-related quality of life studies

A combined systematic review aimed to identify the quality of life and economic evidence for the treatment of partial thickness wounds in adult and paediatric patients with any EB subtype.

Databases and grey literature were searched in March 2022, with updated searches performed in September 2023 and May 2024. A total of 2,124 records were identified across all searches. Following the removal of 712 duplicates, 1,412 records were eligible for primary screening. Of these, 1,135 records were excluded and 277 were taken forward to full-text (secondary) screening. At secondary screening 64 records were eligible for inclusion, with an additional nine records identified via handsearching, resulting in 73 included records representing 59 studies and five HTA records. The 73 included records comprised 5 HTA records, with the remaining 68 records representing 59 individual studies. Of the 68 records, two reported economic evaluation data from HTA records, 36 records (from 22 studies and 4 HTA records) reported HCRU data, and HRQoL data was reported in 46 records (from 38 studies and 3 HTA records).

I.1 Health-related quality-of-life and economic search

Table 73 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Ovid interface	No limit	30 April – 1 May 2024
Medall	Ovid interface - MEDALL	No limit	30 April – 1 May 2024
Cochrane CENTRAL and database of systematic reviews	Tolley Health Economics Ltd	No limit	30 April – 1 May 2024

Database	Platform/source	Relevant period for the search	Date of search completion
The international HTA database	https://database.inahta.org/	No limit	30 April – 1 May 2024
The CRD HTA database	https://www.crd.york.ac.uk/CRDWeb/HomePage.asp	No limit	30 April – 1 May 2024

Abbreviations:

Table 74 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
HTA and regulatory sites (NICE, SMC, HAS, CADTH, PBAC, GBA, ICER)		("epidermolysis bullosa" OR "dystrophic bullosa" OR "junctional bullosa" OR "butterfly skin" OR (partial AND thickness AND wounds))	30 April – 1 May 2024
EconPapers within Research Papers in Economics (RePEc)			30 April – 1 May 2024
University of Sheffield ScHARRHUD utility database			30 April – 1 May 2024
EuroQoL website			30 April – 1 May 2024
Tufts CEA registry			30 April – 1 May 2024

Abbreviations:

Table 75 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
International Society for Pharmacoeconomics and Outcomes (ISPOR)	Conference proceedings	Manual search	Not available	30 April – 1 May 2024
Health Technology Assessment International				
Health Economists' Study Group				
Global Congress in Epidermolysis Bullosa				
DEBRA International				

I.1.1 Search strategies'

The population, intervention, comparators, outcomes, and study methods (PICOS) criteria applied for the identification of evidence relevant to the research objectives are summarised below.

Table 76 PICOS eligibility criteria

Criterion	Eligibility
Population	Adults and children with epidermolysis bullosa (EB)[a]
Intervention & comparators	No restriction
Outcomes	• Economic evaluations – Quality adjusted life years (QALYs) [incremental, total] – Life years (LY) [incremental, total] – Incremental cost-effectiveness ratio (ICER) – Incremental cost-utility ratio (ICUR) – Costs (total, incremental) – Cost per outcomes (e.g., treatment, benefit) – Budget impact per population – Budget impact incidence/ prevalence • Costs/ resource use – Measures of costs – Costs (total, unit) – Costs of adverse events – Direct costs of inpatient and outpatient services

	– Indirect costs (e.g., caregiver burden, travel) – Measures of resource use – Frequency of resource use (e.g., hospitalisation/ inpatient days, accident and emergency visits, outpatient visits, dressing changes) – Outpatient and inpatient healthcare resource utilisation – Work productivity, employment, and work disability • HRQoL (patient and care giver) [b] – Health State Utility values elicited using direct methods: time trade-off (TTO) and standard gamble or from mapping – Preference-Based methods: (e.g., EQ-5D, HUI3, SF-6D, AQoL, QWB, 15D) – Utilities/ disutilities derived from condition specific HRQoL tools – Any grade adverse event utilities/ disutilities – Any health-related quality of life (HRQoL) outcomes [b] Mapping algorithms [b]
Study & publication type	• Economic evaluations – Economic models or evaluations (e.g. cost utility analysis, cost effectiveness analysis, cost minimisation analysis, cost benefit analysis, cost consequence analysis, cost of illness analysis, cost-offset analysis, budget impact analysis) • Costs/ resource use – Any studies reporting original cost and/ or resource use data, including: – Clinical trials – Observational studies – Patient chart reviews – Patient and disease registry studies – Claims data analyses • HRQoL – Studies reporting original HRQoL data [b] • Excluded study types – Case studies – Animal model studies Literature reviews [c]
Limits	• Conference abstracts and publications will be date limited to cover the last 3 full years. Other publication types will not be limited by date. Publications will not be limited by language/ country
Population	Adults and children with epidermolysis bullosa (EB)[a]
Intervention & comparators	No restriction
Outcomes	• Economic evaluations – Quality adjusted life years (QALYs) [incremental, total] – Life years (LY) [incremental, total] – Incremental cost-effectiveness ratio (ICER)

	– Incremental cost-utility ratio (ICUR) – Costs (total, incremental) – Cost per outcomes (e.g., treatment, benefit) – Budget impact per population – Budget impact incidence/ prevalence • Costs/ resource use – Measures of costs – Costs (total, unit) – Costs of adverse events – Direct costs of inpatient and outpatient services – Indirect costs (e.g., caregiver burden, travel) – Measures of resource use – Frequency of resource use (e.g., hospitalisation/ inpatient days, accident and emergency visits, outpatient visits, dressing changes) – Outpatient and inpatient healthcare resource utilisation – Work productivity, employment, and work disability • HRQoL (patient and care giver) [b] – Health State Utility values elicited using direct methods: time trade-off (TTO) and standard gamble or from mapping – Preference-Based methods: (e.g., EQ-5D, HUI3, SF-6D, AQoL, QWB, 15D) – Utilities/ disutilities derived from condition specific HRQoL tools – Any grade adverse event utilities/ disutilities – Any health-related quality of life (HRQoL) outcomes [b] Mapping algorithms [b]
Study & publication type	• Economic evaluations – Economic models or evaluations (e.g. cost utility analysis, cost effectiveness analysis, cost minimisation analysis, cost benefit analysis, cost consequence analysis, cost of illness analysis, cost-offset analysis, budget impact analysis) • Costs/ resource use – Any studies reporting original cost and/ or resource use data, including: – Clinical trials – Observational studies – Patient chart reviews – Patient and disease registry studies – Claims data analyses • HRQoL – Studies reporting original HRQoL data [b] • Excluded study types – Case studies – Animal model studies Literature reviews [c]
Limits	• Conference abstracts and publications will be date limited to cover the last 3 full years. Other publication types will not be limited by date. • Publications will not be limited by language/ country

All searches were conducted by an experienced information scientist and systematic review specialist. Records eligible for inclusion following full-text screening were citation chased. Backwards citation chasing was undertaken via a manual review of the bibliographies of each record, and forward citation chasing was undertaken using Web of Science (Clarivate Analytics).

Study authors were to be contacted should any additional information on identified records be required. The author of one record was contacted during this SLR to obtain a reference list for a record that was an abstract only of an SLR. The author did not respond and therefore the record was excluded without reference checking.

Study selection

Primary screening – title and abstract

Records identified via bibliographic database and conference searches were managed and screened in Covidence. Titles and abstracts were primary screened against the PICOS eligibility criteria independently by two reviewers. Records identified as potentially including relevant data were carried forward for secondary screening. Any conflicts between reviewers were discussed and resolved by a third reviewer.

Secondary screening – full text

Electronic copies of full texts were obtained and screened by two independent reviewers against the PICOS eligibility criteria. Any conference abstracts included for secondary screening were also checked to identify any corresponding posters. Eligible records were taken forward to data extraction, with others excluded with reason reported. Any conflicts between reviewers were discussed and resolved by a third reviewer.

Reporting of study identification follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses literature search extension (PRISMA-S) guidelines.

Data extraction

Following secondary screening, a data hierarchy assessment was performed to identify studies for data extraction based on the relevance of the data they included to inform a cost-effectiveness model. Data extraction was performed in a data extraction template (DET) in Microsoft Excel by a single reviewer and checked by at least one other reviewer, who had not conducted the initial data extraction. Any conflicts between reviewers were discussed and resolved by a third reviewer. The DET included sheets with detailed templates to extract the relevant data for each SLR component (economic, cost and resource use, and utility values to determine HRQoL). The DET also included an overview of all studies that were data extracted, with quality assessment checklists for each component.

Table 77 of search strategy table for Medall

No	Query	Results
1	exp Epidermolysis Bullosa/	5735
2	Rothmund-Thomson Syndrome/	588
3	(((epidermolysis or Junctional or Dystrophic) adj3 bullosa*) or (Kindler syndrom* or Kindler EB or Poikiloderma or Rothmund-Thomson Syndrome or butterfly skin)).ti,ab,ot,kf,kw.	7528
4	(partial* adj3 thick* adj3 wound*).ti,ab,ot,kf,kw.	654
5	1 or 2 or 3 or 4	8978
6	economics/	27531
7	exp "Costs and Cost Analysis"/	270126
8	economics, dental/	1922
9	exp Economics, Hospital/ or Financial management, hospital/	33103
10	Economics, Medical/	9279
11	economics, nursing/	4013
12	economics, pharmaceutical/	3133
13	(economic* or cost or costs or costly or costing or expense or expenses or price or prices or pricing or pharmacoeconomic* or CEA or CUA or CBA or CMA).ti,ab,kf,kw.	1214437
14	exp "fees and charges"/	31436
15	exp budgets/	14207
16	(resource*1 and (allocation or utili* or usage or use*1)).ti,ab,kf,kw.	287928

17	(expenditure* not energy).ti,ab,kw.	38866
18	(value adj1 money).ti,ab,kw.	46
19	(budget* or fiscal or funding or financial or finance*).ti,ab,kw.	251361
20	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	1734061
21	(15D or 15-D or 15 dimension).ti,ab,kw.	6298
22	(eq-5d or eq5d or eq-5 or eq5 or EQ-5D-Y or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol or EQ-5D-3L).ti,ab,ot,hw,kw.	18773
23	(sf6 or sf 6 or SF-6D or short form 6 or short-form 6 or short-form six or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot,hw,kw.	3566
24	(sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or shortform eight).ti,ab,ot,hw,kw.	782
25	(sf10 or sf 10 or short form 10 or short-form 10 or short-form ten or shortform 10 or sf ten or sften or shortform ten or short form ten).ti,ab,ot,hw,kw.	164
26	(sf12 or sf 12 or short form 12 or short-form 12 or short-form twelve or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab,ot,hw,kw.	8061
27	(sf16 or sf 16 or short form 16 or short-form 16 or short-form sixteen or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,ot,hw,kw.	41
28	(sf20 or sf 20 or short form 20 or short-form 20 or short-form twenty or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab,ot,hw,kw.	460
29	(sf36 or sf 36 or short form 36 or short-form 36 or short-form thirty six or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot,hw,kw.	31796

30	(health utilities index* or (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3)).ti,ab,ot,hw,kw.	2383
31	("Child Health Utility 9D Index" or "Child Health Utility 9D" or CHU9D or "CHU 9D" or "CHU-9D").ti,ab,ot,hw,kw,kf.	141
32	("time trade off" or "time tradeoff" or "time trade-off" or TTO).ti,ab,ot,hw,kw.	2446
33	(standard gamble* or SG).ti,ab,ot,hw,kw.	15157
34	("discrete choice" or DCE).ti,ab,ot,hw,kw.	10514
35	(AQoL or "Assessment of Quality of Life").ti,ab,ot,hw,kw.	2437
36	Quality-Adjusted Life Years/	16326
37	(HRQoL or HRQL or HQL or HQOL or H QoL or hr QoL or QoL or (quality adj3 life) or quality time or HYE or HYES or (health* adj3 equivalent*)).ti,ab,ot,hw,kw.	486309
38	quality of life/	287338
39	value of life/	5824
40	uncertainty/	18891
41	(Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of healthlife lost").ti,ab,ot,kw.	6918
42	(HSUV* or health state* value* or health state* preference* or HSPV*).ti,ab,ot,kw.	571
43	(uncertain* or wellbeing or "well being" or "quality of wellbeing" or "index of wellbeing" or "index of well being" or rosser or "willingness to pay").ti,ab,kw.	394167
44	(utility* or disutili*).ti,ab,kw.	275677

45	(illness state*1 or health state* or health status or Quality adjusted life year* or QALY or QALD or DALY* or HALY* or YHL or HYES or YPLL or YHLL or qale or qtime or AQoL* or life year* or ICER or "incremental cost").ti,ab,ot,hw,kw.	227669
46	(burden and (disease or illness or caregiver or home)).ti,ab,kw.	146913
47	(lost adj2 (productivity or work or employment or earnings)).ti,ab,kw.	3527
48	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47	1410399
49	("Pediatric Quality of Life Inventory" or PedsQL or TNO-AZL or TNOAZL or TAPQoL or TACQoL or TAAQoL or "Questionnaire for Adult's Health- related Quality of Life" or "Questionnaire for Adults Health- related Quality of Life" or "Coping with a Disease Questionnaire").ti,ab,kw.	3258
50	("Autoimmune Bullous Disease Quality of Life" or ABQOL or "Treatment of Autoimmune Bullous Disease Quality of Life" or TABQOL).ti,ab,kw.	26
51	("Children's Dermatology Life Quality Index" or CDLQI).ti,ab,kw.	314
52	("Dermatitis Family Impact Questionnaire" or DFIQ).ti,ab,kw.	36
53	("Dermatology Life Quality Index" or DLQI).ti,ab,kw.	3522
54	("EB Disease Activity and Scarring Index" or EBDASI).ti,ab,kw.	13
55	("Epidermolysis Bullosa Burden of Disease" or EB-BoD).ti,ab,kw.	6
56	("Infants and Toddlers Dermatology Quality of Life" or InToDermQoL).ti,ab,kw.	10
57	("Pediatric Quality of Life Inventory version 4" or PedsQL).ti,ab,kw.	2433
58	("Quality of Life Evaluation in Epidermolysis Bullosa" or "EB questionnaire" or "Quality of Life in EB" or QoLEB*).ti,ab,kw.	23
59	("Skindex-29" or "General Health Questionnaire-12" or GHQ-12).ti,ab,kw.	2414

60	("The Quality of Life in Epidermolysis Bullosa" or EB-QoL).ti,ab,kw.	15
61	("Birmingham Epidermolysis Bullosa severity score" or BEBS).ti,ab,ot,hw,kw,kf.	30
62	("Body Surface Area Percentage" or BSAP).ti,ab,ot,hw,kw,kf.	482
63	(iscorEB or iscorEB-c or iscorEB-p).ti,ab,ot,hw,kw,kf.	11
64	("The Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe" or BURQOL-RD).ti,ab,kw.	8
65	("Work Productivity and Activity Impairment Questionnaire" or WPAI).ti,ab,kw.	830
66	49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65	10498
67	48 or 66	1412412
68	20 or 67	2911453
69	5 and 68	564
70	(2023* or 2024*).dt,dp,ed,ep,yr.	2348625
71	69 and 70	76

Table 78 of search strategy table for Embase

No	Query	Results
1	exp epidermolysis bullosa/	9872
2	Rothmund Thomson syndrome/	652
3	(((epidermolysis or Junctional or Dystrophic) adj3 bullosa*) or (Kindler syndrom* or Kindler EB or Poikiloderma or Rothmund-Thomson Syndrome or butterfly skin)).ti,ab,ot,kf,kw.	9893

4	(partial* adj3 thick* adj3 wound*).ti,ab,ot,kf,kw.	853
5	1 or 2 or 3 or 4	12924
6	exp economic evaluation/	367211
7	health economics/	36460
8	socioeconomics/	166592
9	exp health-care-cost/	351946
10	exp pharmacoeconomics/	241184
11	(economic* or cost or costs or costly or costing or expense or expenses or price or prices or pricing or pharmacoeconomic* or CEA or CUA or CBA or CMA).ti,ab,kf,kw.	1544973
12	(resource*1 and (allocation or utili* or usage or use*1)).ti,ab,kf,kw.	378404
13	(expenditure* not energy).ti,ab,kw.	52533
14	(value adj1 money).ti,ab,kw.	45
15	(budget* or fiscal or funding or financial or finance*).ti,ab,kw.	370783
16	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	2549940
17	(15D or 15-D or 15 dimension).ti,ab,kw.	7900
18	(eq-5d or eq5d or eq-5 or eq5 or EQ-5D-Y or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol or EQ-5D-3L).ti,ab,ot,hw,kw.	37612
19	(sf6 or sf 6 or SF-6D or short form 6 or short-form 6 or short-form six or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot,hw,kw.	4685

20	(sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or shortform eight).ti,ab,ot,hw,kw.	1462
21	(sf10 or sf 10 or short form 10 or short-form 10 or short-form ten or shortform 10 or sf ten or sften or shortform ten or short form ten).ti,ab,ot,hw,kw.	271
22	(sf12 or sf 12 or short form 12 or short-form 12 or short-form twelve or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab,ot,hw,kw.	15854
23	(sf16 or sf 16 or short form 16 or short-form 16 or short-form sixteen or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,ot,hw,kw.	75
24	(sf20 or sf 20 or short form 20 or short-form 20 or short-form twenty or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab,ot,hw,kw.	620
25	(sf36 or sf 36 or short form 36 or short-form 36 or short-form thirty six or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot,hw,kw.	62758
26	(health utilities index* or (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3)).ti,ab,ot,hw,kw.	4646
27	("Child Health Utility 9D Index" or "Child Health Utility 9D" or CHU9D or "CHU 9D" or "CHU-9D").ti,ab,ot,hw,kw,kf.	204
28	("time trade off" or "time tradeoff" or "time trade-off" or TTO).ti,ab,ot,hw,kw.	3722
29	(standard gamble* or SG).ti,ab,ot,hw,kw.	22930
30	("discrete choice" or DCE).ti,ab,ot,hw,kw.	15294
31	(AQoL or "Assessment of Quality of Life").ti,ab,ot,hw,kw.	4011
32	quality adjusted life year/	37252
33	(HRQoL or HRQL or HQL or HQOL or H QoL or hr QoL or QoL or (quality adj3 life) or quality time or HYE or HYES or (health* adj3 equivalent*)).ti,ab,ot,hw,kw.	859427

34	"quality of life"/	662003
35	uncertainty/	51511
36	(Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of healthlife lost").ti,ab,ot,kw.	8247
37	(HSUV* or health state* value* or health state* preference* or HSPV*).ti,ab,ot,kw.	875
38	(uncertain* or wellbeing or "well being" or "quality of wellbeing" or "index of wellbeing" or "index of well being" or rosser or "willingness to pay").ti,ab,kw.	499432
39	(utility* or disutili*).ti,ab,kw.	383711
40	(illness state*1 or health state* or health status or Quality adjusted life year* or QALY or QALD or DALY* or HALY* or YHL or HYES or YPLL or YHLL or qale or qtime or AQoL* or life year* or ICER or "incremental cost").ti,ab,ot,hw,kw.	269834
41	(burden and (disease or illness or caregiver or home)).ti,ab,kw.	239661
42	(lost adj2 (productivity or work or employment or earnings)).ti,ab,kw.	5266
43	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42	2071667
44	("Pediatric Quality of Life Inventory" or PedsQL or TNO-AZL or TNOAZL or TAPQoL or TACQoL or TAAQoL or "Questionnaire for Adult's Health- related Quality of Life" or "Questionnaire for Adults Health- related Quality of Life" or "Coping with a Disease Questionnaire").ti,ab,kw.	5777
45	("Autoimmune Bullous Disease Quality of Life" or ABQOL or "Treatment of Autoimmune Bullous Disease Quality of Life" or TABQOL).ti,ab,kw.	45
46	("Children's Dermatology Life Quality Index" or CDLQI).ti,ab,kw.	634
47	("Dermatitis Family Impact Questionnaire" or DFIQ).ti,ab,kw.	73

48	("Dermatology Life Quality Index" or DLQI).ti,ab,kw.	6928
49	("EB Disease Activity and Scarring Index" or EBDASI).ti,ab,kw.	61
50	("Epidermolysis Bullosa Burden of Disease" or EB-BoD).ti,ab,kw.	9
51	("Infants and Toddlers Dermatology Quality of Life" or InToDermQoL).ti,ab,kw.	11
52	("Pediatric Quality of Life Inventory version 4" or PedsQL).ti,ab,kw.	4663
53	("Quality of Life Evaluation in Epidermolysis Bullosa" or "EB questionnaire" or "Quality of Life in EB" or QoLEB*).ti,ab,kw.	57
54	("Skindex-29" or "General Health Questionnaire-12" or GHQ-12).ti,ab,kw.	3123
55	("The Quality of Life in Epidermolysis Bullosa" or EB-QoL).ti,ab,kw.	28
56	("Birmingham Epidermolysis Bullosa severity score" or BEBS).ti,ab,ot,hw,kw,kf.	47
57	("Body Surface Area Percentage" or BSAP).ti,ab,ot,hw,kw,kf.	834
58	(iscorEB or iscorEB-c or iscorEB-p).ti,ab,ot,hw,kw,kf.	21
59	("The Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe" or BURQOL-RD).ti,ab,kw.	14
60	("Work Productivity and Activity Impairment Questionnaire" or WPAI).ti,ab,kw.	2771
61	44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60	19414
62	43 or 61	2074868
63	16 or 62	4245054
64	5 and 63	1262

65	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.	5904966
66	64 not 65	829
67	(2023* or 2024*).yr.	2483757
68	66 and 67	97

Table 79 of search strategy table for Econlit

No	Query	Results
S3	TI (partial* N3 thick* N3 wound*) OR AB (partial* N3 thick* N3 wound*)	0
S2	TI ((Kindler 163yndrome* or Kindler EB or Poikiloderma or Rothmund-Thomson Syndrome or butterfly skin))) OR AB ((Kindler 163yndrome* or Kindler EB or Poikiloderma or Rothmund-Thomson Syndrome or butterfly skin)))	0
S1	TI (((epidermolysis or Junctional or Dystrophic) N3 bullosa*)) OR AB (((epidermolysis or Junctional or Dystrophic) N3 bullosa*))	1

Table 80 of search strategy table for International HTA Database

No	Query	Results
1	Epidermolysis bullosa	1
2	((EB or DEB or DDEB or RDEB or JEB or "RDEB-GI" or "RDEB-I" or "RDEB-GS" or "RDEB-S" or "JEB-GI" or "JEB-GS") and (wound* or thick* or skin* or bullosa*))	0
3	butterfly skin	0
4	(partial* and thick* and wound*)	1
5	oleogel or Filsuvez	1

Table 81 of search strategy table for CRD Dare + CRD NHS EED

No	Query	Results
1	epidermolysis	3
2	bullosa	1
3	(Kindler syndrome).	0
4	Kindler EB	0
5	Poikiloderma	0
6	Rothmund-Thomson Syndrome	0
7	partial thickness wounds	1

Table 82 of search strategy table for Embase conferences

No	Query	Results
1	exp epidermolysis bullosa/	9872
2	Rothmund Thomson syndrome/	652
3	(((epidermolysis or Junctional or Dystrophic) adj3 bullosa*) or (Kindler syndrom* or Kindler EB or Poikiloderma or Rothmund-Thomson Syndrome or butterfly skin)).ti,ab,ot,kf,kw.	9893
4	(partial* adj3 thick* adj3 wound*).ti,ab,ot,kf,kw.	853
5	1 or 2 or 3 or 4	12924
6	exp economic evaluation/	367211
7	health economics/	36460
8	socioeconomics/	166592

9	exp health-care-cost/	351946
10	exp pharmacoeconomics/	241184
11	(economic* or cost or costs or costly or costing or expense or expenses or price or prices or pricing or pharmacoeconomic* or CEA or CUA or CBA or CMA).ti,ab,kf,kw.	1544973
12	(resource*1 and (allocation or utili* or usage or use*1)).ti,ab,kf,kw.	378404
13	(expenditure* not energy).ti,ab,kw.	52533
14	(value adj1 money).ti,ab,kw.	45
15	(budget* or fiscal or funding or financial or finance*).ti,ab,kw.	370783
16	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	2549940
17	(15D or 15-D or 15 dimension).ti,ab,kw.	7900
18	(eq-5d or eq5d or eq-5 or eq5 or EQ-5D-Y or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol or EQ-5D-3L).ti,ab,ot,hw,kw.	37612
19	(sf6 or sf 6 or SF-6D or short form 6 or short-form 6 or short-form six or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot,hw,kw.	4685
20	(sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or shortform eight).ti,ab,ot,hw,kw.	1462
21	(sf10 or sf 10 or short form 10 or short-form 10 or short-form ten or shortform 10 or sf ten or sften or shortform ten or short form ten).ti,ab,ot,hw,kw.	271
22	(sf12 or sf 12 or short form 12 or short-form 12 or short-form twelve or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab,ot,hw,kw.	15854

23	(sf16 or sf 16 or short form 16 or short-form 16 or short-form sixteen or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,ot,hw,kw.	75
24	(sf20 or sf 20 or short form 20 or short-form 20 or short-form twenty or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab,ot,hw,kw.	620
25	(sf36 or sf 36 or short form 36 or short-form 36 or short-form thirty six or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot,hw,kw.	62758
26	(health utilities index* or (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3)).ti,ab,ot,hw,kw.	4646
27	("Child Health Utility 9D Index" or "Child Health Utility 9D" or CHU9D or "CHU 9D" or "CHU-9D").ti,ab,ot,hw,kw,kf.	204
28	("time trade off" or "time tradeoff" or "time trade-off" or TTO).ti,ab,ot,hw,kw.	3722
29	(standard gamble* or SG).ti,ab,ot,hw,kw.	22930
30	("discrete choice" or DCE).ti,ab,ot,hw,kw.	15294
31	(AQoL or "Assessment of Quality of Life").ti,ab,ot,hw,kw.	4011
32	quality adjusted life year/	37252
33	(HRQoL or HRQL or HQL or HQOL or H QoL or hr QoL or QoL or (quality adj3 life) or quality time or HYE or HYES or (health* adj3 equivalent*)).ti,ab,ot,hw,kw.	859427
34	"quality of life"/	662003
35	uncertainty/	51511
36	(Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of healthlife lost").ti,ab,ot,kw.	8247

37	(HSUV* or health state* value* or health state* preference* or HSPV*).ti,ab,ot,kw.	875
38	(uncertain* or wellbeing or "well being" or "quality of wellbeing" or "index of wellbeing" or "index of well being" or rosser or "willingness to pay").ti,ab,kw.	499432
39	(utility* or disutili*).ti,ab,kw.	383711
40	(illness state*1 or health state* or health status or Quality adjusted life year* or QALY or QALD or DALY* or HALY* or YHL or HYES or YPLL or YHLL or qale or qtime or AQoL* or life year* or ICER or "incremental cost").ti,ab,ot,hw,kw.	269834
41	(burden and (disease or illness or caregiver or home)).ti,ab,kw.	239661
42	(lost adj2 (productivity or work or employment or earnings)).ti,ab,kw.	5266
43	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42	2071667
44	("Pediatric Quality of Life Inventory" or PedsQL or TNO-AZL or TNOAZL or TAPQoL or TACQoL or TAAQoL or "Questionnaire for Adult's Health- related Quality of Life" or "Questionnaire for Adults Health- related Quality of Life" or "Coping with a Disease Questionnaire").ti,ab,kw.	5777
45	("Autoimmune Bullous Disease Quality of Life" or ABQOL or "Treatment of Autoimmune Bullous Disease Quality of Life" or TABQOL).ti,ab,kw.	45
46	("Children's Dermatology Life Quality Index" or CDLQI).ti,ab,kw.	634
47	("Dermatitis Family Impact Questionnaire" or DFIQ).ti,ab,kw.	73
48	("Dermatology Life Quality Index" or DLQI).ti,ab,kw.	6928
49	("EB Disease Activity and Scarring Index" or EBDASI).ti,ab,kw.	61
50	("Epidermolysis Bullosa Burden of Disease" or EB-BoD).ti,ab,kw.	9
51	("Infants and Toddlers Dermatology Quality of Life" or InToDermQoL).ti,ab,kw.	11

52	("Pediatric Quality of Life Inventory version 4" or PedsQL).ti,ab,kw.	4663
53	("Quality of Life Evaluation in Epidermolysis Bullosa" or "EB questionnaire" or "Quality of Life in EB" or QoLEB*).ti,ab,kw.	57
54	("Skindex-29" or "General Health Questionnaire-12" or GHQ-12).ti,ab,kw.	3123
55	("The Quality of Life in Epidermolysis Bullosa" or EB-QoL).ti,ab,kw.	28
56	("Birmingham Epidermolysis Bullosa severity score" or BEBS).ti,ab,ot,hw,kw,kf.	47
57	("Body Surface Area Percentage" or BSAP).ti,ab,ot,hw,kw,kf.	834
58	(iscorEB or iscorEB-c or iscorEB-p).ti,ab,ot,hw,kw,kf.	21
59	("The Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe" or BURQOL-RD).ti,ab,kw.	14
60	("Work Productivity and Activity Impairment Questionnaire" or WPAI).ti,ab,kw.	2771
61	44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60	19414
62	43 or 61	2074868
63	16 or 62	4245054
64	5 and 63	1262
65	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.	5904966
66	64 and 65	433
67	(2023* or 2024*).yr.	2483757
68	66 and 67	34

Table 83 of search strategy table for Conference Proceedings Citation index

No	Query	Results
1	((epidermolysis or Junctional or Dystrophic) near/4 bullosa*)	1086
2	((EB or DEB or DDEB or RDEB or JEB or "RDEB-GI" or "RDEB-I" or "RDEB-GS" or "RDEB-S" or "JEB-GI" or "JEB-GS") and (wound* or thick* or skin* or bullosa*))	493
3	butterfly skin	0
4	(partial* NEAR/2 thick* NEAR/2 wound*)	29
5	#4 OR #3 OR #2 OR #1	1524
6	#4 OR #3 OR #2 OR #1 and 2023 or 2024	73

Table 84 of search strategy table for ISPOR+ HTAi+HESG+EBClinNET+DEBRA

No	Query	Results
1	epidermolysis	12
2	bullosa	19
3	(Kindler syndrome).	0
4	Kindler EB	0
5	Poikiloderma	0
6	Rothmund-Thomson Syndrome	0
7	partial thickness wounds	1

Table 85 of search strategy table for Web searches

No	Query	Results
1	epidermolysis bullosa	3
2	dystrophic bullosa	0
3	junctional bullosa	0
4	butterfly skin	0
5	patrial AND thickness AND wounds	0
6	patrial thickness wounds	0
7	Rothmund-Thomson Syndrome	0
8	Poikiloderma	0
9	Kindler	0

Search results

The search results and record selection process are summarized below.

Figure 18. PRISMA diagram of the study selection process

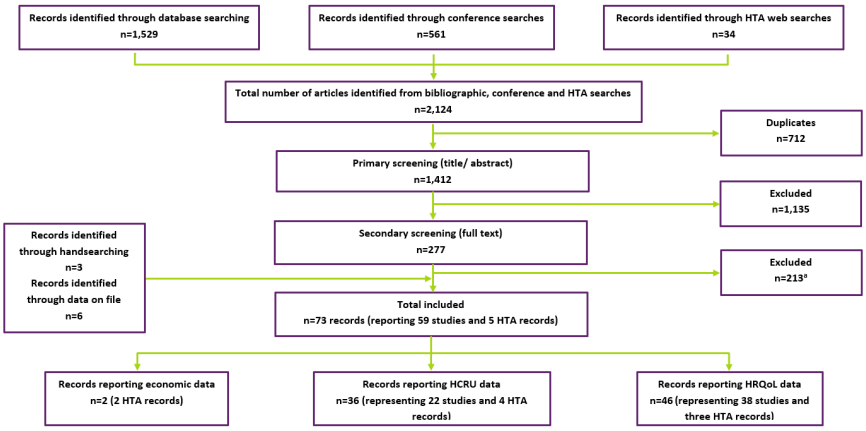


Table 86 of included records

Study	Record
EASE	Amryt Pharma. BEB-13: Reduced frequency of dressing changes in patients treated with Oleogel-S10 over 90 days. 2022. *[DBP CSR]*
	Amryt Pharma. EASE_BEB-13_OLP M12 Report (CSR addendum). 2021. *[12-month OLP CSR]*
	Amryt Pharma. Clinical Study Report Addendum. Double Blind Phase and Open-Label data through the end of study. 2022. *[24-month OLP CSR]*
	Kiritsi, D.; Bruckner, A.; Murrell, D.; Wine Lee, L.; Sprecher, E.; Maher, L.; Löwe, S.; Kern, J. Oleogel-S10 reduces dressing changes burden in patients with epidermolysis bullosa. EADV Congress. 2023.
	Lee, L. W.; Kern, J. S.; Murrell, D.; Lowe, S.; Maher, L.; Cunnigham, T. LB970 Effect of Oleogel-S10 (birch triterpenes) on dressing change frequency and wound infection in epidermolysis bullosa: Analysis from the EASE study. Journal of Investigative Dermatology. 2022; 142(8 Supplement):B22.
Alheggi *et al.* (2022)	Alheggi, A.; Alzakry, L.; Khunayn, R.; Alshareef, R.; Al-Khalid, Y. Skin cleansing and wound care practice in patients with epidermolysis bullosa: A cross-sectional study. Journal of Dermatology and Dermatologic Surgery. 2022; 26(1):13-17.

Angelis *et al.*	Angelis, A.; Kanavos, P.; Lopez-Bastida, J.; Linertova, R.; Oliva-Moreno, J.; Serrano-Aguilar, P.; Posada-de-la-Paz, M.; Taruscio, D.; Schieppati, A.; Iskrov, G.; Brodszky, V.; von der Schulenburg, J.; Chevreul, K.; Persson, U.; Fattore, G. Social/economic costs and health-related quality of life in patients with epidermolysis bullosa in Europe. European Journal of Health Economics. 2016; 17(Supplement 1):31-42.
	Angelis, A.; Mellerio, J.; Kanavos, P. Understanding the socioeconomic costs of dystrophic epidermolysis bullosa in Europe: a costing and health-related quality of life study. Orphanet journal of rare diseases. 2022; 17(1):346.
	Angelis, A.; Kanavos, P.; Mellerio, J.; Roman, J. Understanding the socioeconomic costs of dystrophic epidermolysis bullosa in Europe. Journal of Managed Care and Specialty Pharmacy. 2022; 28(3-A Supplement):S65-S66.
Bourrat *et al.* (2023)	Bourrat, E.; Taieb, C.; Marquie, A.; Causse, P.; Bergqvist, C.; Sauvestre, A.; Bellon, N. Burden of caregivers and out-of-pocket expenditures related to epidermolysis bullosa in France. Journal of the European Academy of Dermatology and Venereology : JEADV. 2023; 37(1):194-203.
Chiarotti *et al.* (2023)	Chiarotti, F.; Kodra, Y.; De Santis, M.; Bellenghi, M.; Taruscio, D.; Care, A.; Petrini, M. Gender and burden differences in family caregivers of patients affected by ten rare diseases. Annali dell'Istituto superiore di sanita. 2023; 59(2):122-131.
Cross-sectional study	Morgan, G.; Back, E.; Rosa, D. Utility Elicitation in Epidermolysis Bullosa: Cross-Sectional Survey Study Report FINAL. 2022:57.
	Morgan, G.; Back, E.; Rosa, D.; Irwin, J.; Ferguson, S.; Carr, E. PCR240 A Cross-Sectional Study of Disease Severity and Health Related Quality of Life in Epidermolysis Bullosa. Value in Health. 2022; 25(12 Supplement):S436.
Chogani *et al.* (2021)	Chogani, F; Parvizi, M.; Murrell, D.; Handjani, F. Assessing the quality of life in the families of patients with epidermolysis bullosa: The mothers as main caregivers. International Journal of Women's Dermatology Part B. 2021;7(5):721-726.

Cuadrado *et al.* (2023)	Cuadrado-Corrales, Natividad; Lopez-de-Andres, Ana; Hernandez-Barrera, Valentin; Carabantes-Alarcon, David; Zamorano-Leon, Jose J.; Omana-Palanco, Ricardo; Del-Barrio, Jose L.; De-Miguel-Diez, Javier; Jimenez-Garcia, Rodrigo; Montoya, Juan J. Clinical Characteristics and Outcomes of Patients Hospitalized with Epidermolysis Bullosa: A Retrospective Population-Based Observational Study in Spain (2016-2021) Biomedicines. 2023; 11(9).
Desai *et al.* (2022)	Desai, A.; Soliman, Y.; Behbahani, S. 34728 Epidermolysis bullosa in the pediatric population: Analysis of the KID database. Journal of the American Academy of Dermatology. 2022; 87(3 Supplement):AB55.
Dufresne *et al.* (2015)	Dufresne, H.; Hadj-Rabia, S.; Taieb, C.; Bodemer, C. Development and validation of an epidermolysis bullosa family/parental burden score. British Journal of Dermatology. 2015;173(6):1405-1410.
Dykman *et al.* (2022)	Dykman, M.; Han, J.; Lunos, S.; Nguyen, A.; Boull, C. 365 Transition of care in patients with epidermolysis bullosa: A survey study. Journal of Investigative Dermatology. 2022; 142(8 Supplement):S62.
Eng *et al.* (2021)	Eng, V.; Solis, D.; Gorell, E.; Choi, S.; Nazaroff, J.; Li, S.; de Souza, M.; Murrell, D.; Marinkovich, M.; Tang, J. Patient-reported outcomes and quality of life in recessive dystrophic epidermolysis bullosa: A global cross-sectional survey. Journal of the American Academy of Dermatology. 2021; 85(5):1161-1167.
Feinstein *et al.* (2022)	Feinstein, J.; Bruckner, A.; Chastek, B.; Anderson, A.; Roman, J. Clinical characteristics, healthcare use, and annual costs among patients with dystrophic epidermolysis bullosa. Orphanet journal of rare diseases. 2022; 17(1):367.
Flannery *et al.* (2020)	Flannery, D; Doyle, C; Hickey; Aherne, F; Kennan, A. Direct costs of epidermolysis bullosa by disease severity. Acta Dermato-Venereologica. 2020;100:(8);44593.
Forghani *et al.* (2021)	Forghani, S.; Jahangiri, R.; Ghasemi, F.; Shirani, R.; Bagheri, H.; Mahmoodi, R.; Bagheri Faradonbeh, S. Economic Burden of Epidermolysis Bullosa Disease in Iran. Medical journal of the Islamic Republic of Iran. 2021; 35:146.

Grocott *et al.* (2013)	Grocott, P.; Graham, T.; Blackwell, R.; Currie, C.; Pillay, E.; Clapham, J.; Graham-King, P.; Hon, J.; Snelson, K. Individualising wound care research: The Woundcare for Epidermolysis Bullosa Project. Wounds UK. 2013;9(3):23-32.
Hernandez *et al.* (2022)	Hernandez, A.; Alonso, F.; Marin, A.; de la Paz, M. Transcultural Validation of a Spanish Version of the Quality of Life in Epidermolysis Bullosa Questionnaire. International Journal of Environmental Research and Public Health. 2022; 19(12):7059.
Horn & Tidman (2002)	Horn, H. M.; Tidman, M. J. Quality of life in epidermolysis bullosa. Clinical and Experimental Dermatology. 2002;27(8):707-710.
Kang *et al.* (2021)	Kang, M.; Chen, J.; Radjenovic, M.; Yang, A.; Feng, G.; Murrell, D. An analysis of the prevalence of osteoporosis and osteopenia in patients with epidermolysis bullosa: A cross-sectional study. Experimental dermatology. 2021; 30(11):1675-1685.
Kiritsi *et al.* (2021)	Kiritsi, D.; Dieter, K.; Niebergall-Roth, E.; Fluhr, S.; Daniele, C.; Esterlechner, J.; Sadeghi, S.; Ballikaya, S.; Erdinger, L.; Schauer, F.; Gewert, S.; Laimer, M.; Bauer, J.; Hovnanian, A.; Zambruno, G.; El Hachem, M.; Bourrat, E.; Papanikolaou, M.; Petrof, G.; Kitzmuller, S.; Ebens, C.; Frank, M.; Frank, N.; Ganss, C.; Martinez, A.; McGrath, J.; Tolar, J.; Kluth, M. Clinical trial of ABCB5+ mesenchymal stem cells for recessive dystrophic epidermolysis bullosa. JCI insight. 2021; 6(22).
Kleinman *et al.* (2023)	Kleinman, E.; Reimer-Taschenbrecker, A.; Haller, C.; Paller, A.; Levy, M.; Eichenfield, L. Gastrostomy tube feeding in epidermolysis bullosa: A multi-center assessment of caregiver satisfaction. Pediatric Dermatology. 2023; 40(2):270-275.
Kýrová & Bučková (2013)	Kýrová J, Bučková H. Quality of life of patients with epidermolysis bullosa. Czech-Slovak Dermatology. 2013;88(3):123-127.
Lai *et al.* (2024)	Lai, J. S.; Nowinski, C.; Rangel, S. M.; Batra, S. T.; Mueller, K.; Chamlin, S.; Ustsinovich, V.; Cella, D.; Mansolf, M.; Paller, A. S. Development of the PROMIS pediatric stigma and extension to the PROMIS pediatric stigma: skin item banks. Quality of Life Research. 2024; 33(3): 865-873.

Lynne *et al.* (2018)	Lynne, V.; Burns, L.; Handsaker, J.; Murdoch, J. Epidermolysis bullosa: management complexities for paediatric patients. British journal of nursing (Mark Allen Publishing). 2018;27(Supplement12): S20-S25.
Manomy *et al.* (2021)	Manomy, P.; Yenamandra, V.; Dabas, G.; Joshi, P.; Ambekar, A.; Sreenivas, V.; Sharma, V. K.; Vatsa, M.; Ravindran, S.; Sethuraman, G. Impact of a Psychodermatological Education Package on the Subjective Distress, Family Burden, and Quality of Life among the Primary Caregivers of Children Affected with Epidermolysis Bullosa. Indian Dermatology Online Journal. 2021;12(2):276-280.
Margari *et al.* (2010)	Margari, F.; Lecce, P.; Santamato, W.; Ventura, P.; Sportelli, N.; Annicchiarico, G.; Bonifazi, E. Psychiatric symptoms and quality of life in patients affected by epidermolysis bullosa. Journal of Clinical Psychology in Medical Settings. 2010;17(4):333-339.
Marty *et al.* (2022)	Marty, M.; Chiaverini, C.; Milon, C.; Costa-Mendes, L.; Kemoun, P.; Mazereeuw-Hautier, J.; Joseph, C. Perception of Oral Health-Related Quality of Life in Children with Epidermolysis Bullosa: A Quantitative and Qualitative Study. JDR clinical and translational research. 2022.
Marty et al. (2023)	Marty, M.; Chiaverini, C.; Milon, C.; Costa-Mendes, L.; Kemoun, P.; Mazereeuw-Hautier, J.; Joseph, C. Perception of Oral Health-Related Quality of Life in Children with Epidermolysis Bullosa: A Quantitative and Qualitative Study. JDR clinical and translational research. 2023; 8(4): 349-355.
Mauritz *et al.* (2021)	Mauritz, P.; Bolling, M.; Duipmans, J.; Hagedoorn, M. The relationship between quality of life and coping strategies of children with EB and their parents. Orphanet Journal of Rare Diseases. 2021;16(1).
Mauritz *et al.* (2022)	Mauritz, P.; Bolling, M.; Duipmans, J.; Hagedoorn, M. Patients' and parents' experiences during wound care of epidermolysis bullosa from a dyadic perspective: a survey study. Orphanet journal of rare diseases. 2022; 17(1):313.
Medina *et al.* (2016)	Medina JAR, G. RMT, Salas-Alanis JC. Stress and quality of life in patients with epidermolysis bullosa. DermatologiaCMQ. 2016;14(2):110-116.

Okata-Karigane *et al.* (2023)	Okata-Karigane, U.; Pathmarajah, P.; Li, S.; Lu, Y.; Tang, J.; Chiou, A. S. 592 Patient-reported outcome measures for chronic itch in epidermolysis bullosa: An exploratory analysis of a randomized controlled trial. Journal of Investigative Dermatology. 2023; 143(5 Supplement):S101.
Pabon *et al.* (2024)	Pabon-Carrasco, Manuel; Caceres-Matos, Rocio; Roche-Campos, Marta; Hurtado-Guapo, Maria Antonia; Ortiz-Romero, Mercedes; Gordillo-Fernandez, Luis M.; Pabon-Carrasco, Daniel; Castro-Mendez, Aurora. Management of Skin Lesions in Patients with Epidermolysis Bullosa by Topical Treatment: Systematic Review and Meta-Analysis. Healthcare (Basel, Switzerland). 2024; 12(2)
Paller *et al.* (2022)	Paller, A.; Pope, E.; Rudin, D.; Malyala, A.; Ramsdell, D.; Johnson, R.; Landy, H.; Murrell, D. A prospective short-term study to evaluate methodologies for the assessment of disease extent, impact, and wound evolution in patients with dystrophic epidermolysis bullosa. Exclude. 2022; 17(1):314.
PEBLES	Jeffs, Eunice; Pillay, Elizabeth; Ledwaba-Chapman, Lesedi; Bisquera, Alessandra; Robertson, Susan; McGrath, John; Wang, Yanzhong; Martinez, Anna; Patel, Anita; Mellerio, Jemima. Costs of UK community care for individuals with recessive dystrophic epidermolysis bullosa: Findings of the Prospective Epidermolysis Bullosa Longitudinal Evaluation Study. Skin health and disease. 2024; 4(1): 1e314 Mellerio J. Natural History of RDEB: news from PEBLES. 2017.
	Mellerio, J. E. Pebles. Acta Dermato-Venereologica. 2020;100(SUPPL 220):44843.
	Mellerio, J.; Pillay, E.; Ledwaba-Chapman, L.; Bisquera, A.; Robertson, S.; Papanikolaou, M.; McGrath, J.; Wang, Y.; Martinez, A.; Jeffs, E. Itch in recessive dystrophic epidermolysis bullosa: findings of PEBLES, a prospective register study. Orphanet journal of rare diseases. 2023; 18(1):235.
	Pillay, E.; Bisquera, A.; Robertson, S.; McGrath, J.; Martinez, A.; Mellerio, J. Treatment costs for individuals with recessive dystrophic epidermolysis bullosa (RDEB): findings of the PEBLES study. Acta Dermato-Venereologica. 2020;100(Suppl 220).
Pourani *et al.* (2022)	Pourani, M.; Vahidnezhad, H.; Youssefian, L.; Rakhshan, A.; Hajimoradi, B.; Abdollahimajd, F.; Uitto, J. 309 Losartan treatment improves recessive dystrophic Epidermolysis bullosa. Journal of Investigative Dermatology. 2022; 142(8 Supplement):S53.

Raymakers *et al.* (2024)	Raymakers, Adam J. N.; Kesselheim, Aaron S.; Mostaghimi, Arash; Feldman, William B. Estimated Spending on Beremagene Geperpavec for Dystrophic Epidermolysis Bullosa. JAMA dermatology. 2024; 160(3): 297-302.
Roman *et al.* (2022)	Roman, J.; Chastek, B.; Anderson, A. Characteristics and burden of illness among patients diagnosed with dystrophic epidermolysis bullosa. Journal of Managed Care and Specialty Pharmacy. 2022; 28(3-A Supplement):S65.
Salamon *et al.* (2024a)	Salamon, Gudrun; Strobl, Sophie; Field-Werners, Ursula; Diem, Anja; Schwieger-Briel, Agnes; Pope, Elena. iscorEB-p: A patient-reported outcome measure for Epidermolysis bullosa. Psychometric properties of the Patient Score from the Instrument for Scoring Clinical Outcome of Research for EB. The British journal of dermatology. 2024.
Salamon *et al.* (2024b)	Salamon, Gudrun; Strobl, Sophie; Field-Werners, Ursula; Welponer, Tobias; Murrell, Dedee F.; Diem, Anja. Translation, cultural adaptation and validation of the German Quality of Life in Epidermolysis Bullosa (QOLEB) questionnaire. Journal of health psychology. 2024;
Sampogna *et al.* (2013)	Sampogna, F.; Tabolli, S.; Di Pietro, C.; Castiglia, D.; Zambruno, G.; Abeni, D. The evaluation of family impact of recessive dystrophic epidermolysis bullosa using the Italian version of the Family Dermatology Life Quality Index. Journal of the European Academy of Dermatology & Venereology. 2013;27(9):1151-5.
Structured Expert Elicitation	Stainer, L.; Ryder, S.; Carr, E.; Collins, C.; Arora, M.; Tolley, K. A Structured Expert Elicitation Exercise Conducted With UK Clinicians to Inform and Validate Inputs for a Cost-Effectiveness Analysis of FILSUVEZ® Gel (Birch Bark Extract) in Epidermolysis Bullosa. 2023.
	Tolley Health Economics. A structured expert elicitation exercise in epidermolysis bullosa to support the cost-effectiveness modelling for Filsuvez gel for the treatment of partial thickness wounds in dystrophic and junctional epidermolysis bullosa. 2022.
Snell *et al.* (2023)	Snell, T.; Stainer, L.; Mather, C.; Hussain, S.; Tolley, K. An Exploratory Study Assessing the Utility Impact in Second Informal Carers of Patients With Epidermolysis Bullosa. 2023.

Snelson *et al.* (2020)	Snelson, K.; Downe, A.; Mellerio, J.; McGrath, J.; Greenblatt, D.; Clapham, J.; Mackenzie, C.; Wharton, S.; Bloor, C. P46 an enhanced model of care for epidermolysis bullosa (EB). 2020.
So *et al.* *(2022a)*	So, J.; Fulchand, S.; Wong, C.; Li, S.; Nazaroff, J.; Gorell, E.; de Souza, M.; Murrell, D.; Teng, J.; Chiou, A.; Tang, J. 194 Patient-reported disease burden in epidermolysis bullosa simplex (EBS). Journal of Investigative Dermatology. 2022; 142(8 Supplement):S33.
So *et al.* *(2022b)*	So, J.; Fulchand, S.; Wong, C.; Li, S.; Nazaroff, J.; Gorell, E.; de Souza, M.; Murrell, D.; Teng, J.; Chiou, A.; Tang, J. A global, cross-sectional survey of patient-reported outcomes, disease burden, and quality of life in epidermolysis bullosa simplex. Orphanet journal of rare diseases. 2022; 17(1):270.
Stefano *et al.* (2021)	Stefano, S.; Grassi, F.; Lalatta, F.; Scuvera, G.; Brena, M.; Grillo, P.; Peves Rios, W.; Guez, S. Family burden of children suffering from epidermolysis bullosa. 2021. Italian Journal of Dermatology and Venereology. 2021;156(5):580-587.
Taboli *et al.* (2010)	Tabolli, S.; Pagliarello, C.; Uras, C.; di Pietro, C.; Zambruno, G.; Castiglia, D.; Sampogna, F.; Abeni, D. Family burden in epidermolysis bullosa is high independent of disease type/subtype. Acta Dermato-Venereologica. 2010;90(6):607-611.
Tabor *et al.* (2024)	Tabor, Aaron; LeQuang, Jo Ann K.; Pergolizzi, Joseph, Jr. Epidermolysis Bullosa: Practical Clinical Tips From the Field. Cureus. 2024; 16(2).
Tang *et al.* (2023)	Tang, J.; Marinkovich, M.; Wiss, K.; McCarthy, D.; Truesdale, A.; Chiou, A.; McIntyre, J.; Moore, A.; Grachev, I. Results from VIITAL: A phase 3, randomized, intrapatient-controlled trial of an investigational collagen type VII gene-corrected autologous cell therapy, EB-101, for the treatment of recessive dystrophic epidermolysis bullosa (RDEB). Journal of Investigative Dermatology. 2023; 143(5):S138-S138.
Togo *et al.* (2023)	Togo, C. C. G.; Zidorio, A. P. C.; Sa, N. M.; Dutra, E. S. Calidad de vida relacionada con la salud y gravedad clinica en personas con 178pidermolysis bullosa: una propuesta para evaluar el deterioro nutricional por el indice de masa corporal (Birmingham Epidermolysis Bullosa Severity Score), Health-related quality. Nutricion hospitalaria. 2023.

Togo *et al.* (2024)	Togo, Camille Cristine Gomes; Zidorio, Ana Paula Caio; Sa, Natan Monsores de; Dutra, Eliane SaidHealth-related quality of life and clinical severity in people with epidermolysis bullosa - A proposal for assessing nutritional compromise by body mass index (Birmingham Epidermolysis Bullosa Severity Score). Calidad de vida relacionada con la salud y gravedad clinica en personas con epidermolisis bullosa: una propuesta para evaluar el deterioro nutricional por el indice de masa corporal (Birmingham Epidermolysis Bullosa Severity Score).2024; 41(2): 400-408.
Torres-Pradilla *et al.* (2023)	Torres Pradilla, Mauricio; Alvarez, Erick; Novoa, Monica; Lozano, Ivonne; Trujillo, Maribel. Oleogel-S10 in Dystrophic Epidermolysis Bullosa: A Case Series Evaluating the Impact on Wound Burden Over Two Years Advances in therapy. 2024; 41(2) 867-877
Verbeeck *et al.* (2023)	Verbeeck, J.; De Backer, M.; Barre, E.; Salvaggio, S.; Deltuvaite-Thomas, V.; Chiem, J.; Kosta, S.; Buyse, M. Including Patient Relevant Endpoints (QUALITY OF LIFE) in Multicomponent Endpoints with Generalized Pairwise Comparisons. 2023.
Woodley *et al.* (2024)	Woodley, David T.; Hao, Michelle; Kwong, Andrew; Levian, Brandon; Cogan, Jon; Hou, Yingping; Mosallaei, Daniel; Kleinman, Elana; Zheng, Kate; Chung, Claire; Kim, Gene; Peng, David; Chen, Mei. Intravenous gentamicin therapy induces functional type VII collagen in recessive dystrophic epidermolysis bullosa patients: An open label clinical trial. The British journal of dermatology. 2024
Wu *et al.* (2023)	Wu, X.; Yan, S.; Jiang, J.; Zhou, T.; Fang, X.; Yang, H.; Bai, X.; Wang, H.; Luo, X. Successful treatment of epidermolysis bullosa pruriginosa by dupilumab. The Journal of dermatology. 2023; 50(6):837-842.
GBA	Gemeinsamer Bundesausschuss. BA Birch bark extract (treatment of wounds associated with epidermolysis bullosa [6 months and older]).
	Gemeinsamer Bundesausschuss. Justification of the resolution of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Birch Bark Extract (treatment of wounds associated with epidermolysis bullosa [6 months and older]). February 2023.
IQWiG	IQWiG Filsuvez Gel (Epidermolysis bullosa).

NICE HST28	NICE [HST28] Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa. https://www.nice.org.uk/guidance/hst28.
NICE ID 3959	NICE [ID3959] Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa. https://www.nice.org.uk/guidance/awaiting-development/gid-ta10868.

Table 87 of excluded records

Excluded records by reason
Duplicate records
de Stefano, S.; Grassi, F. S.; Lalatta, F.; Scuvera, G.; Brena, M.; Grillo, P.; Peves Rios, W. E.; Guez, S. Family burden of children suffering from epidermolysis Bullosa. Italian Journal of Dermatology and Venereology. 2021; 156(2): 580-587.
Frew, J. W.; Martin, L. K.; Nijsten, T.; Murrell, D. F. Erratum: Quality of life evaluation in epidermolysis bullosa (EB) through the development of the QOLEB questionnaire: An EB-specific quality of life instrument (British Journal of Dermatology (2009) 161 (1323-1330)). British Journal of Dermatology. 2010; 162(3): 701.
Gemeinsamer Bundesausschuss. Justification of the resolution of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Birch Bark Extract (treatment of wounds associated with epidermolysis bullosa [6 months and older]). February 2023
Gorell, E.; Eng, V.; Solis, D.; Choi, S.; Nazaroff, J.; Li, S.; de Souza, M.; Murrell, D.; Marinkovich, M. P.; Tang, J. 282 Larger wounds in recessive dystrophic epidermolysis bullosa patients associated with worse quality of life: Results of a global cross-sectional survey. Journal of Investigative Dermatology. 2020; 140(7 Supplement): S34.
NICE [ID3959] Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa. https://www.nice.org.uk/guidance/awaiting-development/gid-ta10868
Okata-Karigane , U.; Pathmarajah, P.; Li, S.; Lu, Y.; Tang, J.; Chiou, A. S. 592 Patient-reported outcome measures for chronic itch in epidermolysis bullosa: An exploratory analysis of a randomized controlled trial. Journal of Investigative Dermatology. 2023; 143(5 Supplement):S101
Snell, T.; Stainer, L.; Mather, C.; Hussain, S.; Tolley, K. An Exploratory Study Assessing the Utility Impact in Second Informal Carers of Patients With Epidermolysis Bullosa. 2023
Stainer, L .; Ryder, S.; Carr, E.; Collins, C.; Arora, M.; Tolley, K. A Structured Expert Elicitation Exercise Conducted With UK Clinicians to Inform and Validate Inputs for a Cost-Effectiveness Analysis of FILSUVEZ® Gel (Birch Bark Extract) in Epidermolysis Bullosa. 2023
Tang, J .; Marinkovich, M.; Wiss, K.; McCarthy, D.; Truesdale, A.; Chiou, A.; McIntyre, J.; Moore, A.; Grachev, I. Results from VIITAL: A phase 3, randomized, intrapatient-controlled trial of an investigational collagen type VII gene-corrected autologous cell therapy, EB-101, for the treatment of recessive dystrophic epidermolysis bullosa (RDEB). Journal of Investigative Dermatology. 2023; 143(5):S138-S138
Harricharan, S. Richard, ME.; Roman, J.; Forsythe, A. The Economic and Humanistic Burden of Dystrophic Epidermolysis Bullosa (DEB)- A Systematic Literature Review. 2021.
Hiremagalore, R. OP74 MANAGING EB IN A RESOURCE LIMITED SETTING. 2020.
Mahajan, R.; Bishnoi, A.; Manjunath, S.; Kishore, K.; De, D.; Murrell, D. F.; Handa, S. 17891 Quality of life score in Indian patients with epidermolysis bullosa and its correlation with clinical severity assessment scores. Journal of the American Academy of Dermatology. 2020; 83(6 Supplement): AB202.
Mellerio, J. E. OP20 PEBLES. 2020.
Pillay, E. I.; Jeffs, E.; Bisquera, A.; Robertson, S.; McGrath, J.; Martinez, A. E.; Mellerio, J. E. Treatment costs for individuals with recessive dystrophic epidermolysis bullosa (RDEB): Findings of the pebles study. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 58.
Excluded on outcomes

Adni, T.; Martin, K.; Mudge, E. The psychosocial impact of chronic wounds on patients with severe epidermolysis bullosa. Journal of Wound Care. 2012; 21(11): 528-538.

Agustin, Maulidina; Mahadewi, Anita; Danarti Retno. Bone marrow transplantation and bone marrow-derived mesenchymal stem cell therapy in epidermolysis bullosa: A systematic review. Pediatric dermatology 2024

Anonymous. Patient-reported outcomes and quality of life in dominant dystrophic epidermolysis bullosa: A global cross-sectional survey. Pediatric dermatology. 2022; 39(6): 1007.

Anonymous. With birch bark extract against epidermolysis bullosa: CHMP recommends approval of Filsuvez gel. Deutsche Apotheker Zeitung. 2022; 162(8).

Baardman, R.; Bolling, M. C. The importance of accurate epidemiological data of epidermolysis bullosa. British Journal of Dermatology. 2022; 186(5): 765-766.

Bageta, M.; Balboa, P. L.; Glover, R.; Cooper, C.; Papaioannou, D.; Julious, S.; Dimairo, M.; Biggs, K.; Petrof, G.; Martinez, A. E. Mesenchymal stromal cells infusions in children with recessive dystrophic epidermolysis bullosa (MissionEB): A randomised controlled trial. Pediatric Dermatology. 2022; 39(SUPPL 1): 35.

Bageta, M.; Balboa, P. L.; Glover, R.; Cooper, C.; Papaioannou, D.; Julious, S.; Dimairo, M.; Biggs, K.; Petrof, G.; Martinez, A. Mesenchymal stromal cells infusions in children with recessive dystrophic epidermolysis bullosa (MissionEB): A randomised controlled trial. Pediatric Dermatology. 2023; 40(Supplement 2): 5.

Bageta, M. L.; Balboa, P. L.; Glover, R.; Cooper, C.; Papaioannou, D. E.; Julious, S.; Dimairo, M.; Biggs, K.; Petrof, G.; Martinez, A. E. Mesenchymal stromal cells infusions in children with recessive dystrophic epidermolysis bullosa. (MissionEB): a randomized controlled trial. British Journal of Dermatology. 2023; 189(3): E42-E43

Bageta, M.; Balboa, P. L.; Yerlett, N.; Rybak, A.; Petrof, G.; Martinez, A. Management of acute desloughing of the oesophageal lining in patients with dystrophic epidermolysis bullosa: a case series of six paediatric patients. British Journal of Dermatology 2023; 189(3): E41-E42

Bischof, Johannes; Hierl, Markus; Koller, Ulrich. Emerging Gene Therapeutics for Epidermolysis Bullosa under Development. International journal of molecular sciences 2024; 25(4).

Bishnoi, A.; Manjunath, S.; Kishore, K.; De, D.; Handa, S.; Murrell, D. F.; Mahajan, R. Hindi translation and validation of quality of life score in Indian patients with epidermolysis bullosa; and its correlation with the clinical severity assessment scores: A cross-sectional study. Indian Journal of Dermatology, Venereology & Leprology. 2022; 88(2): 177-183.

Blanchet-Bardon, C.; Bohbot, S. Using Urgotul dressing for the management of epidermolysis bullosa skin lesions. Journal of wound care. 2005; 14(10): 490-491.

Brena, M.; Tadini, G.; Marchisio, P.; Pilo, C.; Guez, S. The italian registry for patients affected by epidermolysis bullosa. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 43.

Bruckner, A. L.; Fairclough, D. L.; Feinstein, J. A.; Lara-Corrales, I.; Lucky, A. W.; Tolar, J.; Pope, E. Reliability and validity of the instrument for scoring clinical outcomes of research for epidermolysis bullosa (iscorEB). British Journal of Dermatology. 2018; 178(5): 1128-1134.

Bruckner, A. L.; Feinstein, J. A.; Peoples, K.; Lara-Corrales, I.; Pope, E. A multicenter cohort study evaluating patient-reported outcomes in epidermolysis bullosa. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 67-68.

Bruckner, A.; Feinstein, J.; Peoples, K.; Lara-Corrales, I.; Pope, E. P103 a multicenter cohort study evaluating patient-reported outcomes in epidermolysis bullosa. 2020.

Bruckner, A. L.; Losow, M.; Wisk, J.; Patel, N.; Reha, A.; Lagast, H.; Gault, J.; Gershkowitz, J.; Kopelan, B.; Hund, M.; Murrell, D. F. The challenges of living with and managing epidermolysis bullosa: Insights from patients and caregivers. Orphanet Journal of Rare Diseases. 2020; 15(1) (no pagination).

Bruckner, A.; Kern, J. S.; Murrell, D. F.; Lwe, S.; Maher, L. The effect of Oleogel-S10 (birch triterpenes) on procedural pain and dressing change frequency in dystrophic epidermolysis bullosa (DEB): Analysis from the EASE study. Pediatric Dermatology. 2022; 39(5): 803.

Bruckner, A.; Kern, J. S.; Murrell, D. F.; Maher, L.; Cunnigham, T. EASE study demonstrates efficacy of OLEOGEL-S10 (birch triterpenes) on wound healing in patients with dystrophic epidermolysis bullosa (DEB). Pediatric Dermatology. 2022; 39(5): 779.

Bruckner, A.; Kern, J. S.; Sprecher, E.; Fernandez, M.; Cunningham, T.; Sumeray, M.; Murrell, D. F. 615 Efficacy and safety of Oleogel-S10 (birch triterpenes) for recessive dystrophic epidermolysis bullosa (RDEB): Results of 3 months double-blind treatment of the phase 3 study 'EASE'. Journal of Investigative Dermatology. 2021; 141(5 Supplement): S107.

Brun, J.; Chiaverini, C.; Devos, C.; Leclerc-Mercier, S.; Mazereeuw, J.; Bourrat, E.; Maruani, A.; Mallet, S.; Abasq, C.; Phan, A.; Vabres, P.; Martin, L.; Bodemer, C.; Lagrange, S.; Lacour, J. P.; Research Group of the French Society of Pediatric, Dermatology Pain and quality of life evaluation in patients with localized epidermolysis bullosa simplex. Orphanet Journal Of Rare Diseases. 2017; 12(1): 119.

Burd, A.; Huang, L. Advanced skin, scar and wound care centre for children: A new era of care. Indian Journal of Plastic Surgery. 2012; 45(2): 184-92.

Cestari, T.; Prati, C.; Menegon, D. B.; Prado Oliveira, Z. N.; Machado, M. C. R.; Dumet, J.; Nakano, J.; Murrell, D. F. Translation, cross-cultural adaptation and validation of the Quality of Life Evaluation in Epidermolysis Bullosa instrument in Brazilian Portuguese. International Journal of Dermatology. 2016; 55(2)(): e94-e99.

Chan, J. M.; Weisman, A.; King, A.; Maksomski, S.; Shotwell, C.; Bailie, C.; Weaver, H.; Bodan, R.; Guerrero, E.; Zmazek, M.; Khuu, P. Occupational therapy for epidermolysis bullosa: clinical practice guidelines. Orphanet Journal Of Rare Diseases. 2019; 14(1): 129.

Chernyshov, P. V.; Marron, S. E.; Tomas-Aragones, L.; Pustisek, N.; Gedeon, I.; Suru, A.; Tiplica, G. S.; Salavastru, C. M.; Nikolic, M.; Kakourou, T.; Valari, M.; Yordanova, I.; Darlenski, R.; Sampogna, F. Initial validation of the epidermolysis bullosa-specific module of the Infants and Toddlers Dermatology Quality of Life questionnaire. Dermatologic Therapy. 2020; 33(6): e14128.

Chang, C.; Chang, C.; Chang, H. P87 oral care program improves the life quality of patients with epidermolysis bullosa: a Taiwanese perspective. 2020.

Chateau, Antoinette V.; Aldous, Colleen; Dlova, Ncoza; Blackbeard, David. 'It breaks my heart': Healthcare practitioners' caring for families with epidermolysis bullosa. Health SA = SA Gesondheid. 2023; 28(2355).

Rogers, C.; Gibson, M.; Kern, J.; Martin, L.; Robertson, S.; Daniel, B.; Su, J.; Murrell, D. P27 which outcome measures are the best for clinical trials in epidermolysis bullosa. 2020.

De Stefano, S.; Lalatta, F.; Tadini, G.; Grassi, F. S.; Rossetti, D.; Salera, S.; Brena, M.; Lopopolo, A.; Picciolini, O.; Spinelli, A.; Montani, G.; Scuvera, G.; Guez, S. Family burden of children suffering from Epidermolysis Bullosa. European Journal of Human Genetics. 2019; 27: 737-738.

Delgado-Miguel, C.; Miguel-Ferrero, M.; Munoz-Serrano, A. J.; Diaz, M.; Maseda, R.; De Lucas, R.; Lopez-Gutierre, J. C. Improving survival in epidermolysis bullosa patients with squamous cell carcinoma: Long-term results from a national reference centre. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 49.

Delgado-Miguel, C.; Miguel-Ferrero, M.; Munoz-Serrano, A. J.; Leal, N.; Triana, P.; LopezGutierre, J. C. EB patients need EB specialized surgeons: The role of paediatric surgeons in epidermolysis bullosa. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 67.

Doolan, B. J.; McGrath, J. A.; Mellerio, J. E. Beremagene geperpavec (B-VEC) gene therapy for the treatment of cutaneous wounds in patients with dystrophic epidermolysis bullosa: a critically appraised research paper. British Journal of Dermatology. 2024 190(3): 340-342

Downe, A.; Drislane, C.; Mellerio, J. E.; Greenblatt, D. T. Teledermatology in rare disease. British Journal of Dermatology. 2020; 183(SUPPL 1): 171.

Dures, E.; Rumsey, N.; Morris, M.; Gleeson, K. A Cross Sectional, Observational Survey to Assess Levels and Predictors of Psychological Wellbeing in Adults with Epidermolysis Bullosa. Health Psychology Research. 2013; 1(1): e4.

Gorell, E.S.; Eng, V.; Solis, D.; Choi, S.; Nazaroff, J.; de Souza, M.; Murrell, D.; Marinkovich, M.P.; Tang, J.Y. P29 relationships between wound size, clinical manifestations, and quality of life in recessive dystrophic epidermolysis bullosa: a global cross- sectional survey. 2020.

Eichstadt, S.; Tang, J. Y.; Solis, D. C.; Siprashvili, Z.; Marinkovich, M. P.; Whitehead, N.; Schu, M.; Fang, F.; Erickson, S. W.; Ritchey, M. E.; Colao, M.; Spratt, K.; Shaygan, A.; Ahn, M. J.; Sarin, K. Y. From Clinical Phenotype to Genotypic Modelling: Incidence and Prevalence of Recessive Dystrophic Epidermolysis Bullosa (RDEB). Clinical, Cosmetic and Investigational Dermatology CCID. 2019; 12: 933-942.

Eismann, E. A.; Lucky, A. W.; Cornwall, R. Hand function and quality of life in children with epidermolysis bullosa. Pediatric Dermatology. 2014; 31(2): 176-182.

Eng, V.; Solis, D.; Choi, S.; Nazaroff, J.; Li, S.; Tang, J. 935 Clinical manifestations and quality of life in patients with recessive dystrophic epidermolysis bullosa. Journal of Investigative Dermatology. 2019; 139(5 Supplement): S161.

Esca¡mez, M. OP8 CLINICAL RESEARCH. 2020.

Jeffs, E,; Pillay, E,; Bisquera, A.; Robertson, S.; McGrath, J.; Martinez, A.; Mellerio, J. P74 itch and pain reported by individuals with recessive dystrophic epidermolysis bullosa (RDEB): findings of the PEBLES study. 2020.

Jeffs, E.; Pillay, E.; Bisquera, A.; Robertson, S.; McGrath, J.; Martinez, A.; Mellerio, J. P75 quality of life reported by individuals with recessive dystrophic epidermolysis bullosa (RDEB): findings of the PEBLES study. 2020.

Fine, J. D.; Johnson, L. B.; Weiner, M.; Suchindran, C. Assessment of mobility, activities and pain in different subtypes of epidermolysis bullosa. Clinical & Experimental Dermatology. 2004; 29(2): 122-7.

Frew, J. W.; Martin, L. K.; Nijsten, T.; Murrell, D. F. Quality of life evaluation in epidermolysis bullosa (EB) through the development of the QOLEB questionnaire: An EB-specific quality of life instrument. British Journal of Dermatology. 2009; 161(6): 1323-1330.

Fuentes, I.; Guttmann-Gruber, C.; Tockner, B.; Diem, A.; Klausegger, A.; Cofre-Araneda, G.; Figuera, O.; Hidalgo, Y.; Morande, P.; Palisson, F.; Rebolledo-Jaramillo, B.; Yubero, M. J.; Cho, R. J.; Rishel, H. I.; Marinkovich, M. P.; Teng, J. M. C.; Webster, T. G.; Prisco, M.; Eraso, L. H.; Pinon Hofbauer, J.; South, A. P. Cells from discarded dressings differentiate chronic from acute wounds in patients with Epidermolysis Bullosa. Scientific Reports. 2020; 10(1): 15064.

Fulchand, S.; Harris, N.; Li, S.; Barriga, M.; Gorell, E.; De Souza, M.; Murrell, D.; Marinkovich, M. P.; Krishna Yenamandra, V.; Tang, J. Y. Patient-reported outcomes and quality of life in dominant dystrophic epidermolysis bullosa: A global cross-sectional survey. Pediatric Dermatology. 2021; 38(5): 1198-1201.

Petrof, G.; Ogboli, M.; Martinez, A.; Mellerio, J.; Papanikolaou, M.; Heagerty, A.; Moss, C. P106 The epidemiology of EB in the UK: data from the national database. 2020.

Garcia-Romero, M. T.; Becerril-Rico, J.; Dabdoub-Hernandez, A. A. Epidermolysis bullosas: An analysis of the cost of medical care in Mexico. [Spanish]. Medicina Interna de Mexico. 2019; 35(1): 30-38.

Geuens, S. Education and family support/care &social services. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 26.

Gewert, S.; Kiritsi, D.; Schumann, H.; Schwieger-Briel, A.; Schauer, F. Oleogel-S10 for the treatment of epidermolysis bullosa (EB) a 4-patient case series. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 75-76.

Goldschneider, K. R.; Good, J.; Harrop, E.; Liossi, C.; Lynch-Jordan, A.; Martinez, A. E.; Maxwell, L. G.; Stanko-Lopp, D. Pain care for patients with epidermolysis bullosa: Best care practice guidelines. BMC Medicine. 2014; 12(1) (no pagination).

Gorell, E. S.; Eng, V.; Solis, D.; Choi, S.; Nazaroff, J.; De Souza, M.; Murrell, D.; Marinkovich, M. P.; Tang, J. Y. Relationships between wound size, clinical manifestations, and quality of life in recessive dystrophic epidermolysis bullosa: A global cross-sectional survey. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 39-40.

Gorell, E. S.; Wolstencroft, P. W.; de Souza, M. P.; Murrell, D. F.; Linos, E.; Tang, J. Y. Financial burden of epidermolysis bullosa on patients in the United States. Pediatric Dermatology. 2020; 37(6): 1198-1201.

Gorell, E.; Eng, V.; Solis, D.; Choi, S.; Nazaroff, J.; Li, S.; de Souza, M.; Murrell, D.; Marinkovich, M. P.; Tang, J. Larger wounds in recessive dystrophic epidermolysis bullosa patients associated with worse quality of life: Results of a global cross-sectional survey. Journal of Investigative Dermatology. 2020; 140(7): S34-S34.

Hachem, May El; Diociaiuti, Andrea; Zambruno, Giovanna; Samela, Tonia; Ferretti, Francesca; Carnevale, Claudia; Linertova, Renata; Bodemer, Christine; Murrell, Dedee F.; Abeni, Damiano. "Quality of Life in Epidermolysis Bullosa" and "Epidermolysis Bullosa Burden of Disease": Italian translation, cultural adaptation, and pilot testing of two disease-specific questionnaires. Italian journal of pediatrics. 2024; 50(1): 76

Hubl, V.; Salamon, G. P55 facilitating factors for the quality of life of people living with epidermolysis bullosa and their families, identified by health care professionals and experts. 2020.

Harris, N.; Fulchand, S.; Nazaroff, J.; Li, S.; Tang, J. Y. Natural history of spontaneous wound healing in recessive dystrophic epidermolysis bullosa wound types using a mobile photography application. Journal of Investigative Dermatology. 2023; 143(5): S260-S260.

Hernandez-Martin, A.; Aranegui, B.; Escamez, M. J.; De Lucas, R.; Vicente, A.; Rodriguez-Diaz, E.; Bernabeu-Wittel, J.; Gonzalez-Hermosa, R.; Garcia-Patos, V.; Ginarte, M.; Mascaro Jr, J. M.; Corredera, C.; Baselga, E.; Santiago, J. L.; Chaves, A.; Roman, C.; Evole, M.; Martin-Santiago, A.; Torrelo, A.; Del Rio, M.; Feito, M.; Gonzalez-Ensenat, M. A.; Romero, G.; Morcillo-Makow, E.; Abaitua, I.; Garcia-Doval, I. Prevalence of dystrophic epidermolysis bullosa in Spain: A population-based study using the 3-source capture-recapture method. Evidence of a need for improvement in care. Actas Dermo-Sifiliograficas. 2013; 104(10): 890-896.

Hiremagalore, R. Managing EB in a resource limited setting. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 21.

Huang, H.; Aala, W. F.; Onoufriadis, A.; Hsu, C.; McGrath, J. A. Methotrexate improves pruritus in patients with recessive dystrophic epidermolysis bullosa. Journal of Investigative Dermatology. 2023; 143(5): S141-S141.

Hubbard, L. D.; Mayre-Chilton, K. Quality of life among adults with epidermolysis bullosa living with a gastrostomy tube since childhood. Qualitative health research. 2015; 25(3): 310-319.

Hunjan, M.; Bardhan, A.; Zuzarte, L.; Balacco, D.; Harper, N.; Heagerty, A. Are existing validated severity scores for epidermolysis bullosa reflective of the burden of disease in patients with epidermolysis bullosa simplex?. Clinical and experimental dermatology. 2023; 48(6): 706-707.

Jain, S. V.; Harris, A. G.; Su, J. C.; Orchard, D.; Warren, L. J.; McManus, H.; Murrell, D. F. The Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI): grading disease severity and assessing responsiveness to clinical change in epidermolysis bullosa. Journal of the European Academy of Dermatology and Venereology. 2017; 31(4): 692-698.

Jeffs, E.; Pillay, E. I.; Bisquera, A.; Robertson, S.; McGrath, J.; Martinez, A. E.; Mellerio, J. E. Itch and pain reported by individuals with recessive dystrophic epidermolysis bullosa (RDEB): Findings of the pebles study. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 56-57.

Jeffs, E.; Pillay, E. I.; Bisquera, A.; Robertson, S.; McGrath, J.; Martinez, A. E.; Mellerio, J. E. Quality of life reported by individuals with recessive dystrophic epidermolysis bullosa (RDEB): Findings of the pebles study. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 57.

Jeon, I. K.; On, H. R.; Kim, S. C. Quality of Life and Economic Burden in Recessive Dystrophic Epidermolysis Bullosa. Annals of Dermatology. 2016; 28(1): 41791.

Johnson, A. N.; McGuire, K.; McCormick, A.; Rieger, K. E.; Broadwater, L.; Jain, S.; Perrone, L.; Teng, J. M.; Tang, J. Y.; Chiou, A. S. Interim results of a phase I/II, closed label, randomized pilot study for the safety and efficacy of TolaSure gel, 5% w/w targeting aggregated mutant keratin in severe epidermolysis bullosa simplex (TAMES). Journal of Investigative Dermatology. 2023; 143(5): S102-S102.

Joseph, Clara; Marty, Mathieu; Dridi, Sophie-Myriam; Verhaeghe, Veroniek; Bailleul-Forestier, Isabelle; Chiaverini, Christine; Hubiche, Thomas; Mazereeuw-Hautier, Juliette; Deny, Olivier; Declerck, Dominique; Kemoun, Philippe Oral health status in patients with inherited epidermolysis bullosa: a comparative multicenter study. Quintessence international (Berlin, Germany : 1985). 2023; 54(1): 34-43.

Kang, M.; Chen, J.; Yang, A.; Radjenovic, M.; Feng, G.; Murrell, D. Osteoporosis and osteopenia in all types of epidermolysis bullosa - A cross sectional study. Australasian Journal of Dermatology. 2019; 60(Supplement 1): 51.

Kern, J. S.; Schwieger-Briel, A.; Lowe, S.; Sumeray, M.; Davis, C.; Martinez, A. E. Oleogel-S10 Phase 3 study "EASE" for epidermolysis bullosa: study design and rationale. Trials [Electronic Resource]. 2019; 20(1): 350.

Kiritsi, D.; Murrell, D. F.; Bruckner, A. L.; Sprecher, E.; Maher, L.; Cunningham, T.; Kern, J. S. Long-term safety and efficacy of Oleogel-S10 (birch triterpenes) in epidermolysis bullosa wounds: 24-month open-label data from the EASE study. Pediatric Dermatology. 2023; 40(Supplement 2): 35.

Kiritsi, D.; Murrell, D. F.; Sprecher, E.; Bruckner, A. L.; Bodemer, C.; Cunningham, T.; Summeray, M.; Kern, J. S. EASE study demonstrates efficacy of Oleogel-S10 (birch triterpenes) on wound healing and pain in the pediatric Epidermolysis Bullosa population. Pediatric Dermatology. 2022; 39(SUPPL 1): 9.

Kirkorian, A. Y.; Weitz, N. A.; Tlougan, B.; Morel, K. D. Evaluation of wound care options in patients with recessive dystrophic epidermolysis bullosa: A costly necessity. Pediatric Dermatology. 2014; 31(1): 33-37.

Korte, E. W. H.; Welponer, T.; Kottner, J.; van der Werf, S.; van den Akker, P. C.; Horvath, B.; Kiritsi, D.; Laimer, M.; Pasmooij, A. M. G.; Wally, V.; Bolling, M. C. Heterogeneity of reported outcomes in epidermolysis bullosa clinical research: a scoping review as a first step towards outcome harmonization. British Journal of Dermatology. 2023; 189(1): 80-90

Kumari, I. Chronic wound management-epidermolysis bullosa. Journal of Wound Care. 2020; 29(SUPPL 7B): 100.

Lee, S. E.; Lee, S. J.; Kim, S. E.; Kim, K.; Cho, B.; Roh, K.; Kim, S. C. Intravenous allogeneic umbilical cord blood-derived mesenchymal stem cell therapy in recessive dystrophic epidermolysis bullosa patients. JCI Insight. 2021; 6(2) (no pagination).

Lee, S. J.; Kim, K.; Cho, B.; Roh, K.; Kim, S. C.; Lee, S. E. Safety and clinical effects of systemic allogeneic ucb-mscs therapy for patients with RDEB. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 68.

Liemberger, B.; Bischof, J.; Kocher, T.; Ablinger, M.; Murauer, E. M.; Nystrom, A.; Wally, V.; Mayr, E.; Koller, U.; Bauer, J. Non-viral COL7A1 editing as therapy approach for dystrophic epidermolysis bullosa. Journal of Investigative Dermatology. 2023; 143(5): S151-S151.

Loh, C. C.; Kim, J.; Su, J. C.; Daniel, B. S.; Venugopal, S. S.; Rhodes, L. M.; Intong, L. R.; Law, M. G.; Murrell, D. F. Development, reliability, and validity of a novel Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI). Journal of the American Academy of Dermatology. 2014; 70(1): 89-97.e1-13.

Macik, D.; Kowalska-Dabrowska, M. The need of social support, life attitudes and life satisfaction among parents of children suffering from epidermolysis bullosa. Przeglad Dermatologiczny. 2015; 102(3): 211-220.

Magno, J. A.; Mehl, A.; Osti, K. A. Butterfly kit-clinical and logistic support to the newborn with epidermolysis bullosa. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 65.

Mahajan, R.; Bishnoi, A.; Manjunath, S.; Kishore, K.; De, D.; Murrell, D. F.; Handa, S. Quality of life score in Indian patients with epidermolysis bullosa and its correlation with clinical severity assessment scores. Journal of the American Academy of Dermatology. 2020; 83(6): AB201-AB201.

Marinkovich, M. P.; Sridhar, K. J.; Bagci, I. S.; Dolorito, J. A. M.; Keene, D. R.; Yonchek, M.; Blumenthal, R. L.; Spellman, M. C. The Treatment of Wounds Associated with Recessive Dystrophic Epidermolysis Bullosa with Local Injections of Gene-Corrected, Collagen VII-Expressing Autologous Human Dermal Fibroblasts. Molecular Therapy. 2022; 30(4): 376-376.

Marinkovich, M.; Gonzalez, M.; Guide, S.; Bagci, I. S.; Chitra, S.; Agostini, B.; Chen, H.; Parry, T.; Krishnan, S. GEM-3: phase 3 safety and immunogenicity results of beremagene geperpavec (B-VEC), an investigational, topical gene therapy for dystrophic epidermolysis bullosa (DEB). Journal of Investigative Dermatology. 2022; 142(8): S79-S79.

Martin, K.; Geuens, S.; Asche, J. K.; Bodan, R.; Browne, F.; Downe, A.; Garcia Garcia, N.; Jaega, G.; Kennedy, B.; Mauritz, P. J.; Perez, F.; Soon, K.; Zmazek, V.; Mayre-Chilton, K. M. Psychosocial recommendations for the care of children and adults with epidermolysis bullosa and their family: evidence based guidelines. Orphanet Journal Of Rare Diseases. 2019; 14(1): 133.

Martinez, A.; Murrell, D. F.; Bruckner, A. L.; Kern, J.; Maher, L.; Cunningham, T. Safety and efficacy of oleogel-S10 (birch triterpenes) for epidermolysis bullosa: results of a 12-month interim analysis of the open-label phase from the EASE study. British Journal of Dermatology. 2022; 187(Supplement 1): 89.

Mellerio, Jemima E.; Kiritsi, Dimitra; Marinkovich, M. Peter; Haro, Natividad Romero; Badger, Kellie; Arora, Meena; Dziasko, Marc A.; Vithlani, Mansi; Martinez, Anna E. Mapping the burden of severe forms of epidermolysis bullosa - Implications for patient management. JAAD international. 2023; 11: 224-232.

Parvizi, M.; Handjani, F,; Ghahramani, S.; Parvizi, Z. P110 The quality of life in patients with epidermolysis bullosa in Iran: a cross sectional study. 2020.

Murrell, D. F. Epidermolysis bullosa relevant endpoints a debate. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 15-16.

Murrell, D. F.; Bruckner, A. L.; Davis, C.; Maher, L.; Cunningham, T.; Summeray, M. Correlation between wound burden and procedural pain in patients with EB >= 4 years of age: An exploratory analysis from the EASE study. Journal of the American Academy of Dermatology. 2022; 87(3): AB152-AB152.

Murrell, D.; Bruckner, A. L.; Sprecher, E.; Kiritsi, D.; Maher, L.; Cunningham, T.; Kern, J. S. Oleogel-S10 (birch triterpenes) in the treatment of epidermolysis bullosa wounds: 24-month efficacy and safety data from the EASE study. British Journal of Dermatology. 2023; 188(Supplement 4): iv68-iv69.

Murrell, D.; Bruckner, A.; Kern, J.; Maher, L.; Cunningham, T. Safety and efficacy of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: Results of a 12-month interim analysis from the open label phase of the phase 3 study 'EASE'. Pediatric Dermatology. 2023; 40(Supplement 1): 35-36.

Murrell, D.; Sprecher, E.; Bruckner, A.; Bodemer, C.; Cunningham, T.; Sumeray, M.; Kern, J. Efficacy of Oleogel-S10 (birch triterpenes) on wound healing and pain in the pediatric epidermolysis bullosa population from the EASE study. Pediatric Dermatology. 2023; 40(Supplement 1): 39.

Nazaroff, J.; Harris, N.; Tang, J. Y. 900 Online, home-based epidermolysis bullosa patient registry. Journal of Investigative Dermatology. 2023; 143(5 Supplement): S154.

Nazaroff, J.; Harris, N.; Tang, J. Y. Online, home-based epidermolysis bullosa patient registry. Journal of Investigative Dermatology. 2023; 143(5): S154-S154.

Osipowicz, K.; Wozniak, K.; Kowalewski, C.; Kalinska-Bienias, A. Quality of life evaluation in epidermolysis bullosa-questionnaires for patients and fammilies of patients. Journal of the Dermatology Nurses' Association. Conference: 24th World Congress of Dermatology. Milan Italy. 2020; 12(2).

Paller, A. S.; Browning, J.; Nikolic, M.; Bodemer, C.; Murrell, D. F.; Lenon, W.; Krusinska, E.; Reha, A.; Lagast, H.; Barth, J. A.; Group, Essence Study Efficacy and tolerability of the investigational topical cream SD-101 (6% allantoin) in patients with epidermolysis bullosa: a phase 3, randomized, double-blind, vehicle-controlled trial (ESSENCE study). Orphanet Journal Of Rare Diseases. 2020; 15(1): 158.

Parvizi, M. M.; Handjani, F.; Ghahramani, S.; Parvizi, Z. The quality of life in patients with epidermolysis bullosa in Iran: A cross sectional study. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 70.

Penarrocha, M.; Rambla, J.; Balaguer, J.; Serrano, C.; Silvestre, J.; Bagan, J. V. Complete Fixed Prostheses Over Implants in Patients With Oral Epidermolysis Bullosa. Journal of Oral and Maxillofacial Surgery. 2007; 65(7 SUPPL.): 103-106.

Perez, V. A.; Morel, K. D.; Garzon, M. C.; Lauren, C. T.; Levin, L. E. Review of transition of care literature: Epidermolysis bullosa-A paradigm for patients with complex dermatologic conditions. Journal of the American Academy of Dermatology. 2022; 87(3): 623-631.

Petrof, G.; Martinez, A.; Mellerio, J.; McGrath, J.; Harper, N.; Heagerty, A.; Ogboli, M.; Moss, C. The epidemiology of epidermolysis bullosa in the UK: data from the national database. British Journal of Dermatology. 2020; 183: 45271.

Price, H.; Murrell, D. F.; Kern, J. S.; Maher, L.; Cunnigham, T. Safety and efficacy of Oleogel-S10 (birch triterpenes) in patients with dystrophic epidermolysis bullosa (DEB): 12-month interim analysis of the open label phase from the EASE study. Pediatric Dermatology. 2022; 39(5): 799.

Popp, Courtney; Miller, William; Eide, Cindy; Tolar, Jakub; McGrath, John A.; Ebens, Christen L. Beyond the Surface: A Narrative Review Examining the Systemic Impacts of Recessive Dystrophic Epidermolysis Bullosa. The Journal of investigative dermatology. 2024

Quintana, L.; Maseda, R.; Illera, N.; Crespo, M.; Butta, N.; Zuluaga, P.; Buno, A.; De Lucas, R.; Escamez, M.; Sacedon, R. 128 Characteristics of anemia and its relationship with disease severity in a Spanish cohort of 84 patients with recessive dystrophic epidermolysis bullosa. Journal of Investigative Dermatology. 2022; 142(12 Supplement): S202.

Quintana, L.; Maseda, R.; Illera, N.; Crespo, M.; Butta, N.; Zuluaga, P.; Buno, A.; De Lucas, R.; Escamez, M.; Sacedon, R. Characteristics of anemia and its relationship with disease severity in a Spanish cohort of 84 patients with recessive dystrophic epidermolysis bullosa. Journal of Investigative Dermatology. 2022; 142(12): S202-S202.

Ramsay, C. A. Cost analysis of the Kozak protocol in the treatment of epidermolysis bullosa. Canadian Medical Association journal. 1984; 130(12): 1526, 1528.

Retrosi, C.; Diociaiuti, A.; De Ranieri, C.; Corbeddu, M.; Carnevale, C.; Giancristoforo, S.; Marchili, M. R.; Salvatori, G.; Atti, M. L. C.; Hachem, M. E.; Raponi, M. Multidisciplinary care for patients with epidermolysis bullosa from birth to adolescence: experience of one Italian reference center. Italian Journal of Pediatrics. 2022; 48(1): 58.

Rogers, C. L.; Gibson, M.; Kern, J. S.; Martin, L. K.; Robertson, S. J.; Daniel, B. S.; Su, J. C.; Murrell, O. G. C.; Feng, G.; Murrell, D. F. A comparison study of outcome measures for epidermolysis bullosa: Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) and the Instrument for Scoring Clinical Outcomes of Research for Epidermolysis Bullosa (iscorEB). JAAD International. 2021; 2(): 134-152.

Rogers, C. L.; Gibson, M.; Kern, J. S.; Martin, L.; Robertson, S.; Daniel, B. S.; Su, J. C.; Murrell, D. F. Which outcome measures are the best for clinical trials in epidermolysis bullosa?. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 38-39.

Saki, N.; Vahedi, S.; Parvizi, M.; Shafie'ei, M.; Hosseini, S.; Ahramiyanpour, N. Topical gabapentin 10% in the treatment of epidermolysis bullosa pruritus: A pilot, double-blind, split-site, randomized controlled trial. Dermatologic therapy. 2022; 35(10): e15767.

Sampogna, F.; Finlay, A. Y.; Salek, S. S.; Chernyshov, P.; Dalgard, F. J.; Evers, A. W. M.; Linder, D.; Manolache, L.; Marron, S. E.; Poot, F.; Spillekom-van Koulil, S.; Svensson, A.; Szepietowski, J. C.; Tomas-Aragones, L.; Abeni, D.; European Academy of, Dermatology; Venereology TaskForce on Quality of, Life Measuring the impact of dermatological conditions on family and caregivers: a review of dermatology-specific instruments. Journal of the European Academy of Dermatology & Venereology. 2017; 31(9): 1429-1439.

Seo, T.; Natsuga, K.; Takashima, S.; Nohara, T.; Ujiie, H. Clinically revertant skin in epidermolysis bullosa: A single-institute experience. Journal of Investigative Dermatology. 2023; 143(5): S141-S141.

Shabir, A.; Natasha H. OP95 quality of life in epidermolysis bullosa: patient and clinician working together. 2020.

So, J. Y.; Nazaroff, J.; Iwummadu, C. V.; Harris, N.; Gorell, E. S.; Fulchand, S.; Bailey, I.; McCarthy, D.; Siprashvili, Z.; Marinkovich, M. P.; Tang, J. Y.; Chiou, A. S. Long-term safety and efficacy of gene-corrected autologous keratinocyte grafts for recessive dystrophic epidermolysis bullosa. Orphanet Journal of Rare Diseases. 2022; 17(1).

So, J.; Iwummadu, V.; Nazaroff, J.; Bailey, I.; McCarthy, D.; Mirza, M.; Tang, J.; Chiou, A. 273 Long-term efficacy and safety of investigational autologous gene-corrected skin sheets (EB-101) for recessive dystrophic epidermolysis bullosa (RDEB). Journal of Investigative Dermatology. 2022; 142(8 Supplement): S47.

Gewert, S.; Kiritsi, D.; Schumann, H.; Schwieger-Briel, A.; Schauer, F. P125 oleogel-s10 for the treatment of epidermolysis bullosa (eb): a 4-patient case series. 2020.

Stevens, L. J. Access to wound dressings for patients living with epidermolysis bullosa - An Australian perspective. International Wound Journal. 2014; 11(5): 505-508.

Stevens, L. J.; McKenna, S.; Marty, J.; Cowin, A. J.; Kopecki, Z. Understanding the outcomes of a home nursing programme for patients with epidermolysis bullosa: An Australian perspective. International Wound Journal. 2014.

SMC 2024, SMC2651, birch bark extract (Filsuvez), https://www.scottishmedicines.org.uk/medicines-advice/birch-bark-extract-filsuvez-uo-pathway-smc2651/

Tabolli, S.; Sampogna, F.; Di Pietro, C.; Paradisi, A.; Uras, C.; Zotti, P.; Castiglia, D.; Zambruno, G.; Abeni, D. Quality of life in patients with epidermolysis bullosa. British Journal of Dermatology. 2009; 161(4): 869-877.

Tang, J.; Marinkovich, M.; Barriga, M.; Bailey, I.; Harris, N.; Rudin, D. 173 Patient reported outcomes following EB-101 treatment of recessive dystrophic epidermolysis bullosa (rdeb) wounds showed durable wound healing and reduction in disease burden. Journal of Investigative Dermatology. 2021; 141(5 Supplement): S31.

Tenedini, E.; Artuso, L.; Bernardis, I.; Artusi, V.; Percesepe, A.; De Rosa, L.; Contin, R.; Manfredini, R.; Pellacani, G.; Giannetti, A.; Pagani, J.; De Luca, M.; Tagliafico, E. Amplicon-based next-generation sequencing: An effective approach for the molecular diagnosis of epidermolysis bullosa. British Journal of Dermatology. 2015; 173(3): 731-738.

Torres-Pradilla, M.; Alvarez, E.; Novoa, M.; Lozano, I.; Trujillo, M. LB1791 Oleogel-S10 (birch bark extract) in dystrophic epidermolysis bullosa: A case series evaluating the impact on wound burden over 2 years. Journal of Investigative Dermatology. 2023; 143(9): B34

Van Scheppingen, C.; Lettinga, A. T.; Duipmans, J. C.; Maathuis, K. G.; Jonkman, M. F. The main problems of parents of a child with epidermolysis bullosa. Qualitative Health Research. 2008; 18(4): 545-56.

Verbeeck, J.; Backer, M. D.; Barre, E.; Salvaggio, S.; Deltuvaite-Thomas, V.; Chiem, J. C.; Kosta, S.; Buyse, M. PCR126 Including Patient Relevant Endpoints (QUALITY OF LIFE) in Multicomponent Endpoints with Generalized Pairwise Comparisons. Value in Health. 2023; 26(6 Supplement): S335.

Verbeeck J1, De Backer M2, Barre E2, Salvaggio S2, Deltuvaite-Thomas V2, Chiem JC3, Kosta S2, Buyse M4Including Patient Relevant Endpoints (QUALITY OF LIFE) in Multicomponent Endpoints with Generalized Pairwise Comparison 2023

Walsh, C.; Leavey, G.; McLaughlin, M. Systematic review of psychosocial needs assessment tools for caregivers of paediatric patients with dermatological conditions. BMJ Open. 2022; 12(1): e055777.

Wang, Shan; Yang, Zhou; Liu, Ying; Zhao, Mu-Tong; Zhao, Juan; Zhang, Huan; Liu, Zong-Yang; Wang, Xiao-Ling; Ma, Lin; Yang, Yong-Hong Application of topical gentamicin-a new era in the treatment of genodermatosis. World journal of pediatrics: WJP. 2021; 17(6): 568-575.

Wodinsky, H. B. Cost analysis of the Kozak protocol as used in an Ontario hospital in the treatment of children with epidermolysis bullosa. Canadian Medical Association Journal. 1984; 130(6): 715-7.
Wong, J.; Khan, M.; Cowan, T.; Murrell, D. Podiatric assessment in children and adults with epidermolysis bullosa: are foot and ankle patient-reported outcome measures (PROMs) able to measure the severity of podiatric involvement among EB patients? International journal of women's dermatology. 2023; 9(1): e046.
Wu, Chong; Jiao, Xin-He. Simple and affordable soft brace application in dystrophic epidermolysis bullosa patients. Frontiers in surgery. 2023; 10: 1189962
Wu, Y. H.; Sun, F. K.; Lee, P. Y. Family caregivers' lived experiences of caring for epidermolysis bullosa patients: A phenomenological study. Journal of Clinical Nursing. 2020; 29(45208): 1552-1560.
Yazdanshenas, A.; Naderi, E.; Moravvej, H.; Heidari, K.; Faghankhani, M.; Vahidnezhad, H.; Mozafari, N. The quality of life in epidermolysis bullosa (EB-QoL) questionnaire: Translation, cultural adaptation, and validation into the Farsi language. International Journal of Women's Dermatology. 2020; 6(4): 301-305.
Yuen, W. Y.; Frew, J. W.; Veerman, K.; van den Heuvel, E. R.; Murrell, D. F.; Jonkman, M. F. Health-related quality of life in epidermolysis bullosa: Validation of the dutch QOLEB questionnaire and assessment in the dutch population. Acta Dermato-Venereologica. 2014; 94(4): 442-447.
Zagoras, T.; Inci, R.; Kantere, D.; Holmstrom, P.; Brostrom, J.; Gillstedt, M.; Polesie, S.; Peltonen, S. Incidence and Prevalence of 73 Different Genodermatoses: A Nationwide Study in Sweden. Acta dermato-venereologica. 2023; 103: adv12404.
Excluded on population
Chu, S. Y.; Wen, C. C.; Weng, C. Y. Gender Differences in Caring for Children with Genetic or Rare Diseases: A Mixed-Methods Study. Children. 2022; 9(5): 627.
Handjani, F.; Kalafi, A. Impact of dermatological diseases on family members of the patients using family dermatology life quality index: A preliminary study in Iran. Iranian Journal of Dermatology. 2013; 16(66): 128-131.
Heelan, K.; Hitzig, S. L.; Knowles, S.; Drucker, A. M.; Mittmann, N.; Walsh, S.; Shear, N. H. Loss of work productivity and quality of life in patients with autoimmune bullous dermatoses. Journal of Cutaneous Medicine and Surgery. 2015; 19(6): 546-554.
Ho, F.; Rustad, A.; Knoll, J.; Rangel, S.; Paller, A. Transition readiness in adolescents and young adults with chronic genetic skin conditions. Pediatric Dermatology. 2023; 40(Supplement 1): 28.
Kalinska-Bienias, A.; Jakubowska, B.; Kowalewski, C.; Murrell, D. F.; Wozniak, K. Measuring of quality of life in autoimmune blistering disorders in Poland. Validation of disease - specific Autoimmune Bullous Disease Quality of Life (ABQOL) and the Treatment Autoimmune Bullous Disease Quality of Life (TABQOL) questionnaires. Advances in Medical Sciences. 2017; 62(1): 92-96.
Kallio, M.; Tornivuori, A.; Miettinen, P. J.; Kolho, K. L.; Relas, H.; Culnane, E.; Loftus, H.; Sawyer, S. M.; Kosola, S. Health-related quality of life and self-reported health status in adolescents with chronic health conditions before transfer of care to adult health care: an international cohort study. BMC Pediatrics. 2024; 24(1): 163
Paller, A. S.; Shei, J.; Rangel, S.; Ramachandran, D.; Puar, N.; Patel, V.; Jackson, K.; Silverberg, J.; Cella, D. 509 PIQ-C, a new PROMIS tool, measures intensity and impact of itch on children with atopic dermatitis. Journal of Investigative Dermatology. 2020; 140(7 Supplement): S69.
Paller, A.; Hajek, A.; Phan, S. Pediatric skin disorders are associated with patient-reported stigma measured by a new modified, validated instrument. Pediatric Dermatology. 2022; 39(5): 797.
Tjokrowidjaja, A.; Daniel, B. S.; Frew, J. W.; Sebaratnam, D. F.; Hanna, A. M.; Chee, S.; Dermawan, A.; Wang, C. Q.; Lim, C.; Venugopal, S. S.; Rhodes, L. M.; Welsh, B.; Nijsten, T.; Murrell, D. F. The development and validation of the Treatment of Autoimmune Bullous Disease Quality of Life questionnaire, a tool to measure the quality of life impacts of treatments used in patients with autoimmune blistering disease. British Journal of Dermatology. 2013; 169(5): 1000-1006.
Yang, B.; Chen, G.; Yang, Q.; Yan, X.; Zhang, Z.; Murrell, D. F.; Zhang, F. Reliability and validity of the Chinese version of the autoimmune bullous disease quality of life (ABQOL) questionnaire. Health and Quality of Life Outcomes. 2017; 15(1) (no pagination).
Excluded on publication type
Agrawal, A.; Bhardwaj, A. Sucralfate-based cream as a novel and cost-effective topical agent in poorly healing ulcers in junctional epidermolysis bullosa. Clinical and experimental dermatology. 2023; 48(2): 138-140.
Dieter, K.; Niebergall-Roth, E.; Daniele, C.; Fluhr, S.; Frank, N. Y.; Ganss, C.; Kiritsi, D.; McGrath, J. A.; Tolar, J.; Frank, M. H.; Kluth, M. A. Corrigendum to ABCB5+ mesenchymal stromal cells facilitate complete and durable wound closure in recessive dystrophic epidermolysis bullosa. Cytotherapy. 2023; 25(9): 1016.
Melendez, M.; Osborn, L.; Bowers, E. Low-dose botulinum toxin improves disease activity and quality of life in epidermolysis bullosa simplex. International journal of dermatology. 2023; 62(8): e466-e468.
SLR for reference checking

Angelis, A.; Tordrup, D.; Kanavos, P. Socio-economic burden of rare diseases: A systematic review of cost of illness evidence. Health Policy. 2015; 119(7): 964-79.
Bodke, A.; Knott, C.; Crossley, O.; Samuels, E.; Tang, M. EE395 Economic Burden and Cost Drivers of Dystrophic Epidermolysis Bullosa: A Systematic Literature Review. Value in Health. 2023; 26(12 Supplement): S126-S127
Bodke A1, Crossley O2, Knott C3, Samuels E4, Tang M5. Exploring the Financial Burden Associated with the Management of Dystrophic Epidermolysis Bullosa (DEB): A Systematic Literature Review (SLR) with Database Review of Future Disease-Modifying Therapies (DMTs) 2024
Crossley, O.; Bodke, A.; Knott, C.; Samuels, E.; Tang, M. EE399 Exploring the Economic Consequences of Caring for Patients With Rare Diseases: A Systematic Literature Review. Value in Health. 2023; 26(12 Supplement) S127
Crossley O1, Bodke A2, Knott C3, Samuels E4, Tang M5. Exploring the Healthcare Resource Utilization (HCRU) Associated with Rare Diseases (RD) in the United States (US): A Systematic Literature Review (SLR) across Six Disease Areas. 2024
Crossley O1, Bodke A2, Knott C3, Samuels E4, Tang M. Exploring the Impact of a Rare Disease (RD) Diagnosis on Work Productivity and Social Activity Impairment: A Systematic Literature Review (SLR) across Six Disease Areas. 2024
Fragkou, D.; Dimoutsi, V.; Galanis, P. The quality of life of children with epidermolysis bullosa. Archives of Hellenic Medicine. 2020; 37(3): 315-322.
Hartley, J.; Bluebond-Langner, M.; Candy, B.; Downie, J.; Henderson, E. M. The physical health of caregivers of children with life-limiting conditions: A systematic review. Pediatrics. 2021; 148(2) (no pagination).
Kaler N1, Rudow M2, Stevenson A3, Dorling P4. Targeted Literature Review Exploring Burden of Disease in Junctional and Dystrophic Epidermolysis Bullosa. 2024
Langan, S. M.; Williams, H. C. A systematic review of randomized controlled trials of treatments for inherited forms of epidermolysis bullosa. Clin Exp Dermatol. 2009; 34(1): 45066.
Marshall, D. A.; Gerber, B.; Lorenzetti, D. L.; MacDonald, K. V.; Bohach, R. J.; Currie, G. R. Are We Capturing the Socioeconomic Burden of Rare Genetic Disease? A Scoping Review of Economic Evaluations and Cost-of-Illness Studies PharmacoEconomics. 2023; 41(12): 1563-1588
Minervini, Giuseppe; Franco, Rocco; Marrapodi, Maria Maddalena; Lo Giudice, Antonino; Cicciu, Marco; Ronsivalle, Vincenzo. Dental implant survival in epidermolysis bullosa patients: A systematic review conducted according to PRISMA guidelines and the Cochrane handbook for systematic reviews of interventions. Heliyon. 2024; 10(2) e24208.
Sequeira, A. R.; Mentzakis, E.; Archangelidi, O.; Paolucci, F. The economic and health impact of rare diseases: A meta-analysis. Health Policy and Technology. 2021; 10(1): 32-44.
Tang, J. Y.; Marinkovich, M. P.; Lucas, E.; Gorell, E.; Chiou, A.; Lu, Y.; Gillon, J.; Patel, D.; Rudin, D. A systematic literature review of the disease burden in patients with recessive dystrophic epidermolysis bullosa. Orphanet Journal of Rare Diseases. 2021; 16(1) (no pagination).
Togo, C. C. G.; Zidorio, A. P. C.; Goncalves, V. S. S.; Hubbard, L.; de Carvalho, K. M. B.; Dutra, E. S. Quality of life in people with epidermolysis bullosa: a systematic review. Quality of Life Research. 2020; 29(7): 1731-1745.
Walsh, C.; Leavey, G.; McLaughlin, M. Systematic review of psychosocial needs assessment tools for caregivers of paediatric patients with dermatological conditions. BMJ Open. 2022; 12(1) (no pagination).
Excluded on study design
Anonymous Erratum to: Patient-reported outcomes and quality of life in dominant dystrophic epidermolysis bullosa: A global cross-sectional survey. Pediatric Dermatology. 2022; 39(6): 1007.
Bodke, A.; Knott, C.; Crossley, O.; Samuels, E.; Tang, M. Economic Burden and Cost Drivers of Dystrophic Epidermolysis Bullosa: A Systematic Literature Review. 2023.
Chateau, A. V.; Blackbeard, D.; Aldous, C. The impact of epidermolysis bullosa on the family and healthcare practitioners: a scoping review. International Journal of Dermatology. 2023; 62(4): 459-475.
Danescu, S.; Salavastru, C.; Sendrea, A.; Tiplica, S.; Baican, A.; Ungureanu, L.; Senila, S.; Morariu, S.; Ignat, S.; Vesa, S.; Cosgarea, R. Correlation between disease severity and quality of life in patients with epidermolysis bullosa. Journal of the European Academy of Dermatology and Venereology. 2019; 33(5): e217-e219.
De Graaf, P. Psychosocial guidelines. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 27.
De Vere Hunt, I.; Halley, M.; Sum, K.; Yekrang, K.; Phung, M.; Good, J.; Linos, E.; Chiou, A. S. A qualitative exploration of the experiences of itch for adults living with epidermolysis bullosa. British Journal of Dermatology. 2022; 187(2): 261-263.
Dufresne, H.; Hadj-Rabia, S.; Bodemer, C. Impact of a rare chronic genodermatosis on family daily life: the example of epidermolysis bullosa. British Journal of Dermatology. 2018; 179(5): 1177-1178.
Frew, J. W.; Cepeda Valdes, R.; Fortuna, G.; Murrell, D. F.; Salas Alanis, J. Measuring quality of life in epidermolysis bullosa in Mexico: Cross-cultural validation of the Hispanic version of the Quality of Life in

Epidermolysis Bullosa questionnaire. Journal of the American Academy of Dermatology. 2013; 69(4): 652-653.

Garcia Rodrigues, M.; Monteiro Soares, M.; Rodrigues, J. D.; Azevedo, L. F.; Pereira Rodrigues, P.; Areias, J. C.; Areias, M. E. Quality of life of parents with children with congenital abnormalities: a systematic review with meta-analysis of assessment methods and levels of quality of life. Quality of Life Research. 2022; 31(4): 991-1011.

Garcia-Doval, I.; Davila-Seijo, P.; Langan, S. M. Updated systematic review of randomized controlled trials of treatments for inherited forms of epidermolysis bullosa. Clinical and Experimental Dermatology. 2013; 38(1): 92-94.

Garcia-Perez, L.; Linertova, R.; Valcarcel-Nazco, C.; Posada, M.; Gorostiza, I.; Serrano-Aguilar, P. Cost-of-illness studies in rare diseases: a scoping review. Orphanet Journal of Rare Diseases. 2021; 16(1) (no pagination).

Gibson, M.; Rogers, C. L.; Murrell, D. F. Successful dapsone therapy in inherited Epidermolysis Bullosa. Australasian Journal of Dermatology. 2021; 62(SUPPL 1): 60.

Harricharan, S.; Richard, M. E.; Roman, J.; Forsythe, A. PSS7 The Economic and Humanistic Burden of Dystrophic Epidermolysis Bullosa (DEB): A Systematic Literature Review. Value in Health. 2021; 24(Supplement 1): S221.

Hou, Ping-Chen; Wang, Han-Tang; Abhee, Stasha; Tu, Wei-Ting; McGrath, John A.; Hsu, Chao-Kai Investigational Treatments for Epidermolysis Bullosa. American journal of clinical dermatology. 2021; 22(6): 801-817.

Kara, M.; Tekgunduz, K. S.; Keskin, H. A cost-effective treatment model in dystrophic epidermolysis bullosa with congenital absence of skin. Dermatologic Therapy. 2018; 31(5) (no pagination).

Lim, Subin; Encarnacion, Iain; O'Connell, Katie A.; Smith, Robert J. Crowdfunding to alleviate financial burdens among patients with epidermolysis bullosa. Archives of dermatological research. 2023; 316(1): 25

Lucky, A. W.; Palisson, F.; Mellerio, J. E. The IVth International Symposium on Epidermolysis Bullosa, Santiago, Chile, 27-29 September 2007. Journal of Dermatological Science. 2008; 49(2): 178-84.

Murphy, S.; Ehritz, C. Clinical Nurse Specialist Practice Strategies for Children With Medical Complexity. Clinical Nurse Specialist. 2021; 35(1): 38-43.

NICE Oleogel-S10 for treating skin wounds associated with epidermolysis bullosa [ID1505].

Pawlak, U.; Rosenberg, M. F. Silicone-based dressings and fixation devices in the management of epidermolysis bullosa: Evidence review of thirty years of clinical experience. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 41-42.

Salamon, G.; Ruberl, A.; Maar, L. P119 psychosocial aspects of epidermolysis bullosa and quality of life. A systematic review. 2020.

Pourali, S.; Gutierrez, Y.; Kohn, A.; Rajkumar, J.; Jones, M.; Ortiz, I.; David, M.; Armstrong, A. Bullous Dermatoses and Depression: A Systematic Review. JAMA dermatology. 2021; 157(12): 1487-1495.

Ramirez, M. N.; Murrell, D. F.; Fine, J. D. Management of epidermolysis bullosa. Expert Opinion on Orphan Drugs. 2013; 1(4): 279-293.

Salamon, G.; Ruberl, A.; Maar, L. Psychosocial aspects of epidermolysis bullosa and quality of life. a systematic review. Acta Dermato-Venereologica. 2020; 100(SUPPL 220): 73.

Soon, K.; Mason, R.; Martinez, A. E.; Mellerio, J. E. The psychological functioning of children with epidermolysis bullosa and its relationship with specific aspects of disease. British Journal of Dermatology. 2020; 182(3): 789-790.

Venugopal, S. S.; Intong, L. R.; Cohn, H. I.; Mather-Hillon, J.; Murrell, D. F. Responsiveness of nonHerlitz Junctional Epidermolysis Bullosa to topical gentian violet. International Journal of Dermatology. 2010; 49(11): 1282-1285.

Shehadeh, W,; Sarig, O.; Bar, J.; Sprecher, E.; Samuelov, L. P130 treatment of epidermolysis bullosa pruriginosa-associated pruritus with dupilumab. 2020.

Publication type

Desai, Amar D.; Singal, Amit; Behbahani, Sara; Soliman, Yssra; Hawryluk, Elena B. Cost of hospitalization for care of children with epidermolysis bullosa in the US. Journal of the American Academy of Dermatology. 2024.

Kantor, J. This Month in JAAD International: December 2023: Patient-reported outcome measures. Journal of the American Academy of Dermatology 2023; 89(6): 1126

Tabor, Aaron; LeQuang, Jo Ann K.; Pergolizzi, Joseph, Jr. Practical Tips on Epidermolysis Bullosa for Caregivers: Part 2 Cureus 2024; 16(3): e55499

Unobtainable records

Bourrat, Emmanuelle. [Cutaneous squamous cell carcinomas: a complication of severe forms of hereditary epidermolysis bullosa] Carcinomes epidermoides cutanes: une complication des formes graves d'epidermolyses bulleuses hereditaires.2023 68(880) 36-38

Crossley, O.; Bodke, A.; Knott, C.; Samuels, E.; Tang, M. Exploring the Economic Consequences of Caring for Patients With Rare Diseases: A Systematic Literature Review. 2023.
Popa, L.; Andreescu, N.; Zimbru, C.; Chirita-Emandi, A.; Farcas, S.; Chilom, D.; Puiu, M. Epidermolysis Bullosa: Literature Review and Three Case Presentation. European Journal of Human Genetics. 2023; 31: 130-131
Ramolino, Gwenaelle. [EB care by a home care nurse: mission impossible?] La prise en charge d'une EB par une infirmiere a domicile, mission impossible? 2023; 68(880): 27-29
WITHDRAWN, ABSTRACT. Estimated Spending on a Novel Gene Therapy for Treatment for Patients With Dystrophic Epidermolysis Bullosa. 2023.
Wong, J.; Cowan, T.; Khan, T.; Murrell, D. Development of an Epidermolysis Bullosa-specific foot assessment instrument (EBDASI Pod). Australasian Journal of Dermatology. 2022; 63(SUPPL 1): 19-20.

I.1.2 Quality assessment and generalizability of estimates

Two quality assessment checklists were used to check the validity, bias, and limitations of each study. Data extracted for the economic evaluation would have been quality assessed using the NICE quality appraisal checklist for economic evaluations, however no records were identified. Cost and resource use publications were quality assessed using the Molinier et al. (2008) checklist. Publications including HRQoL data were appraised using the quality appraisal checklist presented in Picot et al. (2015). The quality assessment checklists were used to check the validity, bias, and independently checked by a second reviewer for any discrepancies.

I.1.3 Unpublished data

NA

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

A combined literature search for economic and quality of life studies was done. See appendix I for description.

J.1.1 Example: Systematic search for […]

A combined literature search for economic and quality of life studies was done. See appendix I for description.

Table 51 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
A combined literature search for economic and quality of life studies was done. See appendix I for description.			

Abbreviations:

J.1.2 Example: Targeted literature search for [estimates]

A combined literature search for economic and quality of life studies was done. See appendix I for description.

Table 52 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
A combined literature search for economic and quality of life studies was done. See appendix I for description.			