Highly Specialised Technology

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HIGHLY SPECIALISED TECHNOLOGY

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

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2. **Company summary of information for patients (SIP)** from Amryt
3. **Clarification questions and company responses**
4. **Patient group, professional group and NHS organisation submissions** from:
   a. DEBRA UK
   b. British Association of Dermatologists
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5. **External Assessment Report** prepared by ScHARR
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   a. Response form
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   a. Anna Martinez, Consultant – clinical expert, nominated by British Association of Dermatologists
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10. **External Assessment Report critique of company response to technical engagement** prepared by ScHARR

11. Expert personal perspectives from:

a. Claire Mather, Director of Member Services - patient expert, nominated by DEBRA

b. James Hinchcliffe, Volunteer Member - patient expert, nominated by DEBRA

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a. Company additional analysis and updated model

13. External Assessment critique of additional company analysis and model prepared by ScHARR

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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly specialised technology evaluation

Filsuvez® gel (birch bark extract) for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

Document B

Company evidence submission

November 2022

File name	Version	Contains confidential information	Date
		Yes/No	

Contents

Tables and Figures

Glossary of abbreviations

Term	Definition
ADLs	Activities of daily living
AE	Adverse event
Ala/nat	Alaska Native
Am/Ind	American or American Indian
ANCOVA	Analysis of covariance
ATC	Anatomical therapeutic chemical
BCC	Basal cell carcinoma
BMI	Body Mass Index
BSA	Body surface area
BSAP	Body surface area percentage
BSC	Best supportive care
BTD	Better than death
CADTH	Canadian Agency for Drugs and Technologies in Health
CAS	Completer analysis set
CASP	Critical Appraisal Skills Programme
CCC	Confirmation of Complete Closure
CCM	Current clinical management
CFB	Change from baseline
CG	Caregiver
CHMP	The Committee for Medicinal Products for Human Use
CHW	Cui, Hung, Wang
CHU9D	Child Health Utility instrument
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
cm^2	Square centimetre
CNS	Clinical nurse specialist
CRD	Centre for Reviews and Dissemination
CSR	Clinical Study Report
CSS	Cross-sectional survey
cTTO	Composite TTO
D	Day
DBP	Double-blind phase
DDD	Defined daily dose
DDEB	Dominant dystrophic epidermolysis bullosa
DEB	Dystrophic epidermolysis bullosa

DET	Data extraction table
DLQI	Dermatology Life Quality Index
EB	Epidermolysis bullosa
EBDASI	Epidermolysis Bullosa Disease Activity and Scarring Index
EBS	Epidermolysis bullosa simplex
eCRF	Electronic case report form
EDBP	End of double blind phase
EMA	European Medicines Agency
EOLP	End of open label phase
EQ-5D	EuroQol 5-Dimension
EQ-5D-Y	EuroQol 5-Dimension Youth
EQ-5D-5L	EuroQol 5-dimension 5 level
EU	European Union
EUCTR	EU Clinical Trials Register
FAS	Full analysis set
FDA	Food and Drug Administration (US)
FLACC	Facial expression, leg movement, activity, cry, and consolability
g	Gram
GOSH	Great Ormond Street Hospital
GST	Guy's and St Thomas'
HRQoL	Health-related quality of life
HS	Health state
HST	Highly specialised technology
HSUV	Health-state utility values
HTA	Health Technology Assessment
ICER (US)	Institute for Clinical and Economic Review
ICH-E9	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, topic E9
ICTRP	International Clinical Trials Registry Platform
IDEA	Investigate, Discuss, Estimate, Aggregate
IDMC	Independent Data Monitoring Committee
INV	Investigator-assessed
IPD	Individual patient data
iscorEB	Instrument for Scoring Clinical Outcomes of Research for Epidermolysis Bullosa
ITT	Intention to treat
JEB	Junctional epidermolysis bullosa - other
JEB-O	Junctional epidermolysis bullosa -severe
JEB-S	Junctional epidermolysis bullosa

KEB	Kindler epidermolysis bullosa
Kg/m^2	Kilograms per metre squared
LS	Least squares
M	Month
MA	Marketing authorisation
MAA	Marketing authorisation application
MDT	Multi-disciplinary team
MHRA	Medicines and Healthcare products Regulatory Agency
mm	millimetre
MOA	Mode of action
MSM	Multi-state modelling
MSP	Multi-stakeholder panel
N, n	Number
NA	Not applicable
NE	Not estimable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NOS	Not otherwise specified
NR	Not reported
OLP	Open-label phase
ONS	Office for National Statistics
OR	Odds ratio
P	Patient
PDUFA	Prescription Drug User Fee Act
PICOS	Population, intervention, comparator, outcomes, study design
PPS	Per protocol set
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
PSS	Personal Social Services
PTs	Preferred terms
PTW	Partial-thickness wounds
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RDEB	Recessive dystrophic epidermolysis bullosa
RDEB-O	Recessive dystrophic epidermolysis bullosa - other
RDEB-S	Recessive dystrophic epidermolysis bullosa - severe
RoB	Risk of bias

RoB-2	Cochrane risk-of-bias tool for randomised trials (2)
ROBINS-I	Risk Of Bias In Non-randomised Studies – of Interventions
RoI	Republic of Ireland
RR	Risk ratio
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety analysis set
SCC	Squamous cell carcinoma
SD	Standard deviation
SE	Standard error
SHELF	Sheffield Elicitation Framework
SEE	Structured Expert Elicitation
SLR	Systematic literature review
SoC	Standard of care
TBSA	Total body surface area
TBWB	Total body wound burden
TE	Triterpene extract
TSQM	Treatment Satisfaction Questionnaire for Medication
TTO	Time trade-off
WHO	World Health Organization

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

This submission covers the technology's full marketing authorisation for this indication. The decision problem is detailed in Table 1.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People aged 6 months and older with: • Dystrophic epidermolysis bullosa (DEB); or • Junctional epidermolysis bullosa (JEB)	People with dystrophic epidermolysis bullosa (DEB) or junctional epidermolysis bullosa (JEB), aged six months and older.	Wording as per the MHRA licence.
Intervention	Birch bark extract	Filsuvez® gel (birch bark extract; Oleogel-S10 during development)	Wording as per MHRA licence-throughout this submission the intervention is referred to as Filsuvez gel.
Comparator(s)	Current clinical management without birch bark extract (including, but not limited to, treatments which can help ease and control infections, pain and other aspects of EB)	As per NICE final scope. In the submission we acknowledge that current clinical management of DEB and JEB partial thickness wounds is heterogeneous but commonly consists of the use of a variety of non-adhesive dressings and bandages, topical antimicrobials, topical steroids, and a variety of other topical agents, all 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	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		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. (Section B.1.3.4).	
Outcomes	The outcome measures to be considered include: • closures of unhealed target wounds • time to wound closure • percentage of surface area of wound healed • change in total body wound burden • incidence and severity of wound infection • pain • change in itching • mortality • adverse effects of treatment • health-related quality of life (for patients and carers)	As per NICE final scope, with further elaboration on change in total body wound burden outcomes measures. Wound burden is measured by two specific outcomes in the pivotal trial: the Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI; *Activity* part of Section I only) a disease specific instrument of wound burden/ severity; and body surface area percentage (BSAP) implemented using the Lund & Browder method, a widely used method to estimate an affected total body surface area. BSAP and EBDASI scores can be used as surrogates for wound burden and disease severity. While both are reported in clinical sections of this submission the cost effectiveness modelling focusses on	NA

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		BSAP as surrogate for severity and is used for burden/ severity health states in the economic model (since it correlates with patient relevant QoL outcomes). Additional information on these clinical endpoints is provided in Section B.2.2.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	As per NICE final scope	NA
Subgroups to be considered	If the evidence allows the following subgroups will be considered. These include: • Dystrophic epidermolysis bullosa (DEB) ▪ dominant DEB ▪ recessive/ severe generalised DEB	Subgroup data are reported for DEB (DDEB and RDEB) and JEB for the primary and first key secondary efficacy endpoints. In the cost effectiveness analysis, transition probabilities to inform patient movements through health states were	Insufficient evidence and lack of clinical rationale to model patients by individual EB subgroup.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Junctional epidermolysis bullosa (JEB) ▪ generalised severe (Herlitz) ▪ generalised intermediate (non-Herlitz)	calculated using the 90-day DBP EASE data (and extrapolated using 12-month OLP data). These transitions were pooled and applied to all subtypes, assuming that Filsuvez gel efficacy does not differ per subtype. A scenario is explored to assess the impact on results when considering RDEB-S patients only.	

Abbreviations: BSAP, body surface area percentage; DDEB, dominant dystrophic epidermolysis bullosa; DEB, dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; EBDASI, epidermolysis bullosa disease activity and scarring index; JEB, junctional epidermolysis bullosa; MHRA, Medicines and Healthcare products Regulatory Agency; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QoL, quality of life; RDEB, recessive dystrophic epidermolysis bullosa.

B.1.2 Description of the technology being evaluated

Table 2 Technology being appraised

UK approved name and brand name	Filsuvez® gel (birch bark extract), referred to as Oleogel-S10 during clinical development.
Mechanism of action	Filsuvez gel is a non-aqueous gel. 1g of gel contains 100mg of extract (as dry extract, refined) from *Betula pendula* Roth, *Betula pubescens Ehrh*, as well as hybrids of both species, cortex (equivalent to 0.5-1.0g birch bark), including 84-95mg triterpenes calculated as the sum of betulin, betulinic acid, erythrodiol, lupeol, and oleanolic acid. Extraction solvent: n-Heptane.(1, 2) Cell culture assays with human primary keratinocytes and fibroblasts, and *ex vivo* studies with porcine skin, show that the extract, including the main component betulin, modulate inflammatory mediators and are associated with activation of intracellular pathways known to be involved in keratinocyte differentiation and migration, wound healing, and closure.(2) The precise mechanism of action of Filsuvez gel in wound healing is not known.(2)
Marketing authorisation/CE mark status	On 21st June, 2022, Filsuvez gel received marketing authorisation in the EU for the treatment of partial thickness wounds (defined in Section B.1.3.1) associated with dystrophic and junctional epidermolysis bullosa (EB) in patients aged 6 months and older, followed by MHRA approval on 11th August, 2022, for the same indication.(3, 4)
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	EMA and MHRA indication: treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients aged 6 months and older.(3, 4) Contraindications: hypersensitivity to the active substance, or to refined sunflower oil. Restrictions: • In case of wound infection, it is recommended to interrupt treatment. Treatment may be reinitiated once the infection has resolved. • In the case of diagnosis of squamous cell carcinoma (SCC) or other skin malignancies, treatment to the affected area should be discontinued. • Other topical products should not be concomitantly used together with Filsuvez gel but rather sequentially or alternatively depending on the clinical need.(2)
Method of administration and dosage	Filsuvez gel is available in two tube sizes containing 9.4g or 23.4g of Filsuvez gel (not all pack sizes may be marketed). The 23.4g tube will be available in the UK. The gel should be applied to the wound surface at a thickness of approximately 1mm and covered by a sterile non-adhesive wound dressing or applied to the dressing so that the gel is in direct contact with the wound. The gel should not be applied sparingly. It should not be rubbed in. The gel should be reapplied at each wound dressing change. The maximum total wound area treated in clinical studies was 5,300cm^2 with a median total wound area of 735cm^2.(2)

	If symptoms persist or worsen after use, or if wound complications occur, the patient's condition should be fully clinically assessed prior to continuation of treatment, and regularly re-evaluated thereafter. For cutaneous application only. Filsuvez gel should be applied to cleansed wounds. Filsuvez gel is not for ophthalmic use and should not be applied to mucous membranes. The posology in paediatric patients (6 months and older) is the same as in adults.(2) Since Filsuvez gel is a topical product it was given an anatomical therapeutic chemical (ATC) code in group D (ATC code: D03AX13), therefore a defined daily dose (DDD) is not required or assigned.(5)
Additional tests or investigations	Patients with EB are referred to the nationally commissioned EB service at birth or soon after, for multidisciplinary care which includes genetic diagnosis.(6, 7) A diagnostic skin biopsy is performed along with blood sampling from the child and family for mutation analysis.(6) Diagnostic tests are carried out by the Robin Eady National EB Diagnostic Laboratory based at Guy's Hospital (London, UK), now incorporated into the Rare Skin Disease laboratory of the South Thames Genomic Medicine Hub at the EB laboratory.(7) Although standard as part of the nationally commissioned EB service, genetic testing is not a requirement for initiation of treatment with Filsuvez gel. No additional test or investigations are required to identify the population for whom the technology is indicated in the marketing authorisation.
List price and average cost of a course of treatment	The list price is £275.33 per 23.4g tube of Filsuvez gel.
Patient access scheme (if applicable)	Amryt Pharmaceuticals have submitted a patient access scheme (PAS) application to PASLU, which consists of [redacted]
Abbreviations: ATC, anatomical therapeutic chemical; cm², square centimetre; DDD, defined daily dose; EB, epidermolysis bullosa, EMA, European Medicines Agency; EU, European Union; g, gram; MHRA, Medicines and Healthcare products Regulatory Agency; mm, millimetre; NHS, National Health Service; SCC, squamous cell carcinoma; UK, United Kingdom.	

The MHRA summary of product characteristics, and the UK public assessment report are presented in Appendix C.(2, 8)

B.1.3 Health condition and position of the technology in the treatment pathway

Please follow the QR code link (Figure 1) to a 2-minute video produced by Amryt Pharmaceuticals: *Understanding epidermolysis bullosa*.

Figure 1 Understanding epidermolysis bullosa (QR code link to video)

B.1.3.1 Overview of the condition

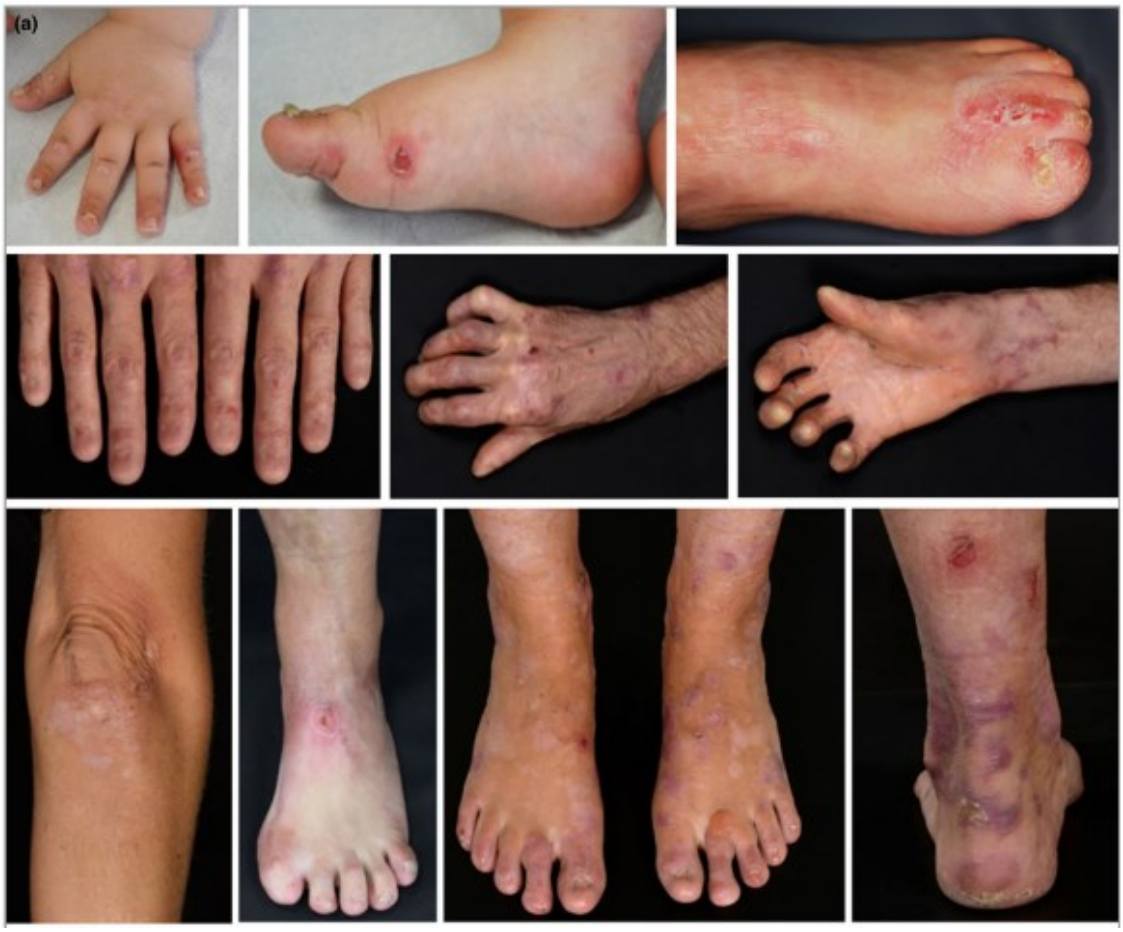
Epidermolysis bullosa (EB) is a complex group of lifelong, rare inherited blistering and skin fragility disorders caused by more than 1,000 known mutations in at least 21 genes encoding anchoring proteins of the dermal-epidermal junction.(9, 10) Four of the major subtypes are dystrophic EB (DEB), which can be dominant (DDEB) or recessive (RDEB), junctional EB (JEB), EB simplex (EBS), and Kindler EB (formerly known as Kindler syndrome), however only DEB (inclusive of RDEB and DDEB) and JEB are relevant to the scope of this appraisal.(9, 11, 12) Each EB type reflects the underlying protein abnormality leading to mechanical disruption of the adhesion and integrity of skin, with the most severe types of EB having disruption to skin physiology into the sublamina densa (in the case of DEB) or the lamina lucida of the cutaneous basement membrane zone (in the case of JEB).(1, 13) In order to diagnose the specific subtype of EB, various factors are considered including mode of inheritance, the specific mutation, the gene and protein implicated, clinical presentation, and immunohistochemical and electron microscopy results.(13, 14) Severe forms of EB, such as DEB and JEB, usually present from birth and so are often diagnosed at birth or in early childhood.(13)

The hallmark of DEB and JEB is skin mechanical fragility causing frequent blistering or erosions in response to minor trauma or friction of the skin surface. Many wounds in EB are classified as partial-thickness wounds, meaning they extend through the epidermis, basement membrane, and into the upper part of the dermis. In DEB and JEB, where disruption to skin physiology can extend into the dermis, there is often a high total body partial-thickness wound burden.(1, 15)

In addition to regular formation of new blisters and wounds, patients with DEB and JEB also have altered wound healing. Wound healing is a complex process underpinned by four phases: haemostasis, inflammation, tissue repair and skin remodelling.(16) This process is dysregulated in EB with limited epithelialisation, keratinocyte migration, and epidermal barrier remodelling.(17-19) As a result of this dysregulation and the inability to restore the epidermal barrier, EB manifests with recurrent partial-thickness wounds and blisters which are debilitating and can occur anywhere on the body. Wounds may also remain unhealed for long periods (often referred to as chronic when not healed within 21 days), and often break down again, resulting in patients presenting with several wounds of varying age and healing ability, leading to a high wound burden and making wound management complex.(19, 20) This chronic cycle of wound formation, healing, and breaking down again means patients present with a high wound burden which is compounded by underlying genetic defects, poor nutritional status, anaemia, pain and pruritis (itching).(13, 21)

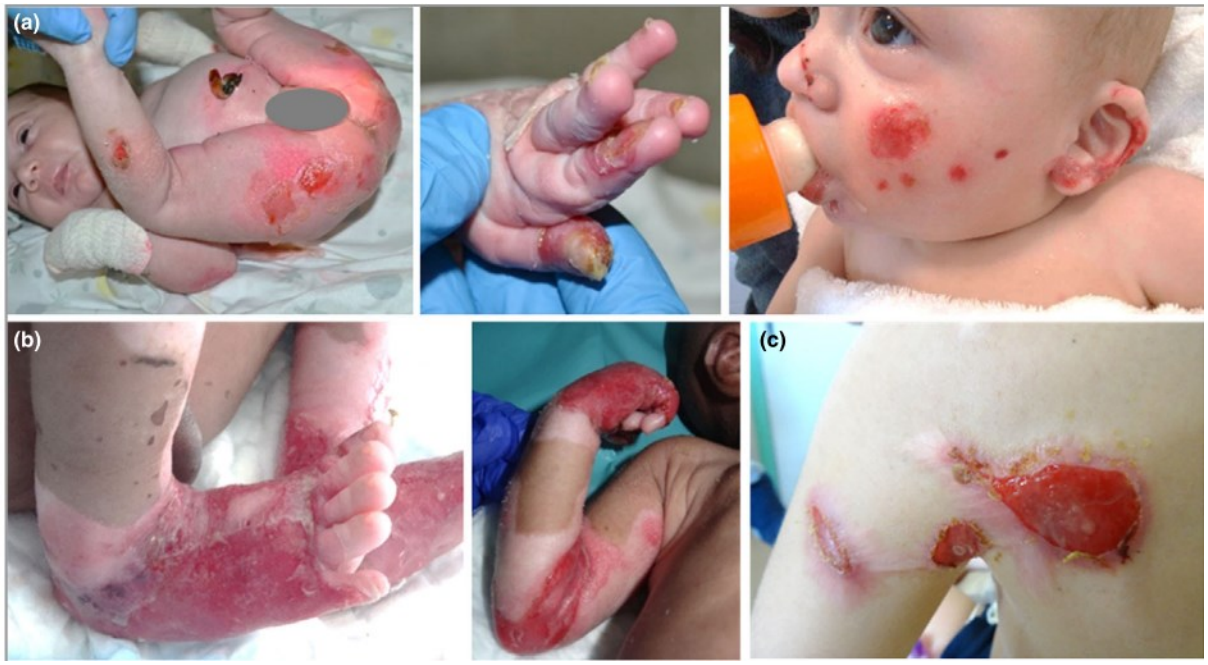
Demonstrative images of EB wounds are provided in Figure 2, Figure 3, and Figure 4, representing a mix of adult and paediatric patients. These are a selection of those published in the Has *et al*. 2020 *Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility*.(9)

Figure 2 Images of DEB



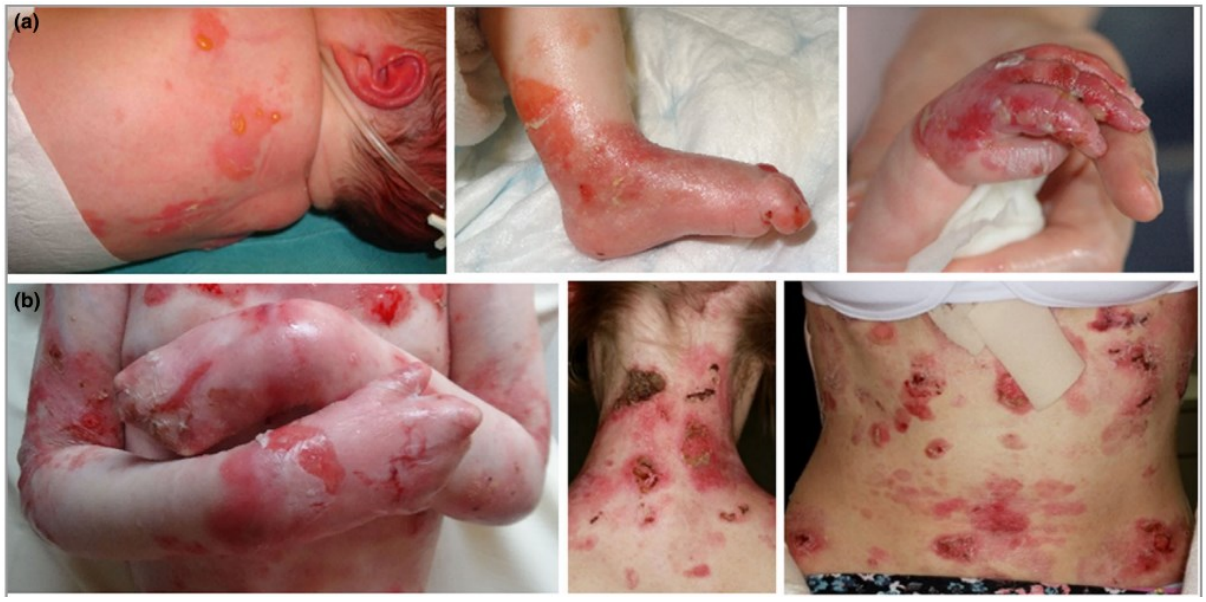
Source: Has C, Bauer JW, Bodemer C, et al. Consensus re-classification of inherited epidermolysis bullosa and other disorders with skin fragility. Br J Dermatol. 2020.(9) (Figure 3(a): Localised, dominant dystrophic epidermolysis bullosa (DDEB) and intermediate recessive DEB (RDEB) often display phenotypic overlap. Skin blistering may be limited in extent and mainly acral and over bony prominences such as elbows and knees. Blisters heal with scarring and may be associated with milia. Nail dystrophy or loss is common. Striate hyperkeratosis of the palms and fingers may cause flexion contractures.)

Figure 3 Images of children with JEB



Source: Has C, Bauer JW, Bodemer C, et al. Consensus re-classification of inherited epidermolysis bullosa and other disorders with skin fragility. Br J Dermatol. 2020.(9) (Figure 2: (a) Severe junctional epidermolysis bullosa (JEB). Neonatal skin blistering and crusting. Granulation tissue of the distal digits, face and ears are typical. In intermediate JEB, blistering may be widespread in infants (b) and lead to chronic over-granulated wounds in babies and older individuals).

Figure 4 Images of patients with severe RDEB



Source: Has C, Bauer JW, Bodemer C, et al. Consensus re-classification of inherited epidermolysis bullosa and other disorders with skin fragility. Br J Dermatol. 2020.(9) (Figure 4: (a) Widespread skin fragility and ulceration in neonates. (b) Extensive blistering and wounds lead to scarring and joint contractures).

EB wounds may be localised or generalised externally,(22) can be characterised as recurrent or chronic, and are subject to bacterial colonisation, itch-scratch cycle, inflammation, impaired cell proliferation and stem cell depletion.(23) Wound assessment should therefore be performed regularly, to ensure management is tailored to the characteristics of individual wounds. Generally, for patients living with EB, larger wounds and a greater total body wound burden are associated with worse disease severity, reduced quality of life, increased use of pain medication, and an increase in the risk of developing anaemia, osteoporosis, and squamous cell carcinoma (SCC).(24)

Altogether, a high wound burden, altered wound healing profile, debilitating symptoms such as pain and pruritis, and additional systemic complications which can carry considerable morbidity and, in some cases, increased mortality risk (such as that associated with SCC), result in a distinct population of DEB and JEB patients with significantly compromised health-related quality of life (HRQoL). Patients living with EB typically experience multiple comorbidities such as scarring in the respiratory tract, constant inflammation in the body, sepsis due to infected wounds, renal amyloidosis, and failure to thrive due to inadequate nourishment. These and other coexisting pathologies represent the main cause of death in a patient with EB. Life expectancy is dependent upon the severity of the disease and can range from less than 1 year with very severe forms such as severe JEB (JEB-S), to normal life expectancy with other forms.(15, 25-27)

B.1.3.2 Epidemiology of EB

DEB and JEB (the focus of this submission) are life-long, chronic, inherited disorders. Global epidemiological data for EB is variable across studies, but the incidence is estimated to be between 19 and 41 per million live births.(13, 28) The most recent published prevalence and incidence data from the NHS national EB service based on data from 2,594 individuals in England and Wales with EB who were enrolled prospectively in the database between 2002 and 2021, including 1,200 live born babies, are summarised in Table 3 for the population relevant to this submission.(7) There was an increase in prevalence of all types of EB over the 19-year period (r= 0.98 for DEB, r= 0.98 for JEB), along with an apparent reduction in birth incidence over the same observed period (r= -0.56 for DEB, r= -0.65 for JEB).(7)

Table 3 Minimum point-prevalence (April 2021), and incidence (between 2002-2021) of DEB and JEB, per 1 million of the population, calculated using UK census data

EB type	Subtype	Prevalence per 1 million of the population	Incidence per million live births (over the 19-year period)	Incidence per million live births (average over the last 5 years)
DEB	Recessive	3.3	8.1	-
	Dominant	6.8	16.4	-
	DEB (NOS)	0.6	0.5	-
	All DEB	10.7	26.1	14.4
JEB	Severe	0.06	5.6	-
	Intermediate	0.34	0.9	-
	Other subtypes	0.6	1.9	-
	All JEB	1.0	8.9	3.7

Abbreviations: DEB, dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; JEB, junctional epidermolysis bullosa; NOS, not otherwise specified.
Minimum prevalence estimates were based on patients who were alive on 22 April 2021

Source: Adapted from Petrof et al. 2022.(7)

For the EB subtypes corresponding to the licensed indication of Filsuvez gel, assuming constant prevalence across the constituent countries of the UK (with adjustment according to ONS mid-2021 population), estimates suggest patient numbers in England of 604 DEB patients and 56 JEB patients (Table 4).

Table 4 Estimated numbers of patients in England

EB type	Subtype	Estimated prevalence based on population for England of 56,489,800
DEB	Recessive	186
	Dominant	384
	DEB (NOS)	34
	All DEB	604
JEB	Severe	3
	Intermediate	19
	Other subtypes	34
	All JEB	56
All DEB/JEB		660

Source: calculated from figures published in Petrof 2022 and adjusted using ONS mid-2021 population estimates.(7, 29)

Abbreviations: DEB, dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; JEB, junctional epidermolysis bullosa; NOS, not otherwise specified

However, the eligible patient population of 660 is an upper estimate of current eligible patients covered by the anticipated marketing authorisation, since it also includes those 6 months and younger (not covered by the licenced indication). In addition, clinical experts when consulted, thought that at any one time up to 150-175 patients will be using Filsuvez gel.

B.1.3.3 Unmet need

DEB and JEB are debilitating, rare, severe and chronically disabling, lifelong conditions with a devastating effect on both paediatric and adult patient quality of life and having a significant impact on the wellbeing and quality of life of their parents/ carers, and family members, including siblings. There is currently no cure, and until the licensing of Filsuvez gel in 2022, there had been no approved therapies for EB of any subtype. Established clinical management of this lifelong disease focuses on wound management, reducing risk of new injury, minimising complications, and improving quality of life as much as possible.(30-34) The overall burden of disease for this small and clinically distinct EB population is substantial, and new therapeutic options are urgently required to address significant unmet needs for improving quality of life, and potentially reducing mortality from the conditions.

B.1.3.4 Existing clinical management and the introduction of Filsuvez gel

The mainstay of treatment of DEB and JEB is wound management, reducing potential for new injury, minimising complications, and improving quality of life.(30-34) Therefore, Filsuvez gel provides a step change in the paradigm of EB treatment as the first licensed therapy for the treatment of partial-thickness wounds associated with DEB and JEB.

A variety of clinical guideline recommendations and expert consensus statements exist for different aspects of EB; however, none were written for a specific country or healthcare system (Table 5). Despite these recommendations for wound care and other aspects of EB, no guidelines have been published that are specific to UK clinical practice, and unmet need for improving patient and carer outcomes with new therapies remains significant.

Table 5 Summary of guidelines including EB management

Badger KS, O'Haver J, Price H. Recommendations for a Comprehensive Management Plan for the Child Diagnosed With Epidermolysis Bullosa. Journal of the Dermatology Nurses' Association. 2013;5(2):72-78.(30)
Denyer J, Pillay E, J C. Best practice guidelines – Skin and wound care in epidermolysis bullosa: An International Consensus. 2017.(11)
El Hachem M, Zambruno G, Bourdon-Lanoy E, *et al*. Multicentre consensus recommendations for skin care in inherited epidermolysis bullosa. Orphanet J Rare Dis. 2014; 9:76.(34)
Fine, J. BMJ Best Practice: Epidermolysis Bullosa. BMJ. 2019.(12)
Goldschneider KR, Good J, Harrop E, *et al*. Pain care for patients with epidermolysis bullosa: best care practice guidelines. BMC Medicine. 2014;12(1):178.(35)
Haynes L. Clinical practice guidelines for nutrition support in Infants and children with epidermolysis bullosa (EB). 2007.(36)
Khan MT, O'Sullivan M, Faitli B, *et al*. Foot care in epidermolysis bullosa: evidence-based guideline. The British journal of dermatology. 2020;182(3):593-604.(37)
Kramer S, Lucas J, Gamboa F, *et al.* Clinical practice guidelines: Oral health care for children and adults living with epidermolysis bullosa. Spec Care Dentist. 2020;40 Suppl 1:3-81.(38)
Martin K, Geuens S, Asche JK, *et al*. Psychosocial recommendations for the care of children and adults with epidermolysis bullosa and their family: evidence-based guidelines. Orphanet J Rare Dis. 2019;14(1):133.(39)
Mellerio JE, Robertson SJ, Bernardis C, *et al*. Management of cutaneous squamous cell carcinoma in patients with epidermolysis bullosa: best clinical practice guidelines. The British journal of dermatology. 2016;174(1):56-67.(40)
Pope E, Lara-Corrales I, Mellerio J, *et al*. A consensus approach to wound care in epidermolysis bullosa. Journal of the American Academy of Dermatology. 2012;67(5):904-917.(33)

EB patients are generally cared for in a multidisciplinary team (MDT) setting. As a rare disease, very few dermatologists or other specialists will have had much exposure to EB, therefore since 2002 clinical care for individuals with DEB and JEB in England, Wales, Scotland, and Northern Ireland has been managed by the nationally commissioned EB service.(6, 7, 41) The national EB service covering the UK is based at four specialist centres; two paediatric centres, and two who manage adult care. The four centres which make up the EB service are Birmingham Women's and Children's NHS Foundation Trust and Great Ormond Street Hospital (GOSH) for Children NHS Foundation Trust which treat children with EB, and University Hospitals Birmingham NHS Foundation Trust and Guy's and St Thomas' (GST) Hospital NHS Foundation Trust, for adults with EB. Centres are led by a consultant dermatologist working with a number of EB clinical nurse specialists (CNS), which cover both the centre and an outreach programme, in conjunction with key specialists as part of the MDT.(6, 7, 41)

In delivering this management, NHS England suggest patients be classified into ‘mild’ or ‘severe’ based on the level of care they require.(6) This mechanism is believed to aid in the logistical organisation and delivery of care but may not always directly correlate with disease/ wound burden, since patients’ demographics and familial familiarity with EB are thought to play an important role. Visits to specialist EB centres in England and contact with both EB nurse specialists and the DEBRA patient group, suggest that the current standard management of EB wounds is highly variable both between centres and between patients themselves, even between patients within the same family.

Due to its lifelong nature, it is recognised that people with EB and their carers become experts in the management of wounds, and their involvement in any disease management choices is paramount.(30, 33, 42) This results in highly heterogenous clinical management strategies, that may not only vary between patients with different subtypes of DEB and JEB, but also on an intra-patient level between wounds in different locations, of different size, and different chronicity, and also over time, both seasonally and over a patient’s lifetime as their disease enters different phases.

The standard of care for EB partial-thickness wounds is therefore heterogenous but commonly consists of the use of a variety of non-adhesive dressings and bandages, topical antimicrobials, topical steroids, and a variety of topical agents, all of which are not 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.(33) Additional recommendations for management of cutaneous manifestations may include: lancing and draining of intact blisters since EB blisters are not self-limiting,(31-34) action to address colonisation and infection of wounds such as the use of antiseptics and topical/ systemic antimicrobials mentioned above,(11, 31, 34) efforts to treat intense pruritus,(30, 32-34, 43) and protection from further cutaneous trauma.(11, 12) 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.(11, 31, 34, 35)

Over the lifetime EB journey 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.(26) While these procedures are significant parts of DEB and JEB clinical management as a whole, they extend beyond the wound care management of which Filsuvez gel is anticipated to become a core part. However, a reduction in the body surface area percentage (BSAP) affected by chronic EB wounds, a reduction in total body wound burden, may reduce the risk of extracutaneous manifestations and long-term complications.

The introduction of Filsuvez gel as part of routine clinical management of DEB and JEB would represent a step change in EB wound management, as there have been no licensed EB-specific treatments, until Filsuvez gel. There is no current clinical pathway of care other than the service user pathway dictated by the NHS service specification of 2013/14.(6) Treatment with Filsuvez gel will be initiated and overseen by four specialist centres (Birmingham Women's and Children's NHS Foundation Trust, University Hospitals Birmingham NHS Foundation Trust, GOSH for Children NHS Foundation Trust, and GST Hospital NHS Foundation Trust), alongside the provision of existing wound care guidance. Once initiated, Filsuvez gel should be applied at each wound dressing change by the patient or their carer. It should be applied directly to the wound surface at a thickness of approximately 1mm 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.(2) It is anticipated that the introduction of Filsuvez gel has the potential to redefine wound care for children and adults with DEB or JEB, and offer them quality of life benefit via accelerated wound healing and the resulting reduction in total body wound burden (as measured by BSAP).

While the company is aware of cell and gene therapies in development for the treatment of EB wounds, none are yet routinely available to DEB and JEB patients outside of clinical trial programmes.(13, 44, 45) Despite these pipeline technologies offering hope to EB patients of a disease altering therapy, the latest published information suggests that none are curative.(13, 44, 45) Therefore, should DEB and JEB patients be eligible for treatment in the future with the new cell and gene therapies,

they will likely still experience partial-thickness wounds, maintaining a place for Filsuvez gel in future clinical management of DEB and JEB wounds.

B.1.3.5 The impact of the condition on the quality of life of patients, their families and carers

Patients (both children and adults) living with EB have a lower quality of life compared to those without EB, an impact that increases with disease severity.(13, 46, 47) Itch and pain linked to wound management severely limit patients' lives, and are ranked as the most challenging aspects of EB that compromise HRQoL.(43, 48, 49) Survey data also indicates that EB places a significant emotional and financial burden on patients and their families.(50-52)

Children with EB often spend a lot of time during their early years in hospital, particularly children with JEB, where they are often hospitalised for long periods of time due to failure to thrive.(53) Care at home can also be traumatic for patients with a high wound burden, and the carers who assist them, as daily bathing, blister lancing/ draining, and dressing changes can be extremely time-consuming (up to four hours per day), painful, and anxiety-provoking particularly for parents caring for young children.(46, 54) 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.(55)

As with many rare diseases, there are few studies that focus on how EB impacts the quality of life of the family. Having a child with EB carries with it a substantial physical and emotional toll, with the potential to affect every aspect of their lives including but not limited to, relationships, emotional/ mental wellbeing, and financial stability.(56, 57) The impact on siblings is often overlooked, however they may also experience an array of difficult emotions, including guilt, sadness, embarrassment, and resentment. The frequency and duration of required hospital stays can impact on the relationship between siblings, and the sibling may spend less quality time with the parents than they otherwise would.(56)

The largest published study to date evaluating the HRQoL of patients and carers with EB in eight EU member states (Angelis *et al.* 2016) estimated the mean EQ-5D utility index score of adult EB patients in the UK as 0.563 (SD: 0.340), substantially lower

than the average age-matched population norm of 0.924 reported by Ara and Brazier (2010).(50, 58, 59) The UK caregiver mean EQ-5D index score reported by Angelis *et al.* 2016 was 0.675 (SD: 0.170), which was also substantially lower than the population norm of 0.906 reported by Ara and Brazier (2010) for UK adults age-matched to the caregiver population of Angelis *et al.* 2016.(50)

While this study demonstrated the diminished HRQoL experienced by both EB patients and their carers; it is noted that a significant proportion of the patients had EBS (38.2% of the n=204 study participants), an EB subtype considered less severe than the DEB and JEB population, for which Filsuvez gel is licensed.(50)

Data was recently published for an analysis of the DEB-only population from the same study which showed that compared to the whole study population, DEB patients had a lower mean EQ-5D utility index score (0.304, SD: 0.449), and caregivers of DEB patients had a slightly higher mean EQ-5D index score (0.713, SD: 0.071).(58)

To further investigate the HRQoL of patients and carers in the population addressed by this submission, Amryt Pharmaceuticals commissioned a cross-sectional study (CSS) of patients living in the UK, Republic of Ireland (RoI) and the United States, "Utility Elicitation in Epidermolysis Bullosa: Cross-Sectional Survey."(60) The objectives of the study were: elicitation of patient and caregiver HRQoL using validated generic and disease specific instruments; to analyse the consequences of EB that have the greatest impact on both patients and caregiver HRQoL; and, to better understand the impact of EB and EB management for patients and caregivers. Both patient and caregiver HRQoL data was collected in the study using the EQ-5D-5L and data were reported by BSAP affected by EB wounds (representative of disease severity).(60)

In total, 78 participants were recruited and responded to the questionnaire, during the data collection period of September 2021-February 2022. Of these, 59 (75.6%) were self-completions by people ≥16 years, eight (10.3%) were completions by people ≥16 years who required some assistance from parents/ caregivers with self-completion, and 11 (14.1%) were proxy completions by parents/ caregivers on behalf of young people/ children under 16 years of age. The majority of respondents were from the US (84.6%), with 12.8% from the UK, and 2.6% from RoI. Of the self-reporters (n=67), the

majority of patients had DEB (44.8% DDEB, 44.8% RDEB), with lower numbers of JEB (9.0%) and Kindler EB (KEB) (1.5%), and the mean age was 26.2 years (SD: 9.00). In the proxy completions (n=11), the majority had JEB (72.7%), with the rest having RDEB (27.3%), and the mean age was 7.9 years (SD: 5.07).(60)

Data from the survey was reported separately for self-reported and proxy-reported completions. The mean EQ-5D was 0.52 (SD: 0.29) in the self-reported completions and 0.50 (SD: 0.37) in the proxy-reported completions; both values similar to the value of 0.57 reported for adult EB patients in Angelis *et al.* 2016. Caregiver HRQoL data was reported for 11 participants in the survey, and had a mean of 0.88 (SD: 0.14), higher than the value of 0.675 reported in Angelis *et al.* 2016, however was collected from a smaller population.(60)

Together these data demonstrate the substantial impact that the condition has on patients and their families/ caregivers. Further consideration of the HRQoL impact on patients and their families, and its application to the cost-effectiveness of Filsuvez gel, is included in B.4.5.

B.1.4 Equality considerations

It is not expected that this evaluation will exclude any people protected by equality legislation, nor lead to recommendations that will have an adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

In line with the decision problem (detailed in Table 1), 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 and RDEB) and JEB, with the following research question:

"What is the efficacy, safety, and tolerability of Oleogel-S10 (birch triterpenes) [now referred to as Filsuvez gel] ***and/ or other interventions considered as established clinical management, for the treatment of partial-thickness wounds associated with DEB and JEB".(61)***

The SLR was undertaken according to the principles of systematic reviewing published in the Cochrane Handbook, and the NICE Methodology Process and Methods guide.(62, 63) The SLR search strategy and study selection methods are described in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

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 (RCT) providing direct head-to-head evidence of the safety and efficacy of Filsuvez gel compared to a control gel arm. 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 current clinical management alone since there is an absence of any other trial evidence of key wound healing endpoints in DEB and JEB patients receiving only standard of care/ current clinical management.

EASE data was derived from a published trial protocol, and a number of published conference records, in addition to unpublished clinical study reports and data on file.(64-85) Since conducting the SLR, the EASE primary, peer-reviewed publication has been published online, as well as a clinical study report addendum reporting the

final 24-month EASE open-label phase data (data on file), and therefore these two records are included as an additional references herein.(86, 87)

The pivotal phase III EASE RCT, summarised in Table 6, represents the most robust source of clinical effectiveness and safety data for Filsuvez gel, and is therefore used exclusively as the primary source of evidence of the relative clinical benefits of the technology in the economic model. Supportive evidence was sought from literature, real world evidence, and structured expert elicitation where data beyond those reported in the pivotal EASE trial were required for the economic analysis (see Section B.3, for methods of expert elicitation).

Table 6 Clinical effectiveness evidence

<table>
<tr><td>Study</td><td colspan="5">EASE(65, 75)
(BEB-13; NCT03068780; EudraCT2016-002066-32)</td></tr>
<tr><td>Study design</td><td colspan="5">Phase III, double-blind, randomised, controlled, 90-day efficacy and safety study with a 24-month open-label, single-arm follow-up phase</td></tr>
<tr><td>Population</td><td colspan="5">Male and female patients with JEB, DEB, or Kindler EB[a]
≥ 4 years of age (protocol amendment later permitted inclusion of patients aged > 21 days)</td></tr>
<tr><td>Intervention(s)</td><td colspan="5">Filsuvez gel (birch triterpenes)</td></tr>
<tr><td>Comparator(s)</td><td colspan="5">Control gel (100g consists of: 85g sunflower oil, 5g Cera flava/ yellow wax, and 10g carnauba wax)</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>✓</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td>✓</td></tr>
<tr><td>No</td><td></td><td>No</td><td></td></tr>
<tr><td>Rationale for use in the model</td><td colspan="5">Primary source of evidence used in the model – phase III pivotal RCT, provides the only head-to-head comparison of Filsuvez gel versus control gel, a proxy to current established clinical management</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">Primary efficacy endpoint:
Proportion of patients with first complete target wound closure within 45 (+/- 7) days of treatment based on investigator assessment
Key secondary (confirmatory) efficacy endpoints[b]:
Time to first wound closure up to 90 ± 7 days of treatment
Incidence of first complete wound closure of EB target wound
Incidence of wound infection [c]
Maximum severity of wound infection [c]
CFB in total body wound burden/ disease activity (EBDASI)
CFB in itching (Itch Man Scale/ Leuven Itch Scale)
Other secondary endpoints:
CFB in EB target wound size
CFB in BSAP affected by EB PTW (Lund and Browder method)
CFB in background and procedural pain (FLACC, Wong-Baker FACES)</td></tr>
</table>

	Response to treatment (TSQM) CFB in sleep quality (Likert scale) Number of days missed from school or work Incidence, severity, and relatedness of AEs Local tolerability

Abbreviations: AE, adverse event; BSAP, body surface area percentage; CFB, change from baseline; DEB, dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; EBDASI, epidermolysis bullosa disease activity and scarring index; FLACC, Face, Legs, Activity, Cry, Consolability scale; g, gram; JEB, junctional epidermolysis bullosa; PTW, partial-thickness wounds; RCT, randomised controlled trial; TBSA, total body surface area; TSQM, treatment satisfaction questionnaire for medication.
The outcome marked in bold is incorporated into the model.

[a] Inclusion criteria permitted patients with Kindler EB, however no patients with Kindler EB were recruited.
[b] Key secondary efficacy endpoints were tested hierarchically; once a non-significant result was achieved, the remaining key secondary efficacy endpoints became exploratory rather than confirmatory.
[c] As evidenced by AEs and/ or use of topical and/ or systemic antibiotics.

As denoted in Table 6, from the outcomes listed that were collected in the EASE trial and are specified in the decision problem addressed by this submission (Table 1), change from baseline in body surface area percentage (BSAP) affected by EB partial-thickness wounds, as evidenced by clinical assessment based on the 'Lund and Browder' chart, is incorporated into the cost effectiveness analysis.

In the EASE trial, total body wound burden was measured using the Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) disease severity score and by the total body surface area (TBSA) affected by EB partial-thickness wounds, which was measured as BSAP. The EBDASI assessment utilised in EASE was limited to the *Activity* part of Section I (assessment of the skin except for the anogenital region) only, not the full EBDASI instrument, at Day 30, Day 60, and Day 90. BSAP was measured using the Lund and Browder method at baseline, Day 30, Day 60, and Day 90, and the total BSAP was the overall sum of BSAP values recorded for nine anatomical regions.

BSAP was selected as a proxy for disease severity and the basis of the health states in the cost-effectiveness model as it provides the best representation of how wounds across the body are healing contemporaneously, rather than focusing on the closure of one specific target wound which forms the basis of the primary outcome. Further discussion of these endpoints and how they are incorporated in the cost effectiveness analysis is detailed in Section B.4.3.2.1.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Trial methodology of relevant trials

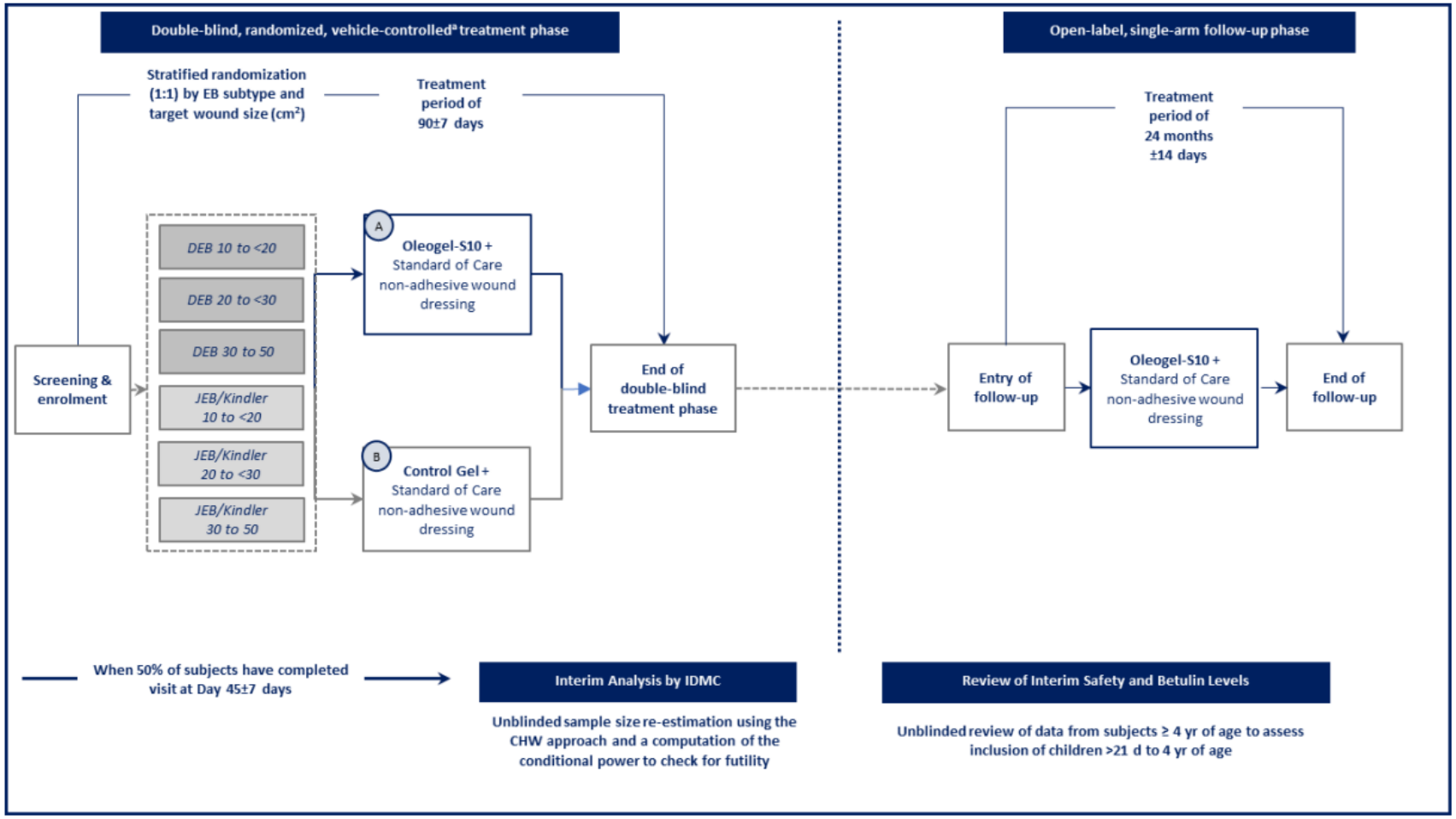
The pivotal phase III EASE trial is a two-phase study: a 90-day randomised, double-blind phase (DBP) of Filsuvez gel *versus* control gel, followed by a 24-month single-arm open-label phase (OLP), during which all participants received Filsuvez gel.(65, 75) A summary of the study design of the EASE trial is described in Table 7, and overview shown in Figure 5. Further detail of the trial methods in the EASE DBP and OLP is provided in Table 8, with a summary of wound selection and assessment methods in Table 9.

Table 7 Summary of trial design of the EASE RCT

Study name	EASE(65, 75) (previously BEB-13; NCT03068780, EudraCT2016-002066-32)
Objectives	The overarching objective of the EASE DBP was to compare the efficacy, safety and tolerability of Filsuvez gel with a control gel in patients with inherited EB (DEB, JEB and KEB)
Location	Global, multi-centre study. 49 study sites across: Argentina, Australia, Austria, Brazil, Chile, Colombia, Czech Republic, Denmark, France, Georgia, Germany, Greece, Hong Kong, Hungary, Ireland, Israel, Italy, Romania, Russia, Serbia, Singapore, Spain, Switzerland, Ukraine, United Kingdom, and the United States.
Design	Double-blind, randomised, controlled, phase III, 90-day efficacy and safety study with a 24-month open-label, single-arm follow-up phase
Key dates	First subject in DBP: 19 April 2017 First subject in OLP: 24 July 2017 DBP database lock: 26th August 2020 Interim 6-month OLP safety database lock : 21st December 2020 Interim 9-month OLP safety database lock: 21st April 2021 Interim OLP 12-month efficacy database lock: 15 July 2021 Final OLP 24-month database lock: 1st July 2022

Abbreviations: DBP, double-blind phase; DEB, dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; FDA, U.S. Food and Drug Administration; JEB, junctional epidermolysis bullosa; KEB, Kindler epidermolysis bullosa; OLP, open-label phase; RCT, randomised controlled trial.

Figure 5 EASE study design overview



Source: Amryt Pharmaceuticals. EASE end of DBP Clinical Study Report.(75)
Abbreviations: cm², square centimetre; DEB, dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; JEB, junctional epidermolysis bullosa.

Table 8 Summary of methodology of the EASE RCT – DBP and OLP

Study phase	Double blind phase (DBP)(65, 75)	Open-label phase (OLP)(65, 75, 85)
Duration of phase	**90 days**	**24 months**
Sample size	A total of 223 subjects (109, Filsuvez gel; 114, control gel) were randomised and received at least one dose of study medication.	A total of 205 (91.9%) subjects continued into the OLP
Key inclusion criteria	Male and female patients with DEB, JEB, or KEB[a] ≥ 4 years of age (reduced to > 21 days following an IDMC safety review in 2019) EB target wound 10–50 cm^2 in size aged ≥ 21 days and < 9 months outside of the anogenital region	Completion of EASE DBP (or early transfer to OLP at INV discretion)
Key exclusion criteria	EBS[b] EB target wound with clinical signs of local infection Use of systemic antibiotics for wound-related infections within 7 days Administration of systemic or topical steroids within 30 days immunosuppressive or cytotoxic chemotherapy within 60 days Previous stem cell transplant or gene therapy for EB Current and/ or former malignancy including BCC/ SCC	NA
Method of randomisation	Subjects were randomised 1:1 to receive either Filsuvez gel or control gel. Randomisation was conducted according to blinded patient number, and the randomisation key was held solely by an independent statistician. Subjects were stratified according to their EB subtype and target wound size (cm^2) into the following groups: • DEB 10 to < 20; • DEB 20 to < 30; • DEB 30 to 50; • JEB/ KEB[a] 10 to < 20; • JEB/ KEB[a] 20 to < 30; • JEB/ Kindler[a] 30 to 50.	The OLP was single-arm, all subjects were to be treated with Filsuvez gel however OLP data were analysed by prior Filsuvez gel and prior control gel use

Study phase	Double blind phase (DBP)(65, 75)	Open-label phase (OLP)(65, 75, 85)
Duration of phase	**90 days**	**24 months**
Method of blinding	Patients, caregivers, and investigators were blinded to their assigned intervention during the 90-day DBP, through use of a matched control gel as the control arm. An independent unblinded biostatistics team maintained the randomisation scheme key. All randomisation materials, remained restricted until after DBP completion, and subsequent locking of the study database for the DBP.	In the OLP, all subjects were to be treated with Filsuvez gel and there was no blinding applied during that period. Both the investigator and the subject were aware of the treatment to be received.
Intervention	Filsuvez gel (n=109 randomised and received treatment) 100g of Filsuvez gel consists of 10g active pharmaceutical ingredient birch bark extract and 90g sunflower oil. To be administered topically at approximately 1mm (0.04 inch) thickness to the EB target wound and to all areas on the subject's body that were affected by EB partial-thickness wounds. Wound areas were then to be covered with a standard of care non-adhesive wound dressing. The randomised treatment was to be applied during all dressing changes (at least every 4 days) until the EDBP.	Filsuvez gel (n=205 entered the OLP) Topical Filsuvez gel was to be administered to all areas on the subject's body that were affected by EB partial-thickness wounds on Day 0 of the OLP. Wound areas were to be covered with standard of care non-adhesive wound dressings. This procedure was to be repeated during all dressing changes (at least every 4 days) until the end of treatment at Month 24.
Comparator	Control gel (n=114 randomised and received treatment) 100 g of the sterile control gel consists of 85g sunflower oil, 5g Cera flava/ yellow wax, and 10g Carnauba wax. To be administered topically at approximately 1mm (0.04 inch) thickness to the EB target wound and to all areas on the subject's body that were affected by EB partial-thickness wounds. Wound areas were then to be covered with a standard of care non-adhesive wound dressing. The randomised treatment was to be applied during all dressing changes (at least every 4 days) until the EDBP.	The OLP was single-arm, all subjects were to be treated with the intervention, Filsuvez gel
Concomitant medications	The following medications/ therapies were permitted during both the DBP and OLP of the trial: • Liquid antiseptics at each dressing change to clean and/or reduce microbial colonisation of target wounds and additional wounds matching target wound criteria prior to study treatment; • Bathing (e.g., with chlorhexidine, diluted bleach, or salt) prior to study treatment at each wound dressing change;	

Study phase	Double blind phase (DBP)(65, 75)	Open-label phase (OLP)(65, 75, 85)
Duration of phase	**90 days**	**24 months**
	• Systemic antibiotics, except for the treatment of infections of the EB target wound or additional wounds matching target wound criteria; • Inhaled/ ophthalmic/ topical steroids for oesophageal strictures; • Supportive therapy upon the investigator's discretion. During both the DBP and OLP, the following were permitted for treatment of any EB wound, except the EB target wound or additional wounds matching target wound criteria: • Silver sulfadiazine; • Topical antibiotics; • Topical steroids. The following were not permitted on areas of the participants body affected by EB wounds during the DBP: • Skin products such as creams, ointments, gels, or emollients. During the DBP and the OLP, the following were not permitted on target wounds or additional wounds matching target wound criteria unless there was complete wound closure and confirmed epithelialisation before use: • Silver dressings; • Silver sulfadiazine; • Topical antibiotics; • Topical steroids. The following were not permitted until month three of the OLP: • Systemic steroids (except for inhaled, ophthalmic, or topical applications); • Immunosuppressive therapy or cytotoxic chemotherapy; • Systemic antibiotics for treatment of infections of the EB target wound or additional wounds matching the target wound criteria.	
Duration of follow-up, lost to follow-up information	Of the 223 randomised subjects, 199 (89.2%) completed the DBP (91.7%, Filsuvez gel *vs*. 86.8%, control gel), and 24 (10.8%) discontinued (8.3%, Filsuvez gel *vs*. 13.2%, control gel). A total of 205 (91.9%) subjects continued into the OLP. This included 199 subjects who completed the DBP and 6 subjects (all in the control gel group) who discontinued the DBP prematurely due to worsening of the EB target wound status or due to EB target wound infection and continued into the OLP prematurely (at the investigator's discretion).	Of the 205 subjects who entered the OLP, a total of [redacted] completed the OLP, and [redacted] discontinued the OLP. The primary reason for discontinuation was withdrawal of consent [redacted] followed by AE [redacted] and other reasons [redacted]

Study phase	Double blind phase (DBP)(65, 75)	Open-label phase (OLP)(65, 75, 85)
Duration of phase	**90 days**	**24 months**
Primary outcome	Proportion of patients with first complete target wound closure within 45 days based on INV assessment	N/A
Secondary outcomes	<u>Key secondary (confirmatory) efficacy endpoints:</u> • Time to first wound closure up to 90±7 days of treatment • Incidence of first complete wound closure of EB target wound • Incidence of wound infection • Maximum severity of wound infection • CFB in total body wound burden (EBDASI, Section I: Skin, Activity (not Damage), only) • CFB in itching (Itch Man Scale/ Leuven Itch Scale) <u>Other secondary endpoints:</u> • CFB in EB target wound size • CFB in % of TBSA affected by EB PTW • CFB in background and procedural pain (FLACC, Wong-Baker FACES) • Response to treatment/ treatment satisfaction (TSQM) • CFB in sleep quality (Likert scale) • Number of days missed from school or work • Incidence, severity, and relatedness of AEs • Local tolerability <u>Post-hoc analyses</u> • Dressing change frequency	• Incidence of Target Wound Infection in the OLP • Maximum Severity of Wound Infection in the OLP (between baseline and Month-24) • CFB in Total Body Wound Burden in the OLP (EBDASI, Section I: Skin, Activity (not Damage), only; Months 3, 12, 24) • CFB in BSAP affected by PTW by Visit (Months 3, 12, 24) • CFB in itching (Itch Man Scale/ Leuven Itch Scale; Month 3 only) • CFB in background and procedural pain (FLACC, Wong-Baker FACES; Month-3 only) • CFB in sleep quality (Likert scale) (Month-3 only) • Number of days missed from school or work (Month-3 only) • Status of target wounds by visit (Month-3 only) • CFB in disease severity by the iscorEB (Months 12, 24) • CFB in patients' quality of life as assessed by the EQ-5D (Months 12, 24) • Response to treatment/ treatment satisfaction (TSQM)

Abbreviations: AE, adverse event; BCC, basal cell carcinoma; BSAP, body surface area percentage; CFB, change from baseline; cm^2, square centimetre; DBP, double blind phase; DEB, dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; EBDASI, epidermolysis bullosa disease activity and scarring index; EBS, epidermolysis bullosa simplex; EDBP, end of double blind phase; EQ-5D, EuroQol 5-dimension; FLACC, Face, Legs, Activity, Cry, Consolability scale; g, gram; IDMC, Independent Data Monitoring Committees; INV, investigator-assessed; JEB, junctional epidermolysis bullosa; KEB, Kindler EBV; OLP, open label phase; mm, millimetre; n, number; N/A, not applicable; PTW, partial-thickness wound; RCT, randomised controlled trial; SCC, squamous cell carcinoma; TBSA, total body surface area; TSQM, treatment satisfaction questionnaire for medication.

[a] Previously known as Kindler syndrome. KEB patients were eligible for inclusion in the EASE trial however no patients with KEB were recruited.

[b] One participant with EBS was included in each intervention arm of the EASE trial (recruited before the V4.0 protocol amendment excluded EBS participants).

Table 9 Summary of wound selection and assessment methods in EASE

Study phase	Double blind phase (DBP)(65, 75)	Open-label phase (OLP)(65, 75, 85)
Target wound criteria	EB partial-thickness wound identified by investigator 10–50cm^2 in surface area > 21 days and < 9 months old Outside the anogenital region Target wound identified with two appropriate anatomical landmarks on either side of it. The baseline reference image was taken with these landmarks. Future visits will refer to the baseline reference image to ensure that the correct wound is assessed. All other wounds that matched target wound criteria were to be photo-documented similarly. Target wound must involve loss of the epidermis, with extension into the dermis allowable.	Target Wound criteria as per the DBP
Target wound assessment method	For the assessment of wound closure and re-epithelialization, the investigator will photograph the EB target wound and all other wounds that match target wound criteria with the ARANZ Silhouette® system. This system measures accurately, precisely, and reliably, provides high quality imaging, and a standardised documentation. A 3D model of the wound based on photographic data, derives measurements of the model, and records standardised notes. Automatic flash ensures consistent lighting across images.	Target wound assessment method is as per the DBP The target wound closure categories included closed, not closed, not assessed, and missing. The category of not closed was further divided into 3 subcategories: unchanged from baseline; improved from baseline; and worsened from baseline.
Target wound assessment schedule	Visits: Days 0, 7 (+/- 2), 14 (+/- 5), 30 (+/- 7), 45 (+/- 7), 60 (+/- 7), 90 (+/- 7; end of DBP). Plus, a confirmation of complete closure (CCC) of the EB target wound visit, up to 1 week+2 days after first complete closure. Post-treatment assessments will be made within one week of wound closure to determine durability of healing.	The status of target wounds was not included as an OLP efficacy endpoint in the SAP; however, an assessment was performed at OLP baseline and Month 3.

Abbreviations: CCC, confirmation of complete closure; cm^2, square centimetre; DBP, double-blind phase; EB, epidermolysis bullosa; OLP, open-label phase, SAP, statistical analysis plan.

B.2.3.2 Demographics and baseline characteristics of participants of relevant trials

The baseline demographics and target wound characteristics of participants in the EASE trial DBP, are summarised in Table 10.

B.2.3.2.1 Baseline demographics and wound characteristics in the EASE DBP

The pivotal EASE trial of Filsuvez gel included both paediatric and adult participants, which is representative of the EB population seen in clinical practice, since EB onset is usually from birth, although diagnosis may come later depending on the clinical presentation. Following an Independent Data Monitoring Committee (IDMC) safety review in 2019, the lower age limit of children/ infants recruitable to EASE was changed from 4 years to 21 days of age, making the EASE trial population more reflective of clinical practice.(65, 75, 88) For the 223 participants randomised in the EASE DBP, the overall median age of participants was 12 years (range: 6 months to 81 years), of which 134 (60.1%) were male and 89 (39.9%) were female.(75)

The EB disease subtypes relevant to the decision problem in this submission, DEB, and JEB, were represented in the EASE trial; 195 (87.4%) participants had DEB, of these,175 (78.5%) had RDEB and 20 (9.0%) had DDEB, while there were 26 (11.7%) JEB participants and 2 (0.9%) with EBS. Although Kindler EB (KEB) was included in the EASE trial protocol, no KEB (n=0) participants were recruited.(75, 88) It should also be noted that prior to the implementation of the V4.0 protocol amendment with excluded EBS participants, one participant with EBS was included in each intervention arm of the EASE trial, which are not relevant to the decision problem addressed in this submission.(75, 88)

Patient demographics and baseline characteristics were generally well balanced between the two treatment groups, however, within the DEB subtype, the Filsuvez gel group had a higher proportion of subjects with RDEB compared to the control gel (83.5%, Filsuvez gel *versus* 73.7%, control gel) and accordingly, a lower proportion of subjects with DDEB (5.5%, Filsuvez gel *versus* 12.3%, control gel).(75)

In the overall EASE population, the mean size of the target wound at baseline was 19.20cm^2 (SD: 9.398cm^2). The majority of the participant population (64.6%) had a target wound sized between 10 to <20 cm^2 (21.1% had a target wound sized between

20 to <30 cm^2, and 14.3% had a target wound sized between 30 to 50 cm^2). Target wound size was well balanced between the two treatment groups.(75)

The median age of the target wound for all participants was 35.5 days and ranged between 21 and 4,745 days. This range falls outside of the trial wound eligibility criteria as fourteen subjects (n=8, Filsuvez gel, n=6, control gel) had wounds over nine months of age (range: 11.5-156 months) because they were enrolled prior to an early protocol amendment that capped target wound age at a maximum of 9 months.(75) This small number of early-recruited participants with older wounds significantly influenced the reported mean wound age (125.4 days, SD: 399.54), thereby the reported median wound age of 35.5 days is a more informative statistic. In the subset of subjects with a target wound age of no more than 9 months (n=208), as per the final protocol, median wound age was 32.0 days.(75, 88) The median wound age was slightly greater in the Filsuvez gel group (39 days, Filsuvez gel *versus* 32 days, control gel).

Total body wound burden (TBWB) was assessed at baseline using EBDASI. In the full analysis set (FAS), the mean EBDASI skin activity score was 19.6 (SD: 11.91) with the majority of patients falling into the 'Mild' EBDASI category (94.2% of all subjects, N=223). However, it is noted that since only part of Section I of the EBDASI assessing Skin Activity (blistering/ erosions/ crusting) was used in this study for assessment of TBWB (excluding the anogenital region assessment), the maximum possible EBDASI score based on Skin Activity only was 100, below the minimum score need to be classified as severe (EBDASI total score: 0-42 Mild, 43-106 Moderate, >106 Severe).(75)

Wound burden was also assessed using the Lund and Browder method to assess the body surface area percentage (BSAP) covered by EB partial-thickness wounds. At baseline, 57.8% of all subjects had <10% BSAP (53.2% and 62.3% in the Filsuvez gel and control gel arms, respectively), 29.1% had 10-25% BSAP (34.9 % and 23.7%, in the Filsuvez gel and control gel arms, respectively), and 12.6% had a BSAP of >25% (11.9% and 13.2%, in the Filsuvez gel and control gel arms, respectively).(75) Overall, baseline wound characteristics were considered fairly well balanced between arms.

The frequency of past medical and surgical events was also fairly well balanced between the arms and high overall, representing an array of comorbidities. These

comorbidities are generally anticipated in subjects with EB, relating to the disease and its complications.(75) The majority of the study participants (93.7%, n=209) had at least one relevant condition other than the EB diagnosis reported, and almost half (49.3%) had undergone at least one surgical or medical procedure.(75)

Overall, EASE participants had significant morbidity, as evidenced by the predominance of severely affected EB subtypes, and the associated substantial burden of disease observed in the subjects' medical histories, baseline laboratory values (e.g., low albumin and haemoglobin), baseline physical examination findings, and prior medications. This was expected and is representative of patients seen in UK clinical practice (as supported by communication with clinical experts).

B.2.3.2.2 Baseline demographics in the EASE OLP

The baseline demographics and target wound characteristics of participants in the EASE trial OLP, are summarised in Table 10. Although all patients were treated with Filsuvez gel during the OLP, baseline demographics are reported by previous DBP treatment allocation, as well as for all subjects.

For the 205 (91.9%) participants who entered the EASE OLP, the overall median age of subjects in the OLP was 12 years (range: 6 months to 81 years); 126 (61.5%) subjects were male and 79 (38.5%) were female.(87) Most (82.4%) subjects were of White race. For EB subtype, a total of 178 (86.8%) subjects had DEB; of these, 160 (78.0%) were RDEB and 18 (8.8%) were DDEB, and 25 participants (12.2%) had JEB, and 2 EBS (with implementation of Version 4.0 of the protocol, subjects with EBS were excluded from study participation).(87) Given the retention of 91.9% of participants from the DBP into the OLP, the balance of demographics was in line with the DBP.

In summary, EASE represents the largest EB clinical trial population to date with aspects of wound and disease characteristics for the enrolled participants well defined, and the participant population representative of the DEB/ JEB population seen in UK clinical practice (as supported by communication with clinical experts).

Table 10 Baseline participant demographics and wound characteristics from the EASE DBP and OLP

		EASE DBP(75, 87)			EASE OLP(87)		
		Filsuvez gel (n= 109)	Control gel (n=114)	All subjects (N=223)	Previously Filsuvez gel (n=100)	Previously control gel (n=105)	All subjects (n=205)
Demographics							
Age, years	**Mean (SD)**	16.8 (13.89)	16.5 (14.57)	16.7 (14.21)	16.8 (14.38)	15.8 (13.94)	16.3 (14.13)
	Median (range)	13.0 (1-71)	12.0 (0[a]-81)	12.0 (0[a]-81)	12.0 (1-71)	12.0 (0[a]-81)	12.0 (0[a]-81)
Age groups, n (%)	**≤4 years**	7 (6.4)	10 (8.8)	17 (7.6)	7 (7.0)	9 (8.6)	16 (7.8)
	4 to <12 years	42 (38.5)	43 (37.7)	85 (38.1)	40 (40.0)	41 (39.0)	81 (39.5)
	12 to <18 years	25 (22.9)	29 (25.4)	54 (24.2)	22 (22.0)	28 (26.7)	50 (24.4)
	≥18 years	35 (32.1)	32 (28.1)	67 (30.0)	31 (31.0)	27 (25.7)	58 (28.3)
Gender, n (%)	**Male**	68 (62.4)	66 (57.9)	134 (60.1)	63 (63.0)	63 (60.0)	126 (61.5)
	Female	41 (37.6)	48 (42.1)	89 (39.9)	37 (37.0)	42 (40.0)	79 (38.5)
Geographic region, n (%)	**Europe**	48 (44.0)	55 (48.2)	103 (46.2)	NR	NR	NR
	South America	33 (30.3)	35 (30.7)	68 (30.5)	NR	NR	NR
	Rest of world	21 (19.3)	17 (14.9)	38 (17.0)	NR	NR	NR
	United States	7 (6.4)	7 (6.1)	14 (6.3)	NR	NR	NR
Race, n (%)	**White**	95 (87.2)	91 (79.8)	186 (83.4)	86 (86.0)	83 (79.0)	169 (82.4)
	Black or Af/Am	1 (0.9)	2 (1.8)	3 (1.3)	1 (1.0)	2 (1.9)	3 (1.5)
	Asian	4 (3.7)	7 (6.1)	11 (4.9)	4 (4.0)	6 (5.7)	10 (4.9)
	Am/Ind or Ala/nat	0	1 (0.9)	1 (0.4)	0 (0)	1 (1.0)	1 (0.5)

		EASE DBP(75, 87)			EASE OLP(87)		
		Filsuvez gel (n= 109)	**Control gel (n=114)**	**All subjects (N=223)**	**Previously Filsuvez gel (n=100)**	**Previously control gel (n=105)**	**All subjects (n=205)**
	Unknown	1 (0.9)	1 (0.9)	2 (0.9)	1 (1.0)	1 (1.0)	2 (1.0)
	N/A[b]	4 (3.7)	8 (7.0)	12 (5.4)	4 (4.0)	8 (7.6)	12 (5.9)
	Other[c]	4 (3.7)	4 (3.5)	8 (3.6)	4 (4.0)	4 (3.8)	8 (3.9)
BMI (kg/m^2)	**Mean (SD)**	16.05 (4.979)	16.31 (5.037)	16.18 (4.999)	16.21 (5.128)	16.29 (5.099)	16.25 (5.101)
EB subtype, n (%)	**RDEB**	**91 (83.5)**	**84 (73.7)**	**175 (78.5)**	**83 (83.0)[d]**	**77 (73.3)[d]**	**160 (78.0)**
	RDEB, generalised severe	62 (56.9)	62 (54.4)	124 (55.6)	55 (55.0)	58 (55.2)	113 (55.1)
	RDEB, generalised intermediate	23 (21.1)	16 (14.0)	39 (17.5)	22 (22.0)	13 (12.4)	35 (17.1)
	RDEB, localised	3 (2.8)	4 (3.5)	7 (3.1)	3 (3.0)	4 (3.8)	7 (3.4)
	RDEB, other	3 (2.8)	2 (1.8)	5 (2.2)	3 (3.0)	2 (1.9)	5 (2.4)
	DDEB	6 (5.5)	14 (12.3)	20 (9.0)	6 (6.0)	12 (11.4)	18 (8.8)
	JEB	**11 (10.1)**	**15 (13.2)**	**26 (11.7)**	**10 (10.0)[d]**	**15 (14.3)[d]**	**25 (12.2)**
	JEB, generalised severe	0	2 (1.8)	2 (0.9)	0 (0)	2 (1.9)	2 (1.0)
	JEB, generalised intermediate	8 (7.3)	9 (7.9)	17 (7.6)	8 (8.0)	9 (8.6)	17 (8.3)
	JEB, localised	1 (0.9)	0	1 (0.4)	1 (1.0)	0 (0)	1 (0.5)
	JEB, other	2 (1.8)	4 (3.5)	6 (22.7)	1 (1.0)	4 (3.8)	5 (2.4)
	EBS	1 (0.9)	1 (0.9)	2 (0.9)	1 (1.0)	1 (1.0)	2 (1.0)
	Kindler	0	0	0	0	0	0
Method of diagnosis n (%)	**Genetic mutation identified**	67 (61.5)	62 (54.4)	129 (57.8)	70 (70.0)	65 (61.9)	135 (65.9)
	Clinical diagnosis only	25 (22.9)	24 (21.1)	49 (22.0)	13 (13.0)	14 (13.3)	27 (13.2)

		EASE DBP(75, 87)			EASE OLP(87)		
		Filsuvez gel (n= 109)	**Control gel (n=114)**	**All subjects (N=223)**	**Previously Filsuvez gel (n=100)**	**Previously control gel (n=105)**	**All subjects (n=205)**
	Immunofluorescence mapping or electron microscopy	16 (14.7)	25 (21.9)	41 (18.4)	16 (16.0)	24 (22.9)	40 (19.5)
	Other	1 (0.9)	3 (2.6)	4 (1.8)	1 (1.0)	2 (1.9)	3 (1.5)
Wound characteristics							
Age of target wound/ days	**Mean (SD)**	124.3 (327.44)	126.4 (459.99)	125.4 (399.54)	128.9 (340.19)	132.5 (476.77)	130.7 (414.78)
	Median (range)	39.0 (21-2920)	32.0 (21-4745)	35.5 (21–4745)	39.5 (21-2920)	32.0 (21-4745)	36.0 (21-4745)
Size of target wound/ cm^2	**Mean (SD)**	18.99 (8.640)	19.41 (10.104)	19.20 (9.398)	18.84 (8.348)	19.81 (10.292)	19.34 (9.384)
	Median (range)	16.00 (10.0-45.6)	15.45 (10.0-49.5)	15.60 (10.0-49.5)	16.00 (10.0-45.6)	15.60 (10.0-49.5)	15.80 (10.0-49.5)
Total BSAP[e], n (%)	**Mean (SD)**	12.06 (9.967)	12.18 (12.215)	12.12 (11.143)	7.41 (6.238)	8.30 (7.552)	7.85 (6.916)
	<10%	58 (53.2)	71 (62.3)	129 (57.8)	54 (54.0)	65 (61.9)	119 (58.0)
	10-25%	38 (34.9)	27 (23.7)	65 (29.1)	35 (35.0)	26 (24.8)	61 (29.8)
	>25%	13 (11.9)	15 (13.2)	28 (12.6)	11 (11.0)	13 (12.4)	24 (11.7)
	Missing	0	1 (0.9)	1 (0.4)	0 (0)	1 (1.0)	1 (0.5)
Total wound burden/ EBDASI[f], n (%)	**Mean (SD)**	19.6 (11.26)	19.6 (12.55)	19.6 (11.91)	16.5 (9.41)	15.8 (8.81)	16.2 (9.10)
	Mild	101 (92.7)	109 (95.6)	210 (94.2)	NR	NR	NR
	Moderate	7 (6.4)	4 (3.5)	11 (4.9)	NR	NR	NR
	Severe	0	0	0	NR	NR	NR
	Missing	1 (0.9)	1 (0.9)	2 (0.9)	NR	NR	NR

		EASE DBP(75, 87)			EASE OLP(87)		
		Filsuvez gel (n= 109)	Control gel (n=114)	All subjects (N=223)	Previously Filsuvez gel (n=100)	Previously control gel (n=105)	All subjects (n=205)
Medical History							
Medical and surgical histories reported for ≥5% of all subjects by preferred term	**Constipation**	36 (33.0)	43 (37.7)	79 (35.4)	32 (32.0)	42 (40.0)	74 (36.1)
	Anaemia	36 (33.0)	40 (35.1)	76 (34.1)	32 (32.0)	37 (35.2)	69 (33.7)
	Oesophageal stenosis	32 (29.4)	31 (27.2)	63 (28.3)	29 (29.0)	30 (28.6)	59 (28.8)
	Pruritus	24 (22.0)	33 (28.9)	57 (25.6)	23 (23.0)	31 (29.5)	54 (26.3)
	Oesophageal dilation procedure	17 (15.6)	17 (14.9)	34 (15.2)	15 (15.0)	17 (16.2)	32 (15.6)
	Gastrostomy	18 (16.5)	18 (15.8)	36 (16.1)	16 (16.0)	18 (17.1)	34 (16.6)
	Iron deficiency anaemia	15 (13.8)	18 (15.8)	33 (14.8)	14 (14.0)	18 (17.1)	32 (15.6)
	Pain	9 (8.3)	23 (20.2)	32 (14.3)	9 (9.0)	21 (20.0)	30 (14.6)
	Malnutrition	16 (14.7)	12 (10.5)	28 (12.6)	14 (14.0)	12 (11.4)	26 (12.7)
	Pseudosyndactyly	11 (10.1)	10 (8.8)	21 (9.4)	11 (11.0)	9 (8.6)	20 (9.8)
	Vitamin D deficiency	11 (10.1)	10 (8.8)	21 (9.4)	11 (11.0)	10 (9.5)	21 (10.2)
	Gastroesophageal reflux disease	8 (7.3)	11 (9.6)	19 (8.5)	7 (7.0)	11 (10.5)	18 (8.8)
	Dental caries	10 (9.2)	8 (7.0)	18 (8.1)	8 (8.0)	8 (7.6)	16 (7.8)
	Dry eye	6 (5.5)	12 (10.5)	18 (8.1)	6 (6.0)	12 (11.4)	18 (8.8)
	Hand repair operation	6 (5.5)	12 (10.5)	18 (8.1)	5 (5.0)	12 (11.4)	17 (8.3)
	Dysphagia	10 (9.2)	5 (4.4)	15 (6.7)	9 (9.0)	5 (4.8)	14 (6.8)

		EASE DBP(75, 87)			EASE OLP(87)		
		Filsuvez gel (n= 109)	Control gel (n=114)	All subjects (N=223)	Previously Filsuvez gel (n=100)	Previously control gel (n=105)	All subjects (n=205)
	Iron deficiency	8 (7.3)	7 (6.1)	15 (6.7)	7 (7.0)	7 (6.7)	14 (6.8)
	Syndactyly	9 (8.3)	6 (5.3)	15 (6.7)	8 (8.0)	6 (5.7)	14 (6.8)
	Wound infection	5 (4.6)	8 (7.0)	13 (5.8)	4 (4.0)	8 (7.6)	12 (5.9)
	Limb operation	7 (6.4)	5 (4.4)	12 (5.4)	7 (7.0)	5 (4.8)	12 (5.9)
	Tooth extraction	3 (2.8)	9 (7.9)	12 (5.4)	2 (2.0)	8 (7.6)	10 (4.9)

Abbreviations: Af/AM=African American; Am/Ind, American or American Indian; Ala/nat=Alaska Native; BMI=body mass index; BSAP, body surface area percentage; cm2, square centimetre; DEB, dystrophic epidermolysis bullosa; DDEB, dominant dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; EB, epidermolysis bullosa simplex; EBDASI, Epidermolysis Bullosa Disease Activity Score Index; EBS, epidermolysis bullosa simplex; JEB, junctional epidermolysis bullosa; kg/m2, kilogram per square metre; N / n, number of subjects; N/A, not applicable; RDEB, recessive dystrophic epidermolysis bullosa; SD, standard deviation.

[a] six months

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

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

[d] Self-calculated values

[e] BSAP measured as total body surface area affected by EB partial-thickness wounds based on "Lund and Browder" chart.

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

B.2.3.3 Methods of expert elicitation

Amryt Pharmaceuticals commissioned a number of projects to elicit quantitative and qualitative expert input which are described in Section B.3.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Statistical analyses of the EASE trial

B.2.4.1.1 Study population for analysis

The statistical analysis is based on the study populations described below. Patients who were randomised but not treated are not assigned to any of the analysis sets.(89)

Table 11 Summary of statistical analysis sets from EASE

	Population	Use in analyses
Full analysis set (FAS)	Includes all randomised patients treated at least once with study treatment. Participants are analysed according to the randomised treatment regimen (if different from the received treatment).	Used as the primary analysis set for all efficacy analyses
Safety analysis set (SAS)	Includes all patients treated at least once with study medication. Participants are analysed according to the treatment regimen received.	Used for all analyses of safety endpoints and the presentation of the study population summaries and patient-level data listings.
Completer analysis set (CAS)	Includes all patients from the FAS who did not discontinue the double-blind phase of the study early, irrespective of the reason for discontinuation. Participants are analysed according to the randomised treatment regimen.	Used for supportive analyses of the primary efficacy endpoint and key secondary endpoints.
Per protocol set (PPS)	Includes all patients who have met the eligibility criteria, received the planned study medication, and have reasonably adhered to all relevant protocol conditions.[a] Participants are analysed according to randomised treatment regimen.	Used for supportive analyses of the primary efficacy endpoint and key secondary endpoints.

Source: Adapted from EASE SAP (v5.0 Final)(89)
Abbreviations: CAS, completer analysis set; FAS, full analysis set; PPS, per protocol set; SAS, safety analysis set
[a] Case-by-case decisions regarding exclusions of patients from the PPS analysis are made prior to final unblinding in a Blind Data Review Meeting (BDRM) which is performed prior to database lock and unblinding of the DBP of the study.

Primary analysis

The assumed true control rate for the primary endpoint, first complete closure of the EB target wound, was 27%. Based on the use of a 2-sided chi-square test of equality of binomial proportions at the alpha=0.05 level of significance, a total sample size of 182 subjects (91 subjects per arm) was expected to provide 80% power to detect an improvement of 20 percentage points (i.e., a true Filsuvez gel rate of 47%). A total of 192 subjects were planned to be enrolled into the study and treated to account for an estimated dropout rate of 5%. The Cochran-Mantel-Haenszel (CMH) test was not used for the sample size estimation since there is no valid information available about expected response rates within the strata.(89)

Following the unblinded interim analysis of efficacy for sample size re-estimation, the IDMC recommended that the sample size be increased by 48 subjects (24 per arm) for a total of 230 evaluable subjects. Due to a slowing rate of enrolment and onset of the COVID-19 pandemic, the Sponsor decided to cease enrolment as of 6th March 2020, at which time 223 subjects were enrolled. After consultation with an independent expert, the Sponsor concluded that the statistical impact of further subject recruitment would most likely be negligible and decided to cease enrolment and proceed to database lock.(89)

All protocol deviations regarding visits and assessments that were modified due to the COVID-19 pandemic were presented in a separate listing.

All categorical (binary and ordinal) data were summarised using frequency counts and percentages of subjects. Continuous variables were summarised using number of observations (n), mean, standard deviation (SD), median, minimum, and maximum, unless otherwise specified. All estimations included a point estimate and the corresponding 2-sided 95% confidence interval (CI).(89)

The primary efficacy endpoint, defined as the proportion of subjects with first complete closure of the EB target wound within 45 days (+/- 7) based on clinical assessment by the investigator, was first compared between treatment groups using the CMH test, stratified by EB subtype and target wound size class. Since the IDMC deemed it necessary to increase the sample size after the unblinded interim analysis, the final statistical analysis of the primary efficacy endpoint was performed based on the Cui,

Hung, Wang (CHW) approach to adjust the estimates provided by the CMH test. The overall level of significance for the primary endpoint analysis was 0.05 (2-sided). If the primary analysis of the primary efficacy endpoint demonstrated superiority at the 5% significance level, hierarchical confirmatory testing of the six key secondary endpoints was to be performed.(89)

Sample size and statistical methods in the OLP

The sample size of 205 in the OLP was the number of subjects who entered the OLP. The OLP efficacy endpoints are analysed using the FAS and summarised by visit unless stated otherwise, and where changes from baseline are measured, this is performed from OLP baseline, Month 0 (not DBP baseline which is Day 0). All safety analyses used the SAS population.(87, 90)

All categorical (binary and ordinal) data were summarised using frequency counts and percentages of subjects. Continuous variables were summarised using number of observations (n), mean, standard deviation (SD), median, minimum, and maximum, unless otherwise specified. All estimations included a point estimate and the corresponding 2-sided 95% confidence interval (CI).(87, 90)

OLP efficacy analyses were not powered for statistical significance, and were confirmatory only.(87, 90)

An updated version of the statistical analysis plan (SAP) was published pertaining to analysis of the final analysis of the OLP (Version 6.0).(90) The changes related to the analysis performed for efficacy at Month 12 and Month 24 was updated to use a new visit window. Previously a year was considered to have 360 days (that is 30 days per month), however it was noted that when capturing the data at the investigator sites, the conventional year length of 365 days was generally used. Thus, the windowing was updated to 365 days ±14 days for Month 12 and to 730 days ±14 days for Month 24. In addition, post-hoc outputs relating to EBDASI and BSAP were created without visit windowing for OLP visits (i.e., using the exact day a patient had a visit and not shifting them into the predefined visit windows to which they best fit), in order to accurately reflect real world data.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of the EASE RCT was performed according to the criteria set out in the Cochrane RoB2 tool.(91) As an RCT, methods employed in the EASE trial to reduce risk of bias were largely effective. The risk-of-bias judgement overall for EASE was 'some concerns', being largely associated with protocol deviations and the potential effect on outcomes, and the appropriateness of analysis sets. The full table of quality assessment is presented in Appendix D.

While overall, 35% of participants had a major protocol deviation regarding the investigational product, the majority involved non-compliance with product administration (in terms of days between dressing changes, for example) and incorrect return of investigational product. While the RoB2 tool necessitates identification of such deviations, it should be recognised that such administration differences are often to be expected in chronic use of topical medicines, and the WHO do not assign a Defined Daily Dose (DDD) for topical products.(5) Furthermore, 7.2% had a major protocol deviation regarding randomisation (mis-stratification), although analyses were performed appropriately with patients in the correct groups.

The EASE trial protocol and SAP did not plan for an intention to treat (ITT) analysis, which is classified as 'some concern' under the RoB2 tool. However, the EASE protocol was developed before the ICH-E9 addendum was operationalised which states that an ITT analysis set is preferred.(92) In EASE, study randomisation and treatment commencement were on the same day minimising the chance of any randomised patients not receiving treatment, therefore the FAS analysis included all randomised, treated patients, and the lack of an ITT analysis carried no risk that may have affected outcomes.(88)

It is challenging to conduct a global, well powered RCT in a rare disease with a topical product with little regulatory precedence, but the action taken to mitigate the lack of ITT appears reasonable.

Therefore, overall, in the context of EB being a rare disease it is felt that the EASE RCT represents a robust source of evidence in terms of both internal and external validity.

B.2.6 Clinical effectiveness results of the relevant studies

Efficacy endpoints are presented and described for the EASE DBP (database lock: 26th August 2020) in Section B.2.6.1, and for the EASE OLP (database lock: 1st July 2022) in Section B.2.6.2.

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

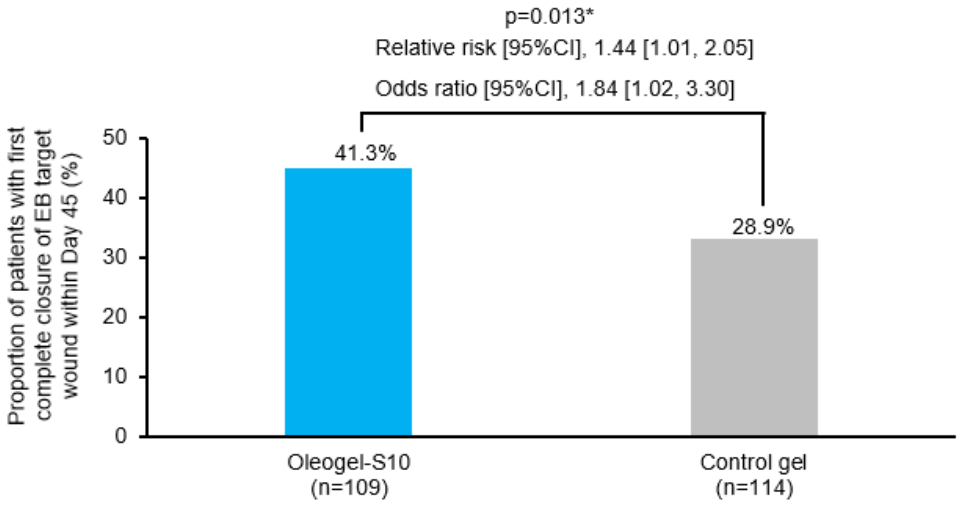
A few unique efficacy endpoints were incorporated in the OLP including assessment of disease severity by iscorEB and quality of life by EQ-5D, both patient-reported outcome (PRO) assessments that were added in Protocol Version 6.0, approximately 2.5 years after the study was initiated.(87, 88) As a result of their later addition, site implementation of iscorEB and EQ-5D occurred slowly and few subjects had baseline assessments, which resulted in limited data and made interpretation of change from baseline assessments unmeaningful.

B.2.6.1 Clinical effectiveness results from the EASE DBP

The clinical efficacy results of the EASE double-blind phase (DBP) (database lock: 26th August 2020) are summarised in Table 12.

The primary efficacy endpoint of EASE was met; Filsuvez gel treatment statistically significantly increased the probability of target wound closure by Day 45 (+/- 7) by 44% compared to the control gel (41.3% *versus* 28.9%; risk ratio 1.44 [95% CI: 1.01, 2.05]; *P*=0.013) (Figure 6).(75, 79) This was further supported by subgroup analysis by EB subtype, described in Section B.2.7.

Figure 6 The proportion of patients with first complete target wound closure within 45 (+/- 7) days in the EASE trial DBP



Source: Murrell DF, et al. Presented at, EADV Virtual Congress, 29-31 October 2020. D3T03.3B.(79)
Abbreviations: CI, confidence interval; DBP, double-blind phase; EB, epidermolysis bullosa; n, number of subjects.; IDMC, Independent Data Monitoring Committee.
**Pre-specified adjustment to account for IDMC interim sample size re-estimation*

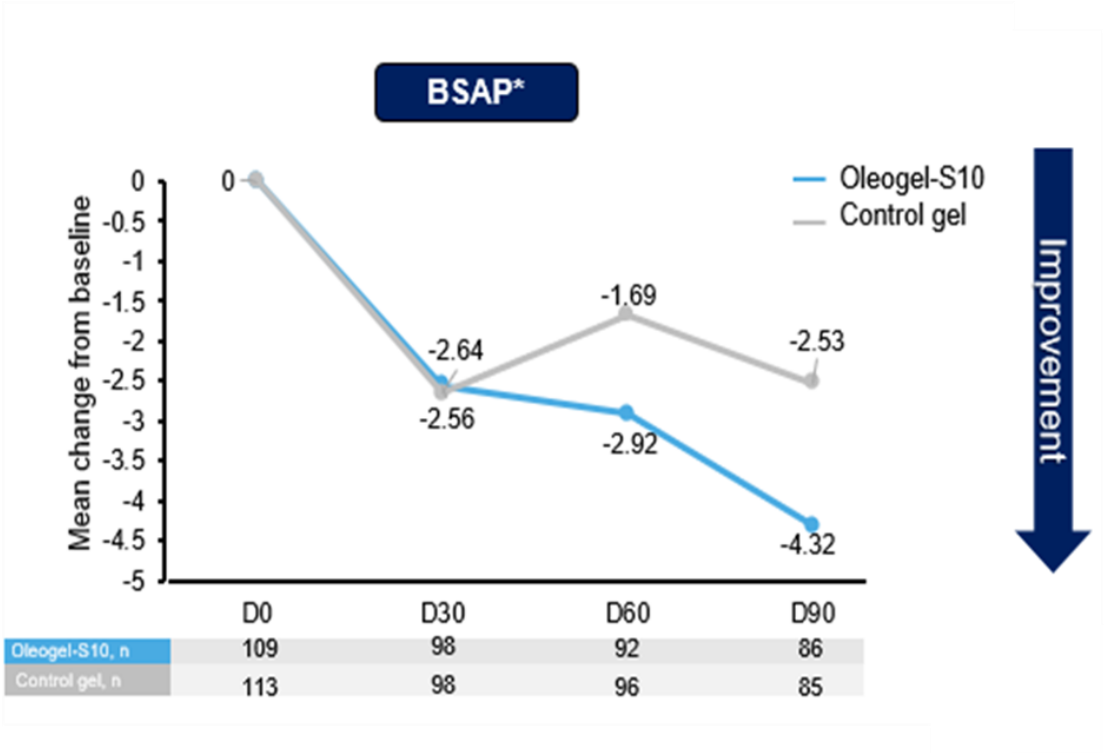
Since the primary endpoint achieved statistical significance, hierarchical testing of the key secondary endpoints was performed. There was no significant difference (*P*=0.302) in median time to first complete closure of target wound by day 90 based on clinical assessment (first key secondary endpoint) between patients receiving Filsuvez gel (92 days) and those receiving control gel (94 days); therefore, further analyses of key and other secondary endpoints were non-confirmatory and descriptive only.

The proportion of participants with first complete closure of target wound by Day 90 based on investigator assessment was 50.5% in the Filsuvez gel group, and 43.9% in the control gel group (*P*=0.296).(75)

Incidence of target wound infection up to Day 90 based on AE reporting or use of antibiotics was low in both arms (1.8% in the Filsuvez gel group and 4.4% in the control gel arm). Maximum severity of target wound infections was reported based on AE reporting only, with one mild infection in a patient receiving Filsuvez gel, and three moderate and one severe infection in patients receiving the control gel.(75)

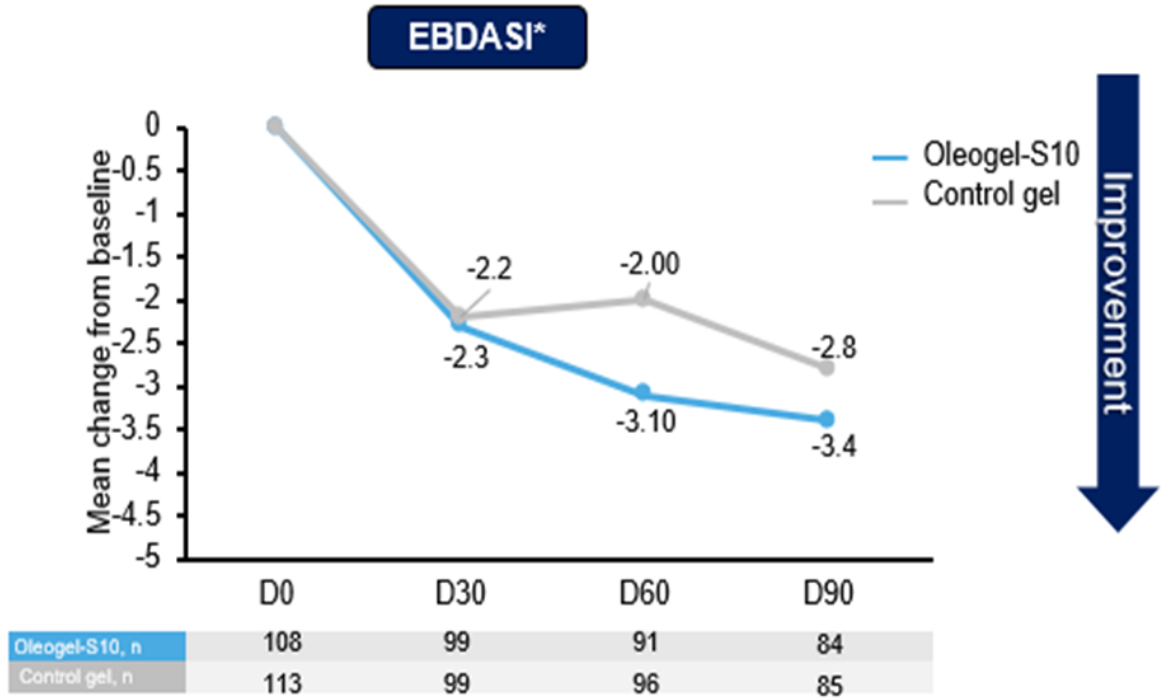
Accelerated wound healing with Filsuvez gel (demonstrated by the primary endpoint) was accompanied by reductions in change from baseline in BSAP affected with partial-thickness wounds (BSAP, -4.32% by day 90, *versus* -2.53% in the control group) (Figure 7), and change from baseline in disease activity/ severity as measured by EBDASI (-3.4 at day 90 *versus* -2.8 in the control group) (Figure 8).(75, 79)

Figure 7 Change in BSAP by Day 90



Source: Murrell DF, et al. Presented at, EADV Virtual Congress, 29-31 October 2020. D3T03.3B.(79)
Abbreviations: BSAP, body surface area percentage.
**At all timepoints, comparison between Filsuvez gel vs. control gel was not significant*

Figure 8 Change in EBDASI by Day 90



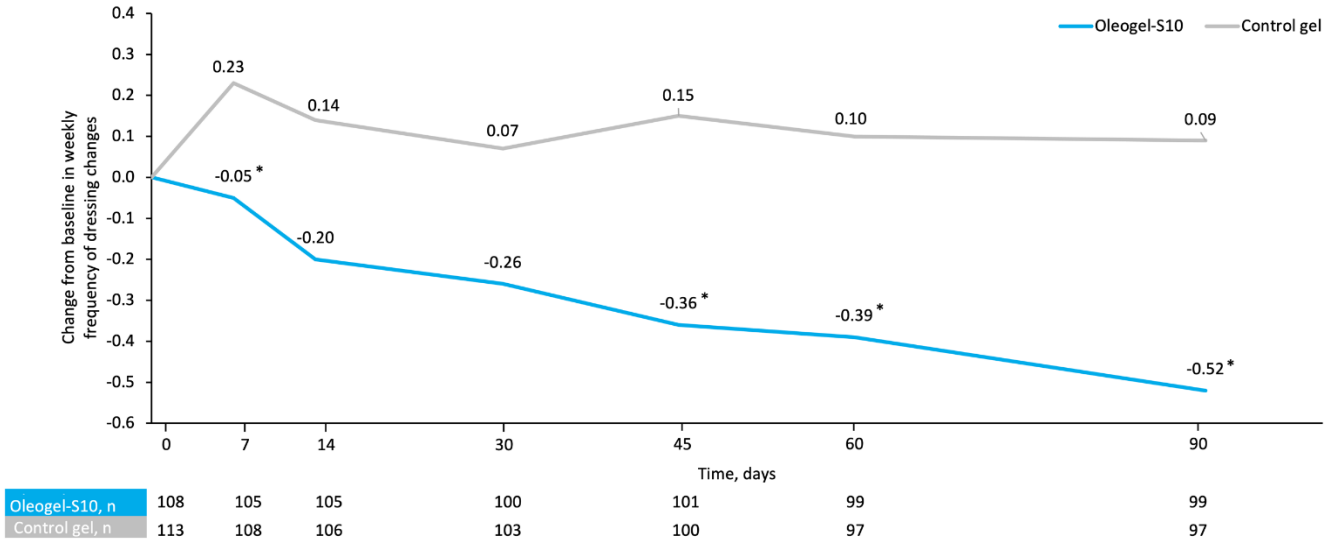
Source: Murrell DF, et al. Presented at, EADV Virtual Congress, 29-31 October 2020. D3T03.3B(79)
Abbreviations: EBDASI, Epidermolysis Bullosa Disease Activity and Scarring Index.
**At all timepoints, comparison between Filsuvez gel vs. control gel was not significant*

At Day 90, subjects in both groups showed slight improvements from baseline in itching as measured by the Itch Man scale in patients aged 4 to 13 years (-0.44 Filsuvez gel group *versus* -1.0 in the control gel group; *P*=0.182). Subjects ≥14 years were evaluated using the Leuven Itch scale and results for each of the six domain scores showed a reduction from baseline for subjects in the Filsuvez gel group. Mean decreases from baseline were also observed in most, but not all, of the domains in the control gel group.(75)

The analysis of target wound size based on the blinded evaluation of photographs demonstrated that the mean improvement (i.e., reduction in target wound size) was greater in the Filsuvez gel group than in the control gel group at Day 90, indicative of improved healing with Filsuvez gel.

Favourable trends were also observed for Filsuvez gel compared to control gel in change in procedural pain (pain resulting from dressing changes) at Day 90, measured using Wong-Baker FACES for participants aged ≥4 years and FLACC for those aged <4 years (Wong-Baker FACES: -1.32 with Filsuvez gel *versus* -0.18 with the control gel; FLACC: -2.57 with Filsuvez gel *versus* -1.17 with control gel. Moreover, this reduction in procedural pain was supported by an observed reduction in the required frequency of dressing changes compared to the control gel at Days 45, 60, and 90 (Day 45: -0.38 *versus* 0.18, *P*=0.003; Day 60: -0.42 *versus* 0.13, *P*=0.005; Day 90: -0.55 *versus* 0.11, *P*=0.001 [post-hoc analysis]) (Figure 9).(75) For background pain, low numbers hampered the analysis of patients aged <4 years using the FLACC score, but mean change from baseline to day 90 was -0.94 in the Filsuvez group and -1.11 in the control group for patients aged ≥4 years using the Wong-Baker FACES score.

Figure 9 Change from baseline in weekly frequency of dressing changes during the EASE trial double-blind phase



Source: Kern et al. (2022).(86)
Frequencies are calculated based on the response at each visit. Daily dressing changes are assigned a frequency of 1.000, dressing changes every 2 days are assigned a value of 0.5000 etc. Where a combination of frequencies is reported the frequency is calculated for each and then the mean value is taken e.g., dressings every 1–2 days; (1.000 + 0.500)/2 = 0.750. Frequencies per day are multiplied by 7 to obtain the weekly frequency.
** Analysis of covariance (ANCOVA) was conducted and a statistically significant difference between Oleogel-S10 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).*

Small mean decreases from baseline in the sleep assessment score (i.e., improvements) were observed in both treatment groups at Day 90 (-0.8 and -1.0 in the Filsuvez gel control gel arms, respectively).

Throughout the DBP, the mean number of days missed from school or from work due to EB since the last study visit was comparable between treatment groups. At the Day 90 visit, the mean number of days missed from school or from work was 4.7 days and 5.0 days in the Filsuvez gel and control gel groups, respectively. At Day 90, the proportion of subjects who reported missed work or school because of problems associated with EB was slightly lower in the Filsuvez gel group (61.1%) compared to the control gel group (64.9%).

Only subjects ≥14 years of age completed a treatment satisfaction questionnaire. At Day 90, treatment satisfaction was generally similar between treatment groups.

Table 12 Summary of clinical efficacy results from the EASE DBP

Study name		**EASE DBP (90 days)(75)**	
Analysis type		**Full analysis set**	
Intervention		**Filsuvez gel**	**Control gel**
Size of study group		109	114
Primary endpoint	**Name**	**Proportion of patients with first complete target wound closure within 45 days based on INV assessment**	
	n (%)	Closure: 45 (41.3) Non-closure: 64 (58.7)	Closure: 33 (28.9) Non-closure: 81 (71.1)
	Relative risk (95% CI)	1.44 (1.01, 2.05)	
	Odds ratio (95% CI)	1.84 (1.02, 3.30)	
	***P*-value**	0.013[a]	
Key secondary endpoint	**Name**	**Time to first complete closure of target wound by day 90 based on clinical assessment**	
	Median [days] (95% CI)[b]	92.0 (50.0, NE)	94.0 (89.0, NE)
	***P*-value**	0.302	
Key secondary endpoint	**Name**	**Proportion of patients with first complete closure of target wound by day 90 based on INV assessment**	
	n (%)	Closure: 55 (50.5) Non-closure: 54 (49.5)	Closure: 50 (43.9) Non-closure: 64 (56.1)
	Relative risk (95% CI)	1.16 (0.88, 1.52)	
	Odds ratio (95% CI)	1.34 (0.78, 2.32)	
	***P*-value**	0.296[c]	
Key secondary endpoint	**Name**	**Incidence of target wound infection up to day 90 based on AE reported and/ or use of topical/ systemic antibiotics**	

	n (%)	Infection: 2 (1.8) No infection: 107 (98.2)	Infection: 5 (4.4) No infection: 109 (95.6)
	Relative risk (95% CI)	0.44 (0.08, 2.34)	
	Odds ratio (95% CI)	0.43 (0.08, 2.33)	
	***P*-value**	0.326[d]	
Key secondary endpoint	**Name**	**Maximum severity of target wound infection up to day 90 based on AE reporting of PTs only**	
	n (%)	Mild: 1 (0.9) Moderate: 0 Severe: 0 Life-threatening: 0 Death: 0	Mild: 0 Moderate: 3 (2.6) Severe: 1 (0.9) Life-threatening: 0 Death: 0
Key secondary endpoint	**Name**	**Change from baseline to day 90 in total body wound burden (assessed using EBDASI)**	
	Mean (SD)	n=84 -3.4 (7.22)	n=85 -2.8 (7.53)
	LS Mean (SE)	n=84 -0.44 (0.90)	n=85 -0.56 (0.85)
	95% CI of LS mean	-2.22, 1.35	-2.25, 1.12
	Difference in LS means (SE)	0.12 (0.86)	
	95% CI of difference in LS means	-1.58, 1.83	
	***P*-value**	0.887[e]	
Key secondary endpoint	**Name**	**Change from baseline in itching (assessed using Itch Man Scale for patients aged 4-13 years and Leuven Itch Scale for patients aged 14 years and over)**	
	Mean change in Itch Man Scale	n=39 -0.44	n=43 -1.0
	***P*-value**	0.182[f]	

	Leuven Itch Scale	Frequency: -8.13 Severity: -4.95 Duration: -0.93 Consequence: -4.39 Distress: -0.44 Surface area: -1.54	Frequency: -10.14 Severity: -10.76 Duration: 0.98[g] Consequence: -3.54[g] Distress: -0.26 Surface area: 0.68
	***P*-value[f]**	Frequency: 0.344 Severity: 0.528 Duration: 0.779 Consequence: 0.940 Distress: 0.797 Surface area: 0.598	
Other secondary endpoint	**Name**	**Percentage change from baseline in EB target wound size at day 90**	
	Mean (SD)	n=75 -54.35 (82.792)	n=81 -48.73 (71.492
	LS Mean (SE)	n=75 -58.83 (12.42)	n=81 -52.55 (11.57)
	95% CI of LS mean	-83.37, -34.29	-75.40, -29.69
	Difference in LS means (SE)	-6.28 (12.46)	
	95% CI of difference in LS means	-30.90, 18.33	
	***P*-value**	0.615[h]	
Other secondary endpoint	**Name**	**Change from baseline to day 90 in BSAP (TBSA affected by EB PTW) assessed on the Lund and Browder chart**	
	Mean (SD)	n=86 -4.32 (7.027)	n=85 -2.53 (8.852)
	LS Mean (SE)	n=86	n=85

		-3.41 (0.82)	-2.13 (0.79)
	95% CI of LS mean	-5.03, -1.80	-3.68, -0.58
	Difference in LS means (SE)	-1.28 (0.80)	
	95% CI of difference in LS means	-2.87, 0.30	
	***P*-value**	0.111[j]	
Other secondary endpoint	**Name**	**Change from baseline in procedural pain to day 90 (assessed using FLACC for patients <4 years of age, and Wong-Baker Faces for those ≥4 years of age)**	
	Mean change in Wong-Baker FACES score	n=76 -1.32	n=78 -0.18
	***P*-value**	0.051[f]	
	Mean change in FLACC score	n=7 -2.57	n=6 -1.17
	***P*-value**	NE	
Other secondary endpoint	**Name**	**Change from baseline in background pain to day 90 (assessed using FLACC for patients <4 years of age, and Wong-Baker Faces for those ≥4 years of age)**	
	Mean change in Wong-Baker FACES score	n=79 -0.94	n=79 -1.11
	***P*-value**	0.771[f]	
	Mean change in FLACC score	n=7 -0.71	n=6 0.0
	***P*-value**	NE	
Other secondary endpoint	**Name**	**Change from baseline in impact of wounds on sleep quality (Likert Scale) to Day 90**	
	Mean (SD)	n=40 -0.8 (2.17)	n=37 -1.0 (3.22)
	LS Mean (SE)	n=40	n=37

		-0.75 (0.50)	-1.12 (0.46)
	95% CI of LS mean	-1.75, 0.25	-2.05, -0.20
	Difference in LS means (SE)	0.37 (0.57)	
	95% CI of difference in LS means	-0.77, 1.51	
	***P*-value**	0.519[k]	
Other secondary endpoint	**Name**	**Number of days missed from school or work until day 90**	
	Mean [days] (SD)	n=54 4.7 (7.50)	n=57 5.0 (7.57)
	Proportion who had missed days, n (%)	33 (61.1)	37 (64.9)
Other secondary endpoint	**Name**	**Response to treatment (TSQM) before wound dressing changes at day 90 in patients aged ≥4 years of age**	
	LS mean (SE)	n=22 4.77 (0.38)	n=22 4.47 (0.32)
	95% CI of LS mean	4.00, 5.54	3.82, 5.11
	Difference in LS means (SE)	0.30 (0.44)	
	95% CI of difference in LS means	-0.60, 1.20	
	***P*-value**	0.501[l]	

Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; BSAP, body surface area percentage; CI, confidence interval; DBP, double-blind phase; EB, epidermolysis bullosa; EBDASI, epidermolysis bullosa disease activity and scarring index; FLACC, face, legs, activity, cry, consolability scale; INV, investigator-assessed; LS, least squares; n, number; NE, not estimable; PTs, preferred terms; SD, standard deviation; SE, standard error; TBSA, total body surface area; TSQM, Treatment Satisfaction Questionnaire for Medication.

[a] CMH statistical test with CHW adjustment applied; CMH test stratified by EB subtype and target wound size class. Odds ratio >1 represents a favourable outcome for Filsuvez gel treatment.

[b] Parameter and model estimates based on a Log-rank test performed without consideration of any stratification.

[c] CMH statistical test stratified by EB subtype and target wound size class. Odds ratio >1 represents a favourable outcome for Filsuvez gel treatment.

[d] CMH statistical test stratified by EB subtype and target wound size class. Odds ratio <1 represents a favourable outcome for Filsuvez gel treatment.

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

[f] Parameter and model estimates based on a 2-sided Wilcoxon Rank Sum test using the van Elteren extension stratified by EB subtype and target wound size class.

*[g] Scaled-up values used for these domains (values recorded with an incorrectly sized scale were converted to a common scale and multiplied by 10 as: Scaled-up subscore = [(recorded answer*10)/actual VAS length]*10. Actual VAS length used as provided by the study clinical team).*

[h] Parameter and model estimates based on an ANCOVA on the percentage change from baseline with Treatment group and EB Subtype as fixed effects and size of target wound at baseline as a covariate.

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

[j] Parameter and model estimates based on an ANCOVA on the change from baseline with treatment group and EB subtype as fixed effects and baseline W-QoL Scale score baseline as a covariate.

[k] Parameter and model estimates based on an ANCOVA on the TSQM overall score with treatment group and EB subtype as fixed effects and TSQM overall score at day 7 as a covariate.

B.2.6.2 Clinical effectiveness results from the EASE OLP

The final, 24-month analysis of the EASE OLP where all patients were treated with Filsuvez gel, took place in Q3 2022 with a database lock date of 1st July 2022. Table 13 presents a summary of the efficacy endpoint data, where data are presented by prior randomised treatment arm from the DBP, and also for all patients.

As described in Table 8, the endpoints collected in the OLP were very similar to those collected in the DBP, with addition of EQ-5D and iscorEB. Most endpoints carried through from the DBP were collected to Month 3 of the OLP, only, while BSAP, EBDASI, incidence and severity of wound infection, and the EQ-5D and iscorEB instruments were collected at both 12 and 24 months, in addition. As described in Section B.2.4.1, the OLP efficacy analyses were not powered for statistical significance.

The number of subjects with BSAP and EBDASI scores recorded within-visit windows (365±14 days for Month 12 and 730±14 days for Month 24) in the OLP was lower than expected largely due to the impact of COVID-19. Therefore, a post hoc analysis of the summary statistics output was also produced without visit windows in the OLP.(87)

When OLP visit windows are included, at Month 24, mean total BSAP scores were comparable to OLP baseline scores (OLP baseline: 7.4%; Month 24: [redacted] in the former Filsuvez gel group, while the former control gel group had a reduction in BSAP from OLP baseline (OLP baseline: 8.3%; Month 24: [redacted] results for both treatment groups reflect reductions in BSAP from DBP baseline [redacted] in the former Filsuvez gel group and [redacted] in the former control gel group) over a 2-year period, demonstrating that the accelerated wound healing leading to improvements in BSAP during the DBP, was maintained. When OLP visit windows were excluded, both treatment groups showed further improvement from OLP baseline at Month 24 in BSAP scores.(87)

When OLP visit windows are included, at Month 24, mean EBDASI skin activity scores were generally comparable to OLP baseline scores in both treatment groups, reflecting reductions in wound burden from the DBP baseline ([redacted] in both groups), over a 2-year period. When OLP visit windows were excluded both treatment groups showed further improvement from OLP baseline at Month 24 in wound burden based on mean EBDASI skin activity scores. Figure 10 and Figure 11 summarise the

continued improvements in BSAP and EBDASI with Filsuvez gel treatment from the DBP through to Month 24 of the OLP.

The incidence and maximum severity of target wound infections were consistent between the prior Filsuvez gel and prior control gel arms, throughout the 24-month OLP while both groups maintained reductions in itching below the DBP baseline value at Month 3 of the OLP, according to the Itch Man and Leuven Itch scales. Furthermore, the effects on procedural and background pain achieved in the DBP were also maintained at Month 3 of the OLP in the former Filsuvez gel group. The analysis of the impact of wounds on sleep showed a slight increase (better sleep) from OLP baseline to Month 3 in patients who received Filsuvez gel in the DBP, and a slight increase (worse sleep) in those who previously received the control gel. In addition, a decrease in the number of days of school or work missed because of problems with EB was observed in both treatment groups when compared between the DBP and the OLP (to Month 3).

When overall treatment satisfaction scores, reflecting a subject feeling satisfied (results for somewhat satisfied, satisfied, very satisfied, or extremely satisfied) were grouped, treatment satisfaction decreased in both treatment groups from OLP baseline to Month 3.

No clear trends were observed in either treatment group for disease severity (iscorEB) or quality of life (EQ-5D) assessments. Of note, both the iscorEB and EQ-5D instruments were added during the conduct of the study (Version 4.0 protocol amendment), resulting in small numbers of subjects who completed these assessments, particularly at OLP baseline.

Figure 10 [redacted]

A

B

Figure 11 [redacted]

A

B

Table 13 Summary of clinical efficacy results from EASE OLP

Study name	EASE OLP (24 months)(87)								
Timepoint	Month-3			Month-12			Month-24		
Analysis type	Full analysis set								
Intervention	Former Filsuvez gel	Former control gel	All patients	Former Filsuvez gel	Former control gel	All patients	Former Filsuvez gel	Former control gel	All patients
Size of study group	100	105	205	100	105	205			
Name	Maximum severity of target wound infection from OLP Day 0 based on AE reporting of PTs for wound infection								
Incidence, n (%)	NR	NR	NR	4 (4.0)	3 (2.9)	7 (3.4)			
Severity, n (%)									
Mild	NR	NR	NR	2 (50.0)	0	2 (28.6[a])			
Moderate				0	3 (100.0)	3 (42.9[a])			
Severe				2 (50.0)	0	2 (28.6[a])			
Life-threatening				0	0	0			
Death				0	0	0			
Missing				0	0	0			
Name	Maximum severity of additional wound infection from OLP Day 0 based on AE reporting of PTs for wound infection								
Incidence, n (%)	NR	NR	NR	0	3 (2.9)	3 (1.5)			
Severity, n (%)									
Mild	NR	NR	NR	0	3 (100.0)	3 (100.0)			
Moderate				0	0	0			
Severe				0	0	0			
Life-threatening				0	0	0			
Death				0	0	0			
Missing				0	0	0			
Name	Change from OLP Day 0 in total body wound burden (assessed by EBDASI)								
Mean (SD)	n=73 -1.0 (5.79)	n=70 0.4 (5.85)	n=143 -0.3 (5.84)	n=55 -0.4 (6.26)[b] n=58	n=50 -0.3 (6.62)[b] n=53	n=111 -0.7 (6.65)			

Study name	EASE OLP (24 months)(87)								
Timepoint	Month-3			Month-12			Month-24		
Analysis type	Full analysis set								
Intervention	Former Filsuvez gel	Former control gel	All patients	Former Filsuvez gel	Former control gel	All patients	Former Filsuvez gel	Former control gel	All patients
Size of study group	100	105	205	100	105	205	[redacted]	[redacted]	[redacted]
				-0.5 (6.20)	-0.9 (7.17)				
LS mean (SE)	n=73 -0.45 (0.92)	n=70 1.05 (0.90)	NR	n=55 -0.81 (1.28)[b] n=58 -0.61 (1.23)	n=50 -1.41 (1.20)[b] n=53 -2.01 (1.20)	NR	[redacted]	[redacted]	[redacted]
95% CI of the LS mean	-2.28, 1.37	-0.74, 2.83	NR	-3.36, 1.74[b] -3.04, 1.82	-3.80, 0.98[b] -4.39, 0.37	NR	[redacted]	[redacted]	[redacted]
Difference in LS means (SE)	-1.50 (0.95)		NA	0.60 (1.22)[b] 1.40 (1.22)		NA	[redacted]		[redacted]
95% CI of difference in LS means	-3.37, 0.37		NA	-1.83, 3.03[b] -1.02, 3.82		NA	[redacted]		[redacted]
P-value[c]	0.116		NA	0.625[b] 0.253		NA	[redacted]		[redacted]
Name	Change from OLP Day 0 in total body wound burden (assessed by EBDASI) without visit windowing (post-hoc analysis)								
Mean (SD)	n=86 -0.7 (5.63)	n=89 0.9 (6.12)	n=175 0.1 (5.92)	n=67 -1.0 (6.39)	n=73 -0.9 (6.27)	n=140 -0.9 (6.31)	[redacted]	[redacted]	[redacted]
Name	Change from OLP Day 0 in BSAP of TBSA affected by EB PTW (using Lund and Browder chart)								
Mean (SD)	n=72 -0.22 (4.127)	n=69 -0.06 (5.422)	n=141 -0.14 (4.788)	n=56 -1.63 4.462)[b] n=58 -1.91 (4.461)	n=50 -1.11 7.635)[b] n=53 -1.29 (7.469)	n=106 -1.39 (6.140) n=111 -1.61 (6.065)	[redacted]	[redacted]	[redacted]
LS mean (SE)	n=72 0.49 (0.75)	n=69 1.00 (0.74)	NR	n=56 -1.95 (1.10)[b] n=58 -2.06 (1.00)	n=50 -1.30 (1.04)[b] n=53 -1.79 (0.99)	NR	[redacted]	[redacted]	[redacted]
95% CI of the LS mean	-0.99, 1.98	-0.47, 2.47	NR	-4.12, 0.23[b]	-3.36, 0.76[b]	NR	[redacted]	[redacted]	[redacted]

Study name	EASE OLP (24 months)(87)								
Timepoint	Month-3			Month-12			Month-24		
Analysis type	Full analysis set								
Intervention	Former Filsuvez gel	Former control gel	All patients	Former Filsuvez gel	Former control gel	All patients	Former Filsuvez gel	Former control gel	All patients
Size of study group	100	105	205	100	105	205	[redacted]	[redacted]	[redacted]
				-4.05, -0.07	-3.76, 0.18				
Difference in LS means (SE)	-0.51 (0.79)		NA	-0.65 (1.05)[b] -0.27 (1.00)		NA	[redacted]		[redacted]
95% CI of difference in LS means	-2.07, 1.06		NA	-2.73, 1.42[b] -2.25, 1.72		NA	[redacted]		[redacted]
P-value[d]	0.523		NA	0.535[b] 0.791		NA	[redacted]		[redacted]
Name	Change from OLP Day 0 in BSAP of TBSA affected by EB PTW (using Lund and Browder chart) without visit windowing (post hoc analysis)								
Mean (SD)	n=85 -0.18 (4.087)	n=87 0.34 (6.295)	n=172 0.08 (5.310)	n=67 -1.54 (4.493)	n=73 -1.54 (6.447)	n=140 -1.54 (5.578)	[redacted]	[redacted]	[redacted]
Name	Change from OLP Day 0 in itching (assessed using Itch Man Scale for patients aged 4-13 years and Leuven Itch Scale for patients aged 14 years and over)								
Mean change in Itch Man scale (SD)	n=31 0.3 (1.13)	n=36 0.00 (1.03)	n=67 0.1 (1.08)	NR	NR	NR	[redacted]	[redacted]	[redacted]
P-value[e]	0.396		NA	NR		NA	[redacted]		[redacted]
Leuven Itch scale Domain	n= 32-36	n=24-26	n=56-62	NR	NR	NR	[redacted]	[redacted]	[redacted]
Frequency	6.25 (21.856)	1.92 (18.605)	4.44 (20.508)						
Severity[f]	1.99 (20.689)	0.60 (18.362)	1.41 (19.605)						
Duration	-0.98 (30.133)	-8.33 (17.720)	-4.02 (25.802)						
Consequence	1.47 (12.244)	0.28 (9.390)	0.98 (11.078)						
Distress[f]	0.14 (17.909)	-2.46 (21.796)	-0.94 (19.469)						
Surface area	-0.72 (14.926)	-1.92 (12.056)	-1.24 (13.664)						
P-value[d]									
Frequency	0.728		NA	NR		NA	[redacted]		[redacted]
Severity[f]	0.651								
Duration									

Study name	EASE OLP (24 months)(87)								
Timepoint	Month-3			Month-12			Month-24		
Analysis type	Full analysis set								
Intervention	Former Filsuvez gel	Former control gel	All patients	Former Filsuvez gel	Former control gel	All patients	Former Filsuvez gel	Former control gel	All patients
Size of study group	100	105	205	100	105	205	[redacted]	[redacted]	[redacted]
Consequence Distress[f] Surface area	0.412 0.748 0.578 0.346								
Name	Change from OLP Day 0 in procedural pain (assessed using Wong Baker Faces for patients aged ≥4 years of age and FLACC for those <4 years of age)								
Mean change in Wong-Baker FACES score (SD)	n=66 0.2 (2.48)	n=63 0.2 (2.74)	n=129 0.2 (2.60)	NR	NR	NR	[redacted]	[redacted]	[redacted]
P-value[e]	0.723		NA	NR		NR	[redacted]		[redacted]
Mean change in FLACC score (SD)	n=6 -0.50 (2.51)	n=6 2.83 (3.43)	n=12 1.2 (3.35)	NR	NR	NR	[redacted]	[redacted]	[redacted]
P-value	NE		NA	NR		NR	[redacted]		[redacted]
Name	Change from OLP Day 0 in background pain (assessed using Wong Baker Faces for patients aged ≥4 years of age and FLACC for those <4 years of age)								
Mean change in Wong-Baker FACES score (SD)	n=67 0.3 (2.41)	n=62 0.4 (2.38)	n=129 0.3 (2.39)	NR	NR	NR	[redacted]	[redacted]	[redacted]
P-value[e]	0.698		NA	NR		NR	[redacted]		[redacted]
Mean change in FLACC score (SD)	n=6 -1.0 (1.67)	n=6 1.0 (2.19)	n=12 0.0 (2.13)	NR	NR	NR	[redacted]	[redacted]	[redacted]
P-value	NE		NA	NR		NR	[redacted]		[redacted]
Name	Change from OLP Day 0 in impact of wounds on sleep quality (Likert Scale) in patients aged ≥14 years								
Mean (SD)	n=36 -0.2 (2.40)	n=26 0.2 (2.42)	n=62 0.0 (2.39)	NR	NR	NR	[redacted]	[redacted]	[redacted]
LS mean (SE)	-0.22 (0.44)	-0.01 (0.46)	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
95% CI of LS mean	-1.10, 0.67	-0.92, 0.90	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]

Study name	EASE OLP (24 months)(87)								
Timepoint	Month-3			Month-12			Month-24		
Analysis type	Full analysis set								
Intervention	Former Filsuvez gel	Former control gel	All patients	Former Filsuvez gel	Former control gel	All patients	Former Filsuvez gel	Former control gel	All patients
Size of study group	100	105	205	100	105	205	[redacted]	[redacted]	[redacted]
Difference in LS means (SE)	-0.20 (0.57)		NA	NR		NA	[redacted]		[redacted]
95% CI of difference in LS means	-1.34, 0.93		NA	NR		NA	[redacted]		[redacted]
P-value[g]	0.720		NA	NR		NA	[redacted]		[redacted]
Name	Number of days missed from school or work during the past 14 days								
Mean [days] (SD)	n=41 1.5 (2.75)	n=45 1.9 (3.99)	n=86 1.7 (3.44)	NR	NR	NR	[redacted]	[redacted]	[redacted]
Proportion who had missed days, n (%)	15 (36.6)	17 (37.8)	32 (37.2)	NR	NR	NR	[redacted]	[redacted]	[redacted]
Name	Response to treatment (TSQM) before wound dressing changes in patients aged ≥4 years								
LS mean (SE)	4.75 (0.20)	4.71 (0.20)	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
95% CI of LS mean	4.35, 5.15	4.30, 5.12	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
Difference in LS means (SE)	0.04 (0.25)		NA	NR		NA	[redacted]		[redacted]
95% CI of difference in LS means	-0.47, 0.55		NA	NR		NA	[redacted]		[redacted]
P-value	0.870		NA	NR		NA	[redacted]		[redacted]
Name	Disease Severity using the iscorEB Score by Visit (using LOCF)								
Mean CFB in total iscorEB score (SD)	NR	NR	NR	n=4 -8.0 (30.06)	n=5 11.6 (30.13)	n=9 2.9 (29.99)	[redacted]	[redacted]	[redacted]
95% CI mean	NR	NR	NR	-55.8, 39.8	-25.8, 49.0	-20.2, 25.9	[redacted]	[redacted]	[redacted]
Name	HRQoL by Visit using the EQ-5D scale VAS (using LOCF)								
Mean CFB in EQ-5D-Y/ EQ-5D-Y proxy (SD)	NR	NR	NR	n=3 -6.7 (15.28)	n=4 7.5 (22.17)	n=7 1.4 (19.52)	[redacted]	[redacted]	[redacted]

Study name	EASE OLP (24 months)(87)								
Timepoint	Month-3			Month-12			Month-24		
Analysis type	Full analysis set								
Intervention	Former Filsuvez gel	Former control gel	All patients	Former Filsuvez gel	Former control gel	All patients	Former Filsuvez gel	Former control gel	All patients
Size of study group	100	105	205	100	105	205	[redacted]	[redacted]	[redacted]
95% CI mean	NR	NR	NR	-44.6, 31.3	-27.8, 42.8	-16.6, 19.5	[redacted]	[redacted]	[redacted]
Mean CFB in EQ-5D-5L (SD)	NR	NR	NR	n=0 - (--)	n=1 -5.0 (--)	n=1 -5.0 (--)	[redacted]	[redacted]	[redacted]
95% CI mean	NR	NR	NR	--, --	--, --	--, --	[redacted]	[redacted]	[redacted]
Mean CFB in EQ-5D-Y/ EQ-5D-Y proxy/ EQ-5D-5L (SD)	NR	NR	NR	n=3 -6.7 (15.28)	n=5 5.0 (22.00)	n=8 0.6 (18.21)	[redacted]	[redacted]	[redacted]
95% CI mean	NR	NR	NR	-44.6, 31.3	-27.8, 42.8	-16.6, 19.5	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; BSAP, body surface area percentage; CFB, change from baseline; CI., confidence interval; EB, epidermolysis bullosa; EBDASI, epidermolysis bullosa disease activity and scarring index; EQ-5D-Y, EuroQol 5-dimension Youth; EQ-5D-5L, EuroQol 5-dimension 5-level; FLACC, face, legs, activity, cry, consolability scale; LOCF, last observation carried forward; LS, least squares; n, number; NE, not estimable; NR, not reported; OLP, open label phase; PTs, preferred terms; PTW, partial-thickness wound; SD, standard deviation; SE, standard error; TBSA, total body surface area.

[a] Percentages calculated from absolute data.

[b] This data was provided as an earlier database lock of 12-month efficacy data and therefore represents fewer patients (lower n) than the 12-month data recorded at the final OLP database lock

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

[d] Parameter and model estimates based on an analysis of covariance (ANCOVA) on the change from baseline with Treatment group, EB Subtype and Target Wound Size class as fixed effects and Total BSAP at baseline as a covariate.

[e] Parameter and model estimates based on a 2-sided Wilcoxon Rank Sum test using the van Elteren extension stratified by EB subtype and target wound size class.

*[f] Scaled-up values used for these domains (values recorded with an incorrectly sized scale were converted to a common scale and multiplied by 10 as: Scaled-up subscore = [(recorded answer*10)/actual VAS length]*10. Actual VAS length used as provided by the study clinical team).*

[g] Parameter and model estimates based on an ANCOVA on the change from baseline with treatment group and EB Subtype as fixed effects and baseline W-QoL Scale score as a covariate.

B.2.7 Subgroup analysis

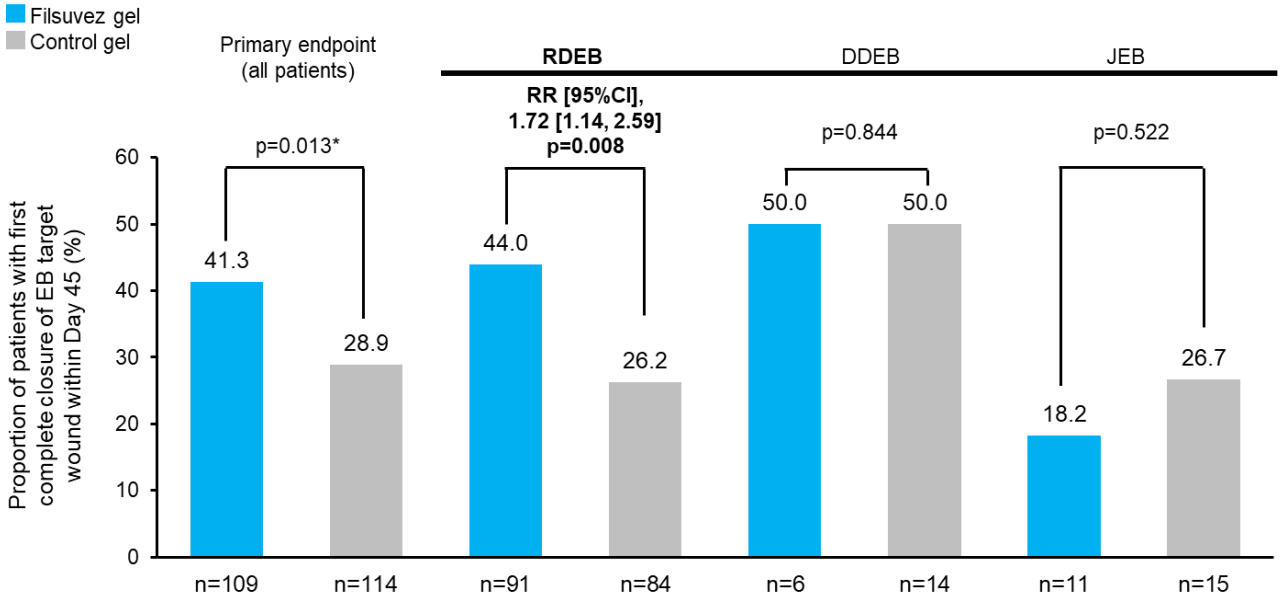
The EASE trial statistical analysis plan (SAP) subgroup analyses by EB subtype (JEB, RDEB, DDEB, KEB [N.B. no KEB participants were recruited]) were prespecified for the primary efficacy endpoint, and the first key secondary efficacy endpoint.(89) Patients with EBS were excluded from the subgroup analysis, as specified in the SAP. No additional information for the statistical analysis of subgroups is available from that described for analysis of the efficacy endpoints in Section B.2.4.1.(89)

Baseline demographics were not reported by subgroup in the EASE trial.

The results for the primary and first key secondary efficacy endpoints by EB subtype are summarised in Appendix E.

The primary endpoint was met in the RDEB subgroup (n=175), with complete target wound closure in 44% of participants treated with Oleogel-S10, *versus* 26.2% treated with control gel (RR 1.72, *P*=0.008) (Figure 12). Median time to first complete closure of target wound by Day 90 (first key secondary endpoint) was numerically shorter in participants treated with Filsuvez gel compared to those receiving the control gel, for the RDEB subgroup (64.0 days versus 94.0 days, *P*=0.175). Caution is applied to interpretating data from the JEB and DDEB subgroups which had low patient numbers (DDEB n=20; JEB n=26).(66, 75)

Figure 12 Analysis of EASE primary endpoint by EB subtype



Source: Bruckner et al. (2021)(66)
**Pre-specified adjustment to account for IDMC interim sample size re-estimation*

B.2.8 Meta-analysis

A meta-analysis is not considered appropriate to the evidence base available since the primary source of efficacy and safety data to address the decision problem is the direct, head-to-head EASE RCT. No additional sources have been identified (B.2.1).

B.2.9 Indirect and mixed treatment comparisons

EASE provides robust head-to-head comparative data for Filsuvez gel *versus* a control gel arm. Since the SLR conducted did not identify any further eligible trial evidence beyond the EASE trial, indirect and mixed treatment comparisons were not warranted.

B.2.10 Adverse reactions

Safety and tolerability data for Filsuvez gel were collected in the EASE RCT during the 90-day DBP and the 24-month OLP.(75, 88) The final safety analyses from the EASE DBP (database lock: 26th August 2020) and the final safety analysis from the EASE OLP (database lock: 1st July 2022) are presented in sections B.2.10.1 and B.2.10.2.

Data from the DBP is reported by treatment arm, while data from the OLP is reported by previous assignment in the DBP (e.g., former Filsuvez gel and former control gel), and for all OLP subjects. During the EASE OLP all patients received open-label Filsuvez gel, therefore patients in the former Filsuvez gel group had received an additional three months of exposure to Filsuvez gel during the 90-day DBP.(75, 87, 88)

B.2.10.1 Treatment compliance in EASE DBP and OLP

The mean duration of treatment in the EASE 90-day DBP was 89.0 (SD: 18.34) days in the Filsuvez gel group, and 86.8 (SD: 23.64) days in the control gel group at the end of the DBP. Treatment compliance, in relation to the target wound, was approximately 99% in both groups (99.08% [SD: 9.578] in the Filsuvez gel group, and 98.67% [SD: 9.926] in the control gel group).(75)

The mean treatment duration was [redacted] days in all subjects and treatment compliance was [redacted] at the end of OLP 24-month analysis.(87)

Post-hoc analysis of study medication usage was estimated according to the total number of Filsuvez gel tubes used in either arm (reflecting usage across the DBP and OLP amongst patients originally randomised to the Filsuvez gel arm, and usage in the OLP amongst those randomised to the control gel arm). Across both groups [n=214], the median number of tubes used per 30 days was [redacted] mean [redacted]

Notably, tube usage was found to be [redacted] during the 90-day DBP when compared to the [redacted] Amongst patients randomised to the Filsuvez gel arm, the 90-day DBP mean and median were [redacted] and [redacted] tubes respectively, [redacted]

B.2.10.2 Adverse events from EASE DBP and OLP

Safety data are summarised in Table 14. Further summaries of AEs by preferred term are included in Table 15 and Table 16. Treatment-emergent AEs were defined as AEs that occurred from the first study treatment to 4 weeks after the last study treatment and did not necessarily have a causal relationship to the use of the study medication.

This submission adopts an approach consistent with the Clinical Study Reports (CSRs), whereby treatment-emergent AEs are simply referred to as AEs.

In EASE, all n=223 randomised participants received at least one dose of the study drug and of these, n=199 (89.2%) completed the DBP (91.7%, Filsuvez gel *versus* 86.8%, control gel), and n=24 (10.8%) discontinued (8.3%, Filsuvez gel *versus* 13.2%, control gel).(75) Of those that discontinued, n=5 (3 [2.8%] in the Filsuvez gel group and 2 [1.8%] in the control gel group) discontinued the DBP due to an adverse event (AE), and n=2 (both treated with control gel) discontinued due to worsening of the EB target wound status.(75) The mean duration of treatment in the DBP was 89.0 (SD: 18.43) days in the Filsuvez gel group and 86.8 days (SD: 23.64) in the control gel group. Overall, treatment compliance (specifically in relation to the target wound) was approximately 99% in both groups. At each of the study time points in the DBP, >90% of subjects in both treatment groups reported applying the study medication gel to all wounds.(75)

During the DBP of EASE, the proportion of participants experiencing an AE was similar between the Filsuvez gel arm (81.7%) and the control gel arm (80.7%); as were the proportions experiencing treatment-related AEs (24.8% *versus* 22.8%) and serious AEs (SAE, 6.4% *versus* 5.3%).(75) The high incidence of AEs is consistent with the complex medical and surgical histories of recruited participants at baseline (Section B.2.3.2, Table 10), demonstrative of the range of complications that someone with EB encounters. Only one participant receiving Filsuvez gel experienced a treatment-related SAE; there were no treatment-related SAEs in the control gel arm.(75)

A total of 205 (91.9%) subjects continued into the 24-month OLP, where all participants received open-label Filsuvez gel. A total of [redacted] subjects reported at least one AE.(87)

During the EASE trial, [redacted] was the most frequently reported AE in both treatment groups during the DBP and the OLP (Table 14). It is noteworthy that FDA advice led to the EASE protocol specifying “worsening of wound status, increase in wound size, reopening of wounds, and wound infections should be reported as AEs”, relating to both target and non-target wounds. However, while this resulted in [redacted] AEs, most were not assessed as treatment-related by the

investigator since changes in wound size from visit to visit, as well as reopening of previously closed wounds, are expected in DEB and JEB due to genetic skin fragility and the dynamic nature of EB partial-thickness wounds.

In addition to [redacted] overall, the most frequently reported AEs (≥5% of all subjects) were: [redacted]. These conditions are also all consistent with the course of the DEB and JEB disease. [redacted] had at least one SAE in the OLP; of these, [redacted]

There were [redacted] during the 24-month OLP, with [redacted] occurring >30 days after the last date of study medication administration (i.e., this death was not treatment-emergent). None of the deaths were considered related to study treatment, and all were assessed as consistent with the course of the disease.

A total of [redacted] were withdrawn from the OLP because of AEs. These include [redacted] subjects who had treatment-related AEs leading to study withdrawal [redacted]

The safety and tolerability data from EASE demonstrate that Filsuvez gel is well tolerated in DEB and JEB patients and most AEs reported are mild or moderate, with most associated with the EB condition rather than related to treatment. Discontinuation of treatment due to AEs was low, and accordingly, treatment compliance was high.

Table 14 Summary of safety and tolerability outcomes from EASE (DBP and OLP; SAS)

	EASE DBP (90-day)(75)		EASE OLP (24-month)(87)		
	Filsuvez gel	Control gel	Former Filsuvez gel	Former Control gel	All subjects
	n=109	n=114	n=100	n=105	N=205
AEs, n (%)	89 (81.7)	92 (80.7)	[redacted]	[redacted]	[redacted]
AEs related to treatment, n (%)	27 (24.8)	26 (22.8)	[redacted]	[redacted]	[redacted]
Serious AEs, n (%)	7 (6.4)	6 (5.3)	[redacted]	[redacted]	[redacted]
Serious AEs related to treatment, n (%)	1 (0.9)	0 (0)	[redacted]	[redacted]	[redacted]
AEs leading to drug withdrawal, n (%)	3 (2.8)	4 (3.5)	[redacted]	[redacted]	[redacted]
Serious AEs leading to study withdrawal, n (%)	3 (2.8)	2 (1.8)	[redacted]	[redacted]	[redacted]
AEs related to treatment leading to study withdrawal, n (%)	2 (1.8)	0 (0)	[redacted]	[redacted]	[redacted]
AEs due to wound complications,[a] n (%)	67 (61.5)	61 (53.5)	[redacted]	[redacted]	[redacted]
Serious AEs leading to death, n (%)	0 (0)	0 (0)	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event, DBP, double-blind phase; OLP, open-label phase; SAS, safety analysis set.

[a] FDA advice led to the EASE protocol specifying "worsening of wound status, increase in wound size, reopening of wounds, and wound infections should be reported as AEs", relating to both target and non-target wounds. Most were not assessed as treatment-related by the investigator since changes in wound size from visit to visit, as well as reopening of previously closed wounds, are expected in DEB and JEB.

Table 15 Summary of EASE DBP AEs with incidence of >2% in either arm (SAS)

	EASE DBP(75)	
	Filsuvez gel	Control gel
	n=109	n=114
Any AEs	89 (81.7)	92 (80.7)
Injury, poisoning, and procedural complications	69 (63.3)	66 (57.9)
Wound complication	67 (61.5)	61 (53.5)
Fall	4 (3.7)	1 (0.9)
Infections and infestations	37 (33.9)	36 (31.6)
Wound infection	8 (7.3)	10 (8.8)
Wound infection staphylococcal	4 (3.7)	3 (2.6)
Upper respiratory tract infections	4 (3.7)	1 (0.9)
Nasopharyngitis	3 (2.8)	7 (6.1)
Wound infection bacterial	3 (2.8)	5 (4.4)
Pharyngitis	3 (2.8)	0 (0)
Influenza	2 (1.8)	6 (5.3)
Bronchitis	1 (0.9)	3 (2.6)
General disorders and administration site conditions	21 (19.3)	25 (21.9)
Pyrexia	9 (8.3)	15 (13.2)
Application site pruritus	4 (3.7)	1 (0.9)
Administration site pain	3 (2.8)	3 (2.6)
Administration site pruritus	1 (0.9)	4 (3.5)
Skin and subcutaneous tissue disorders	11 (10.1)	15 (13.2)
Pruritus	8 (7.3)	6 (5.3)
Gastrointestinal disorders	11 (10.1)	14 (12.3)
Toothache	3 (2.8)	0 (0)
Respiratory, thoracic, and mediastinal disorders	9 (8.3)	11 (9.6)
Cough	3 (2.8)	8 (7.0)
Oropharyngeal pain	3 (2.8)	2 (1.8)
Blood and lymphatic system disorders	8 (7.3)	6 (5.3)
Anaemia	8 (7.3)	4 (3.5)
Eye disorders	6 (5.5)	2 (1.8)
Ulcerative keratitis	3 (2.8)	0 (0)
Nervous system disorders	1 (0.9)	6 (5.3)
Headache	1 (0.9)	4 (3.5)

Abbreviations: AE, adverse event, DBP, double-blind phase; SAS, safety analysis set.

Table 16 Summary of EASE OLP AEs with incidence of >2% of subjects overall (SAS)

	EASE OLP (24-month)(87)		
	Former Filsuvez gel	Former Control gel	All subjects
	n=100	n=105	N=205
Any AEs	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]
Wound complication	[redacted]	[redacted]	[redacted]
Wound secretion	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Wound infection staphylococcal	[redacted]	[redacted]	[redacted]
Wound infection	[redacted]	[redacted]	[redacted]
Wound infection bacterial	[redacted]	[redacted]	[redacted]
Skin infection	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]
Otitis externa	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]
Wound infection pseudomonas	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Oesophageal stenosis	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]	[redacted]
Toothache	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]
Hypalbuminaemia	[redacted]	[redacted]	[redacted]
Vitamin D deficiency	[redacted]	[redacted]	[redacted]
Malnutrition	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]
Blister	[redacted]	[redacted]	[redacted]

	EASE OLP (24-month)(87)		
	Former Filsuvez gel	Former Control gel	All subjects
	n=100	n=105	N=205
Eye disorder	[redacted]	[redacted]	[redacted]
Ulcerative keratitis	[redacted]	[redacted]	[redacted]
Congenital, familial, and genetic disorders	[redacted]	[redacted]	[redacted]
Syndactyly	[redacted]	[redacted]	[redacted]
Hepatobiliary disorders	[redacted]	[redacted]	[redacted]
Hepatic function abnormal	[redacted]	[redacted]	[redacted]
Abbreviations: AE, adverse event; N / n, number; OLP, open-label phase; SAS, safety analysis set.			

B.2.11 Ongoing studies

As part of the risk management plan for Filsuvez, Amryt Pharmaceuticals will conduct a Category 3 (non-imposed) observational safety and effectiveness evaluation registry-based study in EB. The protocol is in development for discussion with the EMA.

No additional trials of Filsuvez gel for use in DEB and JEB are currently planned.

B.2.12 Interpretation of clinical effectiveness and safety evidence

Dystrophic and junctional EB are severe subtypes of EB, an inherited skin fragility disorder characterised by dynamic, recurrent and chronic partial-thickness wounds that convey a considerable total body wound burden and are often associated with significant systemic complications (Section B.1.3.1). Filsuvez gel is the first treatment licensed for use in DEB and JEB, in patients aged older than six months. The mainstay of treatment for EB partial-thickness wounds has traditionally been a heterogenous armamentarium of bathing, hygiene and blister care practices, use of topicals not specifically licensed for EB, and extensive dressing change routines using a variety of non-adhesive dressings and bandages (Section B.1.3.4). The disease itself and the extensive associated wound care routine, substantially compromises HRQoL in both the child or adult living with DEB or JEB, and their parent/ carer.

EASE is the largest phase III RCT conducted to date in EB patients, recruiting a participant population considered generalisable to UK clinical practice. The population includes DEB and JEB patients, the EB subtypes for which Filsuvez gel is licensed,

and therefore provides pivotal evidence of the relative efficacy and safety of Filsuvez gel *versus* a control gel, which acts as a proxy for current clinical management, in the absence of other data (Section B.2.3). However, while EASE is considered the best source of relative data, it is also noted that the control gel included excipients which, individually, are known to have a potential beneficial effect on wound healing, therefore any comparative data may be a conservative estimate of the relative benefits of Filsuvez gel, in clinical practice.

The EASE RCT included a number of endpoints assessing wound closure and wound burden, both identified as key priorities for treatment, in addition to PROs that considered other important aspects of EB, such as background and procedural pain, itch, sleep, and days missed at work or school. One limitation of the trial design is that EQ-5D and iscorEB were only included in the OLP phase and therefore limited data were collected and there were no comparative data (Section B.2.3).

The primary endpoint of EASE was met, demonstrating a statistically significant beneficial effect of Filsuvez gel on the proportion of patients achieving first complete target wound closure within 45 days during the DBP (41.3% *versus* 28.9%, in the Filsuvez gel and control gel arms, respectively [relative risk 1.44, *P*=0.013]).(75, 86) Accelerated wound healing with Filsuvez gel was accompanied by reductions in overall wound burden as measured by BSAP with partial-thickness wounds and in disease activity as measured by EBDASI (skin activity section). With Filsuvez gel, change from baseline to Month 12 is 6.5%; for context, 1% total body surface area approximately equates to the palmar surface of the hand (although this approximation and differs by age, sex, BMI and ethnic group). [redacted]. These improvements in total body wound burden, were combined with favourable trends in procedural pain and an observed reduction in the required frequency of dressing changes during treatment with Filsuvez gel throughout the DBP of EASE (Section B.2.6). Furthermore, safety data demonstrated that Filsuvez gel was generally well tolerated, throughout the EASE trial, and AEs observed were largely associated with EB itself (Section B.2.10).

DEB and JEB are the most severe forms of EB with patients facing a multitude of daily challenges and a high risk of substantial, long-term complications. The main daily challenges faced by EB patients are pain and pruritus from blistering, which is often intensified during dressing and bandage changes which often take place every other day or daily and may take up to four hours. Therefore, although total body wound burden is only one facet of this lifelong, chronic, painful disease, even modest improvements in wound burden, which can reduce the required frequency of painful and often traumatic dressing changes, would likely have a substantial impact on the quality of life for both the patient and their families, who are pivotal in facilitating their daily care.

Whilst generic and disease-specific HRQoL data from EASE is limited, cross-sectional analyses demonstrated a correlation between a lower total body wound burden, as proxied by BSAP, and better HRQoL as measured by EQ-5D (Appendix P). Thereby, by increasing the speed of wound healing which in turn reduces total body wound burden, Filsuvez gel has the potential to represent a step-change in the care of partial-thickness wounds for patients with DEB and JEB, and exact a meaningful benefit on patient HRQoL. In this chronically disabling, severe disease in children and adults, there has previously been no active or effective treatment, hence, any reduction in disease severity and subsequent HRQoL benefit, is highly valued by patients, their families and clinicians.

This was supported during the EMA consultation of the Ad-Hoc Expert Group (AHEG), where the majority of the clinical experts and all patient representatives considered that, based on the data presented from EASE, an effect, although modest, has been established with Filsuvez gel. Moreover, the reduction in time to perform dressing changes, frequency of dressing changes, and reduction in procedural pain were also discussed during and, although limited, the results were considered to be clinically meaningful relevance for the EB patients and carers.(93)

The data showing a correlation between BSAP and HRQoL has been used as a key input to the economic analysis to demonstrate the cost-effectiveness of Filsuvez gel *versus* current clinical management, alone.

B.3 Methods of expert elicitation

As introduced in Section B.2.3.3, due to the paucity of clinical evidence surrounding DEB and JEB, particularly regarding the natural history and progression of the disease, the precise nature of current established clinical management in the UK, and the costs and resource involved in the treatment of DEB and JEB, Amryt Pharmaceuticals commissioned a number of projects to elicit quantitative and qualitative expert input (Sections B.3.1-B.3.4).

Throughout development of the clinical and cost-effectiveness case for Filsuvez gel, Amryt Pharmaceuticals engaged with a number of UK-based clinicians; their details are presented in Table 17, and hereafter experts are referred to only by their initials.

Table 17 Summary of experts with whom Amryt Pharmaceuticals engaged in the SEE exercises

Clinical expert	Location	Expertise
Prof. Jemima Mellerio (JM)	Guy's and St Thomas' NHS Foundation Trust, UK	Expertise in both adult and children's service
Dr. Anna Martinez (AM)	Great Ormond Street Hospital, UK	Expertise in children's EB service
Dr. Gabriela Petrof (GP)	Great Ormond Street Hospital, UK	Expertise in children's EB service
Dr. Danielle Greenblatt (DG)	Guy's and St Thomas' NHS Foundation Trust, UK	Expertise in adult EB service
Prof. Dedee Murrell (DM)	St George Hospital, University of New South Wales, Sydney, Australia	Expertise in EB
Dr. Sagair Hussain (SH)	DEBRA UK	Patient organisation
Mrs Sharmila Nikapota (SN)	CureEB	Patient organisation (and parent of child with EB)
Prof. Steve Palmer (SP)	Independent Health Economist	Health economics expert
Dr. Andrew Walker (AW)	Independent Health Economist	Health economics expert

B.3.1 SEE of costs and resource use (conducted in UK EB clinical nurse specialists).

The objective of this exercise was to conduct a structured expert elicitation (SEE) exercise with clinical nurse specialists (CNSs) who are experienced in treating patients with DEB and JEB in the UK. It was intended to capture resource use estimates relating to babies, infants/ paediatrics, teenagers, and adults with DEB (RDEB and DDEB) and JEB. A three – stage process was planned with questionnaire administration as phase 1, results compilation as phase 2, and a multi-disciplinary validation meeting scheduled as the final phase.

Unfortunately, despite early indications of positive recruitment, it did not prove possible to engage identified CNSs to participate in this exercise. Concerns were expressed as to the time commitments clashing with clinical responsibilities and that information exchange might involve disclosure of data felt to be confidential or sensitive in nature. Efforts were taken to reassure CNSs but unfortunately the engagement with the exercise was unsuccessful and no data on costs and resource use associated with EB in the UK were collected. Accordingly, it was decided to seek information on resource-related issues as part of the SEE project to elicit clinical expert opinion on a wider range of issues, including resource use estimates associated with CCM (Section B.3.2).

B.3.2 SEE to estimate point estimates and uncertainty ranges, for input into the economic model.

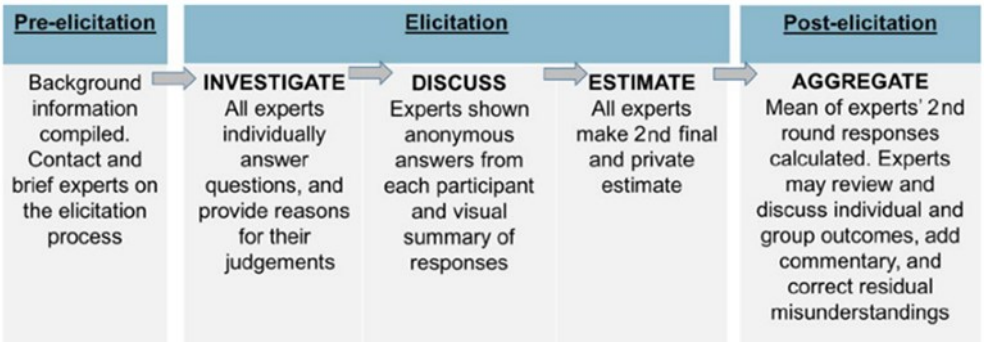
This SEE was originally planned to elicit expert valuation of disease progression, mortality, complications, and quality of life. However, it was decided to include further questions relating to resource use, given the issues of engagement in the nurse SEE costs and resource exercise (Section B.3.1).

Several SEE frameworks and approaches were considered for use in this context. Although in the literature several have been appraised (for example by Bojke *et al.* 2021),(94) such as the Sheffield Elicitation Framework (SHELF), Cookes' classical method and the Delphi method, no one gold standard has been put forward as the most appropriate for use in HTA in the UK. The IDEA protocol, a recognised approach that was also reviewed by Bojke *et al.* (2021), aims to improve the accuracy of expert

judgements and includes several key steps in a four-step elicitation, and a modified Delphi procedure: “Investigate,” “Discuss,” “Estimate” and “Aggregate”. The IDEA protocol is a time-efficient method of elicitation and meets the criteria set out in in the key principles of SEE in healthcare decision making: transparency, fitness-for-purpose, consistency, reflective of uncertainty, recognising bias, suitability of experts, promoting adaptive skills, recognising inter-expert variation, and promoting high performance.(95, 96)

The main stages of the IDEA protocol are shown in, below in Figure 13.

Figure 13 Illustration of the IDEA protocol four-step approach



Source: Hemming et al. 2017 (adapted from Burgman 2015)(95, 96)

Although initially a target was set for n=10 respondents in this exercise, issues with recruiting experts in this field delayed the exercise. Recruitment was closed with four participants so as not to delay further. Four UK-based clinical experts were recruited for the SEE. One has expertise in both adult and children’s services (JM), two have expertise in children’s services (AM and GF), and one has expertise in adult services (DG).

Implementation of the IDEA protocol involved two discreet rounds of one-to-one interviews with experts and concluded with a panel meeting of all respondents to validate findings. All face-to-face Stage 1 and Stage 2 interviews, and the Stage 3 group discussion were guided by an external facilitator. Stage 1 involved contribution of experts’ own opinion and estimates, while Stage 2 included sharing anonymised Stage 1 data from all participants and allowing the opportunity for participants to revise their primary estimates.

To focus discussion on key parameters in the economic model, during Stage 3 the experts were presented with analyses of disease progression and mortality, where there was evidence of different opinions based on analysis of Stage 2 results. General consensus was observed in relation to resource use estimates and HRQoL in Stage 2, therefore further discussion on these elements was limited. Discussion relating to mortality (and cause of death) in Stage 3 also informed assessment of complications (of EB).

Further detail of the methods, materials and results can be found in the SEE report.(97)

B.3.3 A UK multi-stakeholder panel meeting.

This meeting was undertaken on October 6th 2022 with clinical (JM and AM), health economic (SP and AW) and patient representation experts (SH and SN), to obtain validation on the structure of the modelling and other clinical assumptions, and potentially to validate values obtained from other SEE exercises. This enabled validation of the model and also provided narrative to address potential challenges to the choice of methods and model inputs. In addition, the input of experts helped inform exploratory scenario analyses as well as informing the most appropriate base case. The meeting was moderated by an external facilitator.

The methods, materials and results of the MSP can be found in the MSP report.(98)

B.3.4 Validation of the health states for use in a time trade-off exercise, and to inform the health economic model.

A TTO exercise was employed to elicit utility valuations specific to model health state descriptors (further detail presented in Section B.4.5.3.2).(99) The TTO protocol and heath states were validated by UK clinical and patient experts (GP, JM, DG, and SH, Table 17).

The methods (including validation), materials and results of the TTO can be found in the TTO report.(99)

B.3.5 Additional clinical expert engagement

Additional clinical engagement was sought throughout development of the health economic modelling concept and analyses. This included a number of discussions

with a UK clinician with expertise in adult and paediatric EB (JM) regarding formation of the health states and the choice of outcome on which they should be based. In addition, later in the modelling process engagement with a further clinical expert (DM, Table 17) was undertaken to validate the approach of using BSAP to define health states, given the limitations of the other endpoints considered from the EASE trial.

B.4 Cost effectiveness

B.4.1 Cost effectiveness case

A *de novo* cost-effectiveness analysis was developed to estimate the overall cost and HRQoL impact of Filsuvez gel for the treatment of partial-thickness wounds, relative to standard of care alone, for EB patients and their carers over a patient lifetime.

At a patient level, EB wounds are dynamic; overall wound burden will typically fluctuate over time as new wounds develop and others heal. By increasing the rate at which wounds heal when treated with Filsuvez gel (demonstrated via the primary endpoint of the EASE DBP), however, reductions can be achieved in patients' overall wound burden at a given time relative to treatment with current clinical management (CCM) alone. The cost-effectiveness model aims to quantify this reduction on the basis of total body wound burden as proxied by BSAP, an endpoint of the pivotal EASE trial that serves as a surrogate measure for severity and consequent HRQoL impact.

The model base case considers the impacts of reductions in wound burden in terms of resource needs (notably the costs associated with dressing changes, as well as wider primary and secondary care needs), and patient and carer HRQoL as captured in the EASE trial and wider sources.(86)

The base cost effectiveness does not make claims around the potential impact of Filsuvez gel in reducing clinical complications associated with DEB and JEB, in particular risks of complications such as SCC, which tend to be associated with the presence of longer-term chronic wounds. By reducing overall wound burden and disease severity, the likelihood of chronic wounds occurring are reduced and hence risk of SCC and other complications might also plausibly be reduced.

Due to a lack of natural history data in the trial and literature, there is uncertainty associated with disease progression and the risk of SCC and other complications, and as it could not directly be measured in the EASE trial due to short-term follow-up there is uncertainty associated with the impact of Filsuvez gel on reducing complications. SEE methods have been used to explore probabilities of SCC (as a key complication) and the likelihood of reducing SCC in DEB and JEB patients associated with estimates of disease (i.e., total body wound burden as measured by BSAP) progression.(97) The

experts suggested that increased cancer risks compared to the general population would most likely occur in adult RDEB-severe (RDEB-S) patients, though less likely in other subgroups (RDEB-other [RDEB-O], JEB-severe [JEB-S], JEB-other [JEB-O], DDEB). Experts were asked to comment on the likelihood of SCC occurring in more severe patients (i.e., patients with higher wound burden as measured by BSAP coverage). Although uncertainty surrounds this topic given a lack of long-term evidence, experts suggested that the risk of cancer would likely not be directly influenced by BSAP, therefore the impact of continued treatment with Filsuvez gel on complications such as SCC in the long term is uncertain.

Following the SEE, it was decided there was currently insufficient evidence to link use of Filsuvez gel to a reduction in risk of SCC or other complications of EB.(97) Further long-term data collection could be useful to investigate the association between BSAP (and other measures of disease severity), types/ locations of wounds (chronic, other) and the incidence of SCC and other key complications, and whether the use of Filsuvez gel could therefore be indirectly associated with the reduction of SCC/ complications, with life years and HRQoL/ cost implications, for inclusion in the economic model. Therefore, the economic model is limited to the short and longer term HRQoL benefits of Filsuvez gel compared to the use of CCM of DEB and JEB, alone.

B.4.2 Published cost-effectiveness studies

An SLR was conducted to identify relevant studies in published literature relating to prior economic evaluations, cost and resource use data, and HRQoL/ utility data in EB.(100) The research question was as follows:

"What is the cost-effectiveness of Oleogel-S10 (birch triterpenes) compared to standard of care (SoC) for the treatment of wounds associated with epidermolysis bullosa in adult and paediatric patients".(100)

Due to the rarity of DEB and JEB, the inclusion criteria relating to population were widened to include all EB types. An overview of the methodology used to identify economic evaluations including the search strategy, methods of study identification, and the results of the review, is detailed in Appendix G.

No eligible records of any existing cost-effectiveness studies relevant to the technology or to CCM in EB, were identified in the SLR.

B.4.3 Economic analysis

The economic SLR highlighted an absence of previous economic analyses or HTA assessments of EB treatments (Section B.4.3.2), therefore a *de novo* model was required. Given the lack of precedence, an emphasis was placed on obtaining expert EB clinical and health economic input into considerations around model structure (outlined in Section B.3 and B.4.14.1), throughout development, particularly regarding extrapolation beyond the period of the EASE 90-day DBP, and subsequent 24-month OLP.

B.4.3.1 Patient population

The cost-effectiveness analysis considers all patients described in the licence for Filsuvez gel: people aged 6 months and older with partial-thickness wounds associated with DEB or JEB (Table 2).

The pivotal phase III EASE trial, used as the primary source of evidence for the cost-effectiveness analysis, included patients from both EB types relevant to the licence (JEB and DEB). Inclusion criteria were initially restricted to patients aged ≥4 years, but subsequently extended to include patients aged ≥21 days in a trial protocol amendment (see Section B.2.3 for methodology of the EASE trial). While this may potentially have included patients younger than permitted under the MHRA marketing authorisation indication, no children below the age of six months were recruited, hence the trial population reflects the MHRA marketing authorisation for Filsuvez gel.(2)

B.4.3.2 Model structure

In the absence of any direct precedence, potential model structures were assessed according to their capacity to accurately represent and incorporate (a) the nature of the condition in terms of clinical and treatment pathways, (b) direct evidence from short-term trial data, and (c) expert input and uncertainty around longer-term outcomes.

An aggregate health state transition approach was considered most suitable according to these criteria rather than a microsimulation model, particularly given the high data

requirements of microsimulation approaches (either discrete event or discrete time), in the context of a rare and heterogeneous condition. This modelling approach is aligned with several previous NICE technology appraisals (TAs) of technologies treating diseases affecting the skin.(101-105)

The economic model is structured as a cohort-level state transition model including seven distinct health states: six ordinal health states representing differing levels of EB total wound burden, defined as discrete ranges of the BSAP covered by partial-thickness wounds, and death. Individual patient data (IPD) from the EASE trial was used to derive transition probabilities between health states in the economic model (Section B.4.4.1).

B.4.3.2.1 Considerations around health state definition

The primary endpoint in EASE was the proportion of patients with first complete target wound closure within 45 days of study baseline. While important for demonstrating the speed of healing with Filsuvez gel and for regulatory requirements, this was not considered optimal for defining model health states, which aim to reflect the impact of treatment on wound coverage across the entire body rather than in isolated wounds, over a lifetime. Of the secondary endpoints available from the trial, this was most closely represented by BSAP: an objective measure of surface wound coverage across the body, collected in EASE using the Lund and Browder approach and described further in B.2.3.

Two other disease-specific measures included in the EASE trial as secondary endpoints were considered as alternative health state definitions, but both had limitations in the way they were collected in EASE. These were the EBDASI (collected in the DBP and OLP of EASE), and iscorEB (collected in the OLP only), both of which are presented in Appendix M.

The EBDASI is a partially validated, EB-specific, disease activity, and severity instrument that consists of five sections (skin, scalp, mucous membranes, nails, and other epithelialised surfaces), each section comprising an activity score and a damage score.(106) Section I (skin) is the most comprehensive of the five sections, including scores for 12 component skin sites; ears, face, neck, chest, abdomen, back, buttocks, arms, hands, legs, feet and anogenital. While EBDASI is a potentially useful measure

of EB disease severity, the EASE study only collected data using the first of the five main sections (Skin), and only the Activity section (excluding the anogenital region), not the Damage section (Appendix M).

Using the full EBDASI assessment, total wound burden can be rated as mild (EBDASI total score 0-42), moderate (EBDASI total score 43-106) or severe (EBDASI total score >106). Since only Section I of the EBDASI assessing Skin Activity (blistering/ erosions/ crusting) - minus the anogenital region - was collected in EASE, it was not possible for subjects to be classified as having a severe total wound burden (the maximum possible score of the partial EBDASI based on Skin Activity only was 100, which falls below the score needed to be classified as severe [>106]). Therefore, using EBDASI scores weighted by skin sites when the full instrument was not used means interpretation of the scores are difficult as well as presenting operational challenges for use in defining health states reflective of HRQoL outcomes (for use in an economic model). Hence, BSAP was preferred as a simpler and objective surrogate for disease severity and HRQoL impact for the model health states, and determining the treatment effect of Filsuvez gel.

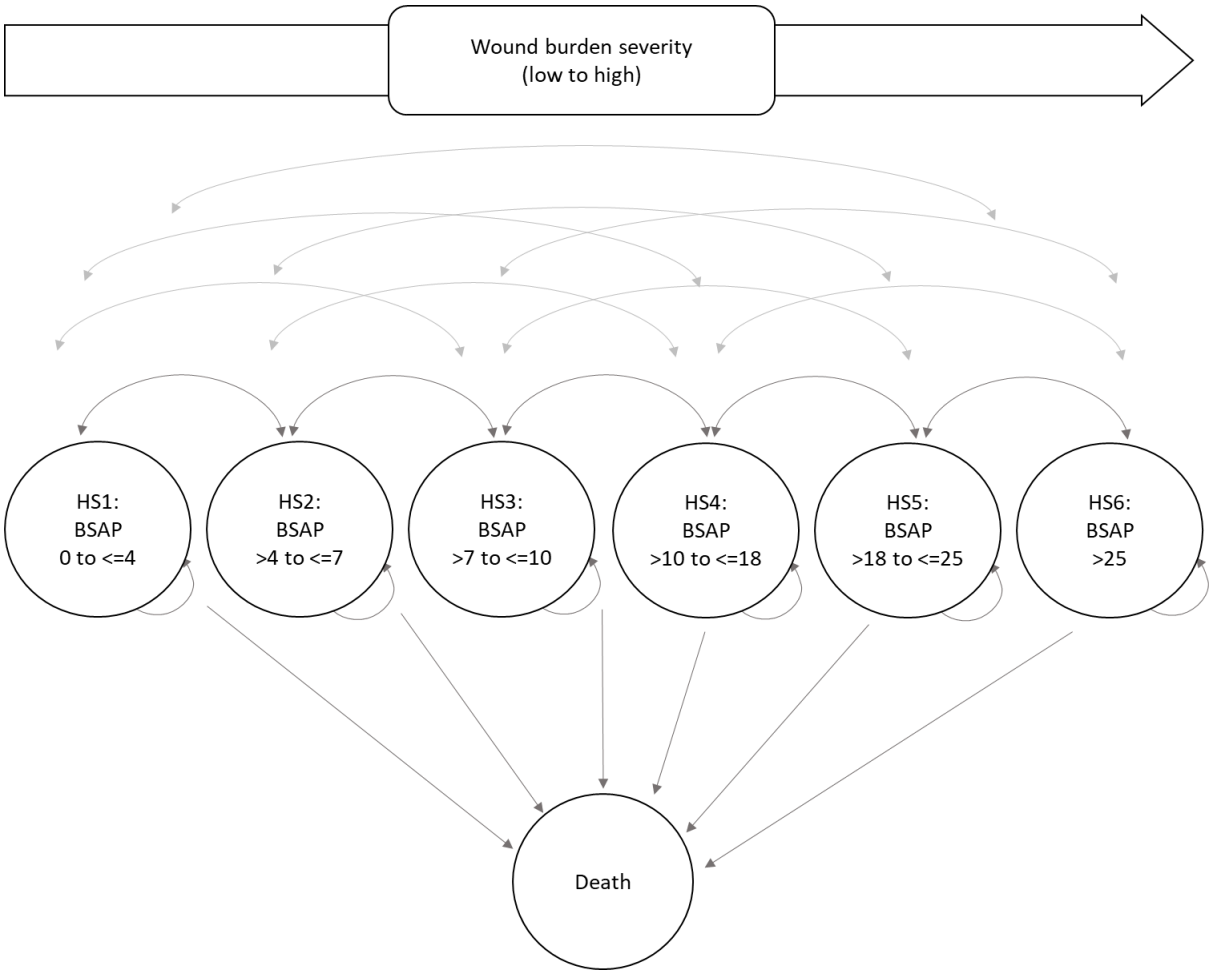
The iscorEB consists of two scored sections, the patient completed section (iscorEB-p) and the clinician completed section (iscorEB-c), with higher scores reflecting worse severity. The clinician-reported section assesses disease severity through five domains of EB involvement: skin involvement, mucosal involvement, internal organ involvement, laboratory abnormalities and complications/ procedures. Scores can be summed to 114 points. The patient-reported section includes 15 questions, assessing the quality of life of patients via seven domains, i.e., pain, itch, essential functions, sleep, daily activities, mood, and impact. Scores can be summed to a maximum of 120 points. The patient section captures the HRQoL impact of EB and therefore is potentially useful as a relevant basis for defining health states to depict EB severity and impact. However, data for the iscorEB were only collected in the OLP of the EASE trial, meaning that comparative data were not available in order to create clinically representative health states or derive transition probabilities based on this measure. In future EB clinical trials, it would be useful to include the iscorEB in the DBP to directly assess the condition specific HRQoL impact of treatments.

Amryt Pharmaceuticals undertook engagement with clinical experts (JM and DM, Table 17) to discuss and validate the modelling approach taken. The nature and output of this engagement is described in Sections B.3.5 and B.4.14, respectively. Engagements concluded that it is appropriate for BSAP to represent proxy disease severity as the basis of wider health states in this economic model, as opposed to a partial EBDASI score, or iscorEB from the OLP, only.

Figure 14 presents the base case model structure based on BSAP categories according to percentage ranges, which correspond to approximately equal distributions of patients in the EASE study at baseline within each category. The percentage ranges are as follows: health state (HS) 1: 0-4%, HS2: 5-7%, HS3: 8-10%, HS4: 11-18%, HS5: 19-24%, HS6: 25%+. For patients in either study arm (the intervention arm - Filsuvez gel in conjunction with CCM, or the control arm - CCM only) the transition between health states is denoted by the pathway arrows.

The number and final categorisation of the health states was developed to provide sufficient granularity to capture improvement or deterioration in patient wound burden (in either treatment arm). The recommendation from a clinical expert advisor (JM), was to collapse the health states into three wider states, to represent differing levels of disease impact on symptoms, complications, disease characteristics and activities of daily living (ADLs). Hence a model scenario is explored, allowing patients to transition through the model as per the six health states, but are grouped into the three health states in terms of all other model outcomes (e.g., resource use/ costs, utilities). Utilities associated with the BSAP health states were derived based on a number of sources, including the EQ-5D data from EASE (Section B.4.5.1) and a separate cross-sectional study (Section B.4.5.3.1) and a separate TTO study, in which vignettes were developed for each BSAP health state (validated with reference to the economic SLR, SEE and MSP).(97, 98, 100) Resource use and cost estimates were also assigned to health states and sourced from EASE, the cross-sectional study and the SEE, and were validated by the economic SLR and MSP).(97, 98, 100)

Figure 14 Model Health States



Data from the EASE trial DBP are used to derive short-term transition probabilities (to day 90) to represent the patient journey over time with each intervention. Longer-term patient trajectories (beyond 90 days) are populated from extrapolations of OLP data in the Filsuvez gel arm, driven by 12-month OLP data and validated using recently available (unpublished) aggregate 24-month OLP analyses, and expected disease pathways as validated by clinical experts. Estimated costs and utility values specific to each health state and/ or treatment arm, derived from a range of sources, are applied within the model to calculate total and incremental health state costs and quality adjusted life years (QALYs), and to establish the expected cost effectiveness of Filsuvez gel *versus* CCM in treating DEB and JEB patients.

The model applies a 30-day cycle length, corresponding to the schedule of DBP visits conducted in the EASE trial, with half-cycle correction applied. Given the lifelong and potentially life-limiting nature of the condition, a lifetime horizon (50 years in the base

case) is adopted, to capture all the relevant effects in DEB and JEB. Patients start the model at age 6 months, as per the Filsuvez gel licence, and are followed through to adulthood. All costs and health benefits are discounted at an annual rate of 3.5% per annum. Table 18 presents the key structural and input data features of the economic model and analysis.

Table 18 Features of the economic analysis

Factor	Chosen values	Justification
Time horizon	50 years	EB is a lifelong disease, with some subtypes assumed to follow broadly the same mortality risks as the general population, therefore a lifetime horizon of 50 years is applied to capture the lifetime costs and health benefits of Filsuvez gel in DEB and JEB.
Cycle length	30 days	30 days is a sufficient time frame to capture movements in health state. 30-day data is available in EASE. Half-cycle correction has been applied in the model to account for patients transitioning mid-cycle.
Model Start Age	Age 6 months	As per the Filsuvez gel treatment licence.(2)
Transition Probabilities	EASE DBP (Section B.4.4.1)	Transition probabilities for both arms have been calculated using the head-to-head 90-day EASE DBP data.
Source of utilities	EASE (EQ-5D-3L and EQ-5D-Y) (Section B.4.5.1)	NICE guidance states a preference for EQ-5D data to be applied where available for estimating utility in adults. Potential issues around the suitability of the EQ-5D in terms of sensitivity and the lack of a tariff specific to the EQ-5D-Y are explored in scenario analyses.
Source of resource use estimates	Literature/ SEE estimates (Section B.4.6.2)	Published evidence is limited and substantial heterogeneity exists.
Mortality	Estimates based on Petrof *et al*. (2022)(7)	Lack of trial evidence and existing natural history evidence in the literature. Kaplan Meier curves presented in Petrof *et al.* 2022, have been used to inform mortality estimates in the model for each EB subtype.
Discontinuation	8.3% at 90 days, 1% per annum thereafter	Aligned with EASE DBP discontinuation rates to 90 days, and conservative estimate based on clinical opinion subsequently

Abbreviations: EQ-5D, EuroQol 5-dimension; EQ-5D-Y, EuroQol 5-dimension Youth; MOA, mode of action; NICE, National Institute for Health and Care Excellence; SEE, structured expert elicitation; TTO, time trade off.

The formal and informal care needs of patients with DEB and JEB can be extensive (Section B.1.3.4), including frequent bathing and dressing of wounds, especially in more severe forms of the disease where a higher wound burden is present. To address the burden on carers, as well as patients, carer HRQoL is accounted for in the model. The number of carers, and the utility value attributed to each carer, are correlated with disease severity, i.e., the number of carers increase, and the carer utility value decreases as EB disease severity worsens (proxied by increasing BSAP). Data from both the CSS and the SEE demonstrated increasing time in terms of carer time spent changing dressings for patients between increasing severity health states.(60, 97) Total QALYs in the model base case reflect the sum of total patient QALYs and total carer QALYs.

Although EASE is the largest RCT conducted in EB to date, there are substantial challenges in deriving transition probabilities for Filsuvez gel and CCM due to relatively low patient numbers and the natural undulation of wound burden at the patient level, caused by continual opening of new wounds and healing of existing wounds over time. A particular limitation of conventional modelling approaches, whereby transition probability matrices are derived directly from observed transitions, is that a number of the permissible health state transitions that require modelling in the extrapolation period may not have been observed during the course of the trial.

To overcome this constraint, transition probability matrices were derived from patient-level data according to mean changes in BSAP and corresponding standard deviations at discrete time points. This follows a broadly similar approach to that described in NICE guidance NG82 (a clinical guideline in visual acuity),(107) whereby mean change in severity (as proxied by BSAP) is assumed to be normally distributed, allowing for distributions across subsequent health states to be estimated from any prior health state.

Using this approach, transition probabilities applied in the first 90 days of the model have been derived from patient-level data from the DBP of the EASE trial (Filsuvez gel and CCM arms). Longer-term transition probabilities for the Filsuvez arm are derived from patient-level data collected in the first 12 months of the OLP corresponding to patients originally randomised to Filsuvez gel. In either arm, extrapolation scenarios are applied to explore the impact of assuming ‘steady state’

assumptions, where no further transitions between health states other than to death are assumed beyond a given time period. Further scenarios are included to consider alternate approaches to longer term patient trajectories to capture longer-term disease trajectories, informed by the literature and expert clinical opinion (see section B.2.3.3 for methods of expert elicitation).

To account for the divergent characteristics, disease trajectories and survival profiles of EB subtypes, aspects of disease progression, mortality, costs, and health benefits are estimated separately for RDEB-severe, RDEB-other, DDEB, and JEB patients within the model, then aggregated to derive an overall prevalence-weighted ICER. Given feedback from phase 3 of the SEE (Section B.3.2), JEB-severe patients have been excluded from the economic analysis, due to the rarity of the condition - experts suggested there is only 1 current existing severe JEB patient -, and the mortality profile. Experts suggested that many severe JEB patients would die before the age of 6 months, which is outside of the Filsuvez gel licence.(97) Therefore, the cost effectiveness model only considers non-severe JEB patients. While important differences exist between EB subtypes in terms of natural history, disease complications and mortality, broader inputs in terms of health state costs, resource use, and HRQoL input parameters are assumed to be the same across EB subtypes. Total lifetime costs and QALYs for EB subtypes are calculated in separate Markov traces, and aggregated back to derive an overall ICER, weighted to reflect the relative prevalence of each subtype.

B.4.3.3 Intervention technology and comparators

As outlined in the decision problem (Table 1), Filsuvez gel is the intervention of interest within the economic analysis and is compared against CCM alone for estimation of relative cost-effectiveness.

B.4.3.3.1 Intervention

As detailed in Table 2, Filsuvez gel is a non-aqueous gel; 1g of gel contains 100mg of refined birch bark extract. The gel should be applied to the wound surface at a thickness of approximately 1mm and covered by a sterile non-adhesive wound dressing or applied to the dressing so that the gel is in direct contact with the wound. The tube containing 23.4g of gel, will be available in the UK.(2)

B.4.3.3.2 Comparator

In the absence of any existing licensed therapeutic treatments in the UK for EB besides Filsuvez gel, the cost effectiveness of Filsuvez gel plus CCM is assessed *versus* CCM without Filsuvez gel (described in Section B.1.3.4). As such, Filsuvez gel is expected to supplement rather than displace CCM, although some influence may be expected on patterns of CCM such as the frequency of dressing changes (expected to be reduced).

In lieu of natural history data (which has been further explored as part of the SEE), the economic model assumes that the control arm of the EASE trial (reported in Section B.2.6.1) is generalisable to, and a suitable proxy for outcomes associated with CCM over a 90-day period. This assumption is expected to be conservative due to improvements in primary and secondary endpoint measures observed in the control arm during the course of the 90-day DBP, potentially indicating some improvement in care arrangements in the trial relative to preceding (and longstanding) treatment. Any potential biases due to control gel effects, due to its excipients having proven wound healing properties (discussed in Section B.2.12), are expected to favour the CCM alone (comparator arm) outcomes in the base case, highlighting that the analysis may provide conservative estimates of the clinical and cost effectiveness of Filsuvez gel.

B.4.4 Clinical parameters and variables

Although the speed of complete closure of individual/ target wounds (as the primary endpoint of the EASE study) is a key component of the benefit of Filsuvez gel, the focus of the economic model is the impact on *total* wound burden, as measured by BSAP affected by partial-thickness wounds, which was a secondary endpoint in the EASE DBP.(86) As reported in B.2.6.1 (Figure 7), Filsuvez gel demonstrated an improvement relative to the control gel in reduction in BSAP (-4.3% *versus* -2.5% in the control gel arm, over 90 days).(75, 86)

While BSAP may not directly capture patient relevant outcomes including pain, itch and other aspects of EB disease, it has been clinically validated as an appropriate measure of total EB wound burden and hence a surrogate for disease severity, especially in the absence of robust data using EB disease-specific measures. Furthermore, BSAP correlated well with HRQoL/ utility measures and iscorEB

(Appendix P). Health states in the model are driven by BSAP based transition probabilities. In a separate time trade off (TTO) study vignettes have been created with patient and clinician input for each of the BSAP health states which provides useful descriptors of the broader outcomes and EB disease burden associated with varying levels of total wound burden and disease severity (Section B.4.5.3.2).

Although EASE is the largest RCT conducted in EB to date, data were collected for a relatively small number of patients (N=223), especially when considering EB subtype subgroups, in JEB, for example (n=26, 11.7%). The relatively short, 90-day EASE DBP also meant that calculating health state transition probabilities based on conventional methods using the number of patients observed to move between health states, resulted in less robust transition probabilities. Using such conventional methods of calculating transition probabilities, as directly observed in EASE, would potentially lead to unrealistic and unrepresentative transitions being used in the model due to data outliers influencing large movements between health states over short periods of time, or leading to transition loops where moving to a worse health state can lead to improved outcomes in time. This could result in misleading cost-effectiveness results for Filsuvez gel compared to CCM where treatment keeps patients in favourable health states.

B.4.4.1 Transitions

Base case utility values have been calculated using a simple distributional approach, aligned with the methodology reported in NICE clinical guidelines for visual acuity.(107) A normal distribution is assumed for the mean change in EASE BSAP across time points, allowing the probability of transitioning to other health states between time *t* and time *t+1* to be calculated according to the mean change and standard deviation of change in BSAP at time *t+1* relative to time *t.* Transition probabilities are derived using this approach, on the basis of the interim 12-month OLP data (database lock 15 July 2021, presented in Appendix O) from EASE (Table 19 and Table 20).

Table 19 Filsuvez gel transition probabilities

Day 0-30						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**

HS1	1.000	0.000	0.000	0.000	0.000	0.000
HS2	0.109	0.891	0.000	0.000	0.000	0.000
HS3	0.000	0.382	0.618	0.000	0.000	0.000
HS4	0.000	0.000	0.368	0.632	0.000	0.000
HS5	0.000	0.000	0.000	1.000	0.000	0.000
HS6	0.000	0.000	0.000	0.000	1.000	0.000
Day 30-60						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1	0.934	0.066	0.000	0.000	0.000	0.000
HS2	0.000	0.993	0.007	0.000	0.000	0.000
HS3	0.000	0.002	0.998	0.000	0.000	0.000
HS4	0.000	0.000	0.003	0.997	0.000	0.000
HS5	0.000	0.000	0.000	0.822	0.178	0.000
HS6	0.000	0.000	0.000	0.000	0.976	0.024
Day 60-90						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1	0.981	0.019	0.000	0.000	0.000	0.000
HS2	0.002	0.997	0.001	0.000	0.000	0.000
HS3	0.000	0.022	0.978	0.000	0.000	0.000
HS4	0.000	0.000	0.024	0.976	0.000	0.000
HS5	0.000	0.000	0.000	0.927	0.073	0.000
HS6	0.000	0.000	0.000	0.000	0.992	0.008
Day 90+						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1	0.966	0.034	0.000	0.000	0.000	0.000
HS2	0.014	0.980	0.006	0.000	0.000	0.000
HS3	0.000	0.069	0.931	0.000	0.000	0.000
HS4	0.000	0.000	0.073	0.927	0.000	0.000
HS5	0.000	0.000	0.000	0.901	0.099	0.000
HS6	0.000	0.000	0.000	0.000	0.982	0.018
Abbreviations: HS, health state.						

Table 20 CCM transition probabilities

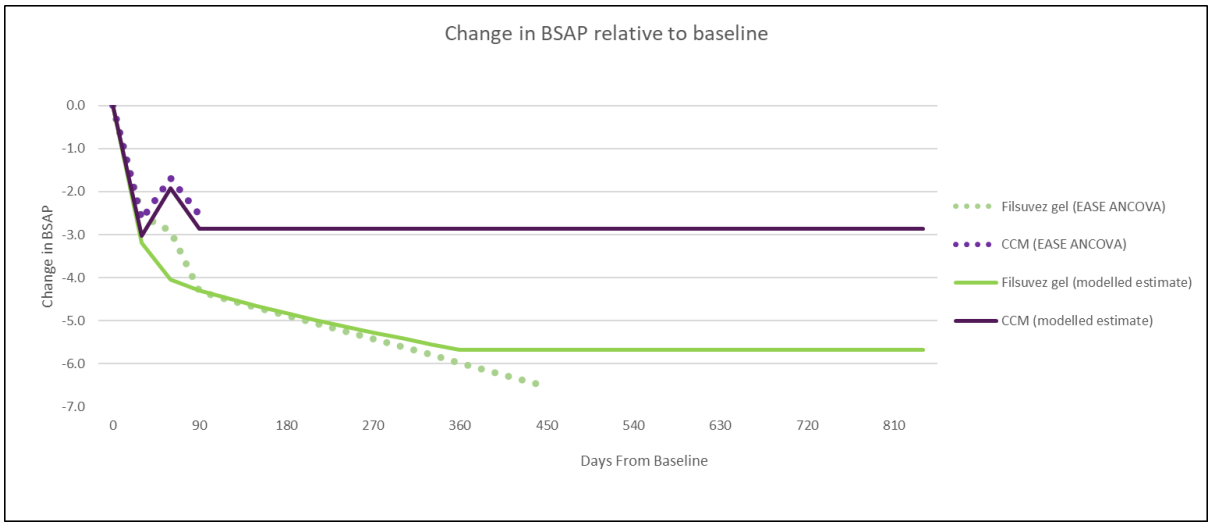
Day 0-30						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1	1.000	0.000	0.000	0.000	0.000	0.000
HS2	0.022	0.978	0.000	0.000	0.000	0.000
HS3	0.000	0.358	0.642	0.000	0.000	0.000
HS4	0.000	0.000	0.284	0.716	0.000	0.000

HS5	0.000	0.000	0.000	0.999	0.001	0.000
HS6	0.000	0.000	0.000	0.000	1.000	0.000
Day 30-60						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1	0.154	0.846	0.000	0.000	0.000	0.000
HS2	0.000	0.155	0.845	0.000	0.000	0.000
HS3	0.000	0.000	0.998	0.002	0.000	0.000
HS4	0.000	0.000	0.000	1.000	0.000	0.000
HS5	0.000	0.000	0.000	0.029	0.971	0.000
HS6	0.000	0.000	0.000	0.000	0.309	0.691
Day 60-90						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1	0.977	0.023	0.000	0.000	0.000	0.000
HS2	0.000	0.980	0.020	0.000	0.000	0.000
HS3	0.000	0.006	0.994	0.000	0.000	0.000
HS4	0.000	0.000	0.005	0.995	0.000	0.000
HS5	0.000	0.000	0.000	0.821	0.179	0.000
HS6	0.000	0.000	0.000	0.000	0.968	0.032
Abbreviations: CCM, current clinical management; HS, health state						

Mean change in BSAP relative to baseline as estimated in the model base case (solid lines) is compared against clinical evidence from the EASE trial, based on ANCOVA analyses (solid lines), in Figure 15. For this analysis, mean BSAP is approximated in the model according to the midpoint BSAP corresponding to each health state, applying a mid-point estimate of 30% BSAP for the highest health state (BSAP of 25% or above). Despite this approximation, aggregate results show a good fit to the observed trial data.

A steady state (where no further transitions are assumed) is applied to the control arm from 90 days, reflecting the clinical assumption that this time period sufficiently captures any control arm effects (see section B.4.7.2). Steady state assumptions are applied to the Filsuvez gel arm from 1 year, reflecting ongoing clinical benefit captured in the EASE DBP. This extrapolation is supported by aggregate data from the EASE 24-month data cut-off summarised in Figure 10.

Figure 15 Comparison of change in BSAP relative to baseline as estimated in the economic model base case and EASE ANCOVA results (pooled across EB types).



Multi state modelling (MSM) in R studio was also initially explored as an alternative approach for calculating transition probabilities. Although this allowed transitions to be generated to and from all health states driven by few data points, it was agreed by health economists present at the MSP (Section B.3.3) that a simpler approach placing less constraints on the data would be more transparent and easier to reconcile against aggregate output from the EASE study.

B.4.4.2 Natural History

There is very limited information in the literature and from clinical trial programmes on the natural disease progression of EB. A recent publication presented a schematic representation of severe RDEB according to 4 phases of the disease using age at diagnosis as timescale for disease severity.(20) To form a basis for further data collection, Amryt Pharmaceuticals has commissioned the construction of an EB conceptual natural history model for RDEB based on literature and expert opinion. This framework is being designed to model the natural history of the disease in terms of health state trajectories and EB-relevant milestones that patients experience (without access to specific new medications i.e. standard of care), with the aim to provide a platform for future EB data to be utilised. The work on the conceptual model has been delayed due to availability of EB experts, with an impact on publication timelines. Therefore, the limited evidence identified in literature has been

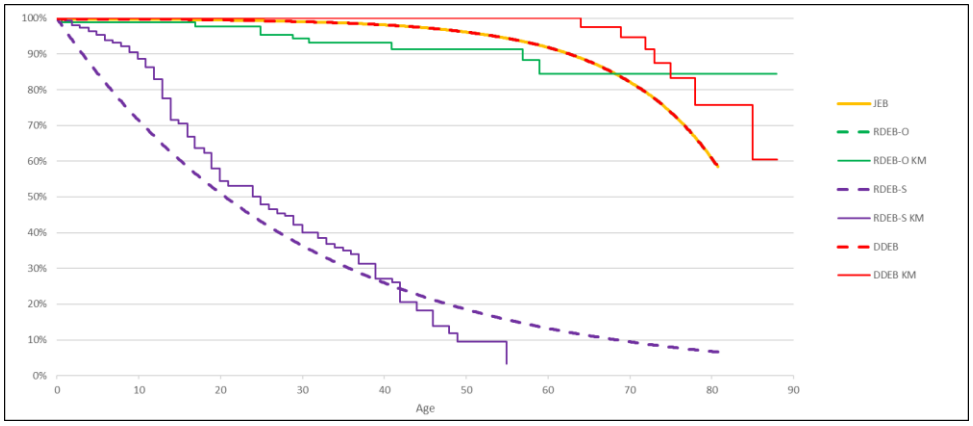
complemented with or validated by expert opinion (Section B.3), in order to support mortality estimation (see Section B.4.4.3) and BSAP extrapolations over time.

B.4.4.3 Mortality

Long-term mortality data has been estimated based on published Kaplan-Meier curves by EB subtype in Petrof *et al*. 2022 (Figure 16).(7) The study uses data available for 2,594 patients with EB who were enrolled in the national EB service database since 2002. Mortality data is reported for RDEB-S, DDEB, RDEB-O, and JEB-S in Petrof *et al.* alongside general population mortality curves, calculated using UK life tables.(29) DDEB, RDEB-O, and JEB (non-severe) patients broadly follow UK general population survival rates; therefore, no excess mortality is applied to these patients in the model. Expert opinion elicited in the SEE exercise suggested that non-severe JEB patients experience mortality risks slightly worse than the general population.(97)

Therefore, a modifier is implemented in the model, to artificially 'age' patients relative to the general population. This accounts for excess mortality for JEB patients applied in a scenario analysis, assuming a mortality profile slightly worse than the general population. RDEB-S patients in the model are associated with a mortality rate of 0.0028 per cycle, meaning that all RDEB-S patients are in the death health state by age 55. Mortality assumptions were explored and validated by clinicians through the SEE process (Section B.3).(97)

Figure 16 Comparison of modelled overall survival and published Kaplan-Meier curves from UK registry data, by EB type.



Source: Petrof et al. 2022 (Kaplan-Meier curves), ONS 2021 (general population mortality).(7, 108)

Abbreviations: DDEB, dominant dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; RDEB, recessive dystrophic epidermolysis bullosa; RDEB-S, recessive dystrophic epidermolysis bullosa-severe.

Mortality profiles for EB subtype were a key area of investigation within the SEE.(97) In Stage 2 of the SEE, there was general consensus that evidence in Petrof *et al.* 2022, which related to all EB subtypes (EBS, JEB, DEB and Kindler EB) was a reasonable representation of current survival rates in the UK, although some differences were evident. Experts felt that 75% of RDEB-S patients could expected to survive to 21 years, whereas Petrof *et al.* 2022 estimated survival to 15 years. There was also consensus that DDEB and RDEB-O patients would have survival rates similar to those experienced by the general population, albeit that 75% of patients might expect to survive to 70 years whereas Petrof *et al.* estimated survival to 82 years. Tabular results of Stage 2 discussions are set out in below. These were then modified in Stage 3 discussions to reflect additional sub-types, but they provide a useful contextual reference to evidence presented in Petrof *et al.* 2022.(7, 97)

Table 21 Validation of survival estimates

Source	Proportion of patients alive	RDEB-S	RDEB-O	DDEB
Petrof *et al.* 2022(7)	**75%**	15 years	82 years	82 years
	Median Survival	25 years	As per general population	
	25%	42 years	As per general population	
Expert opinion (n=4) mean of values.	**75%**	21 years	70 years	70 years
	Median Survival	29 years	79 years	80 years
	25%	42 years	85 years	85 years

Abbreviations: EB, epidermolysis bullosa; DDEB, dominant dystrophic epidermolysis bullosa; RDEB-O, recessive dystrophic epidermolysis bullosa-other; RDEB-S, recessive dystrophic epidermolysis bullosa-severe

Following Stage 3 discussions, individual survival profiles were plotted in charts for RDEB-S, RDEB-O, and DDEB as well as JEB-S, JEB-O.(97) The linear means on each graph were agreed to reflect consensus opinion and the variation in response was deemed reflective of uncertainty surrounding central estimates.

It was also agreed by experts involved in the SEE Stage 3 discussions, that SCC was unlikely to be a major cause of death for RDEB-S patients below the age of 20 and was likely to relate to a number of different causes including gastrointestinal problems, trauma, failure to thrive, renal problems, and in some instances, unknown causes.(97)

Group responses on likely cause of death, as elicited from Stage 3 of the SEE were plotted on separate pie charts for JEB-All, RDEB-S, RDEB-O and DDEB.(97)

B.4.4.4 Wound coverage progression

One area of uncertainty is the nature and shape of a natural disease progression, in terms of BSAP progression, for subtypes of EB. This was a key focus of the SEE exercise.(97) As part of elicitation, experts were asked: *For patients in the UK, what BSAP would you expect for patients aged 5, 10, 15, 20, 30, 40 and 50 years of age (by EB subtype)?*

Whilst there was general agreement on mortality profiles (Section B.4.4.3), there were differences of opinion as to whether JEB-S patients would survive up to 5 years of age and whether RDEB-S patients would survive up to 50 years of age. This had implications for disease progression, and led to amendments in the final estimation of disease progression (Table 22).(97)

Table 22 Results of Stage 3 SEE: disease progression estimates

Aggregated mean estimates from all clinicians: *"For patients in the UK, what BSAP would you expect for patients aged 5,10,15, 20, 30, 40 and 50 years of age (by EB subtype)?"*					
Estimated BSAP by age	**JEB-S**	**JEB-O**	**RDEB-S**	**RDEB-O**	**DDEB**
	Mean	**Mean**	**Mean**	**Mean**	**Mean**
Aged 6 months	28.0	11.3	7.3	5.0	3.0
Aged 5	X	17.7	11.3	6.3	4.3
Aged 10	X	25.0	15.3	7.3	5.0
Aged 15	X	28.5	19.7	8.2	6.0
Aged 20	X	19.3	26.2	9.7	6.7
Aged 30	X	21.7	35.0	11.0	8.0
Aged 40	X	22.7	50.0	12.2	9.2
Aged 50	X	24.3	50.0	15.2	9.5

Abbreviations: EB, Epidermolysis bullosa; DDEB Dystrophic EB; JEB, Junctional EB; RDEB-O, Recessive dystrophic EB-Other; RDEB-S, Recessive dystrophic EB-Severe; BSAP, Body Surface Area Percentage
X = Patients not expected to survive
Red text: Stage 3 amendments to Stage 2 results

These profiles are plotted in separate figures for JEB-S, JEB-O, RDEB-S, RDEB-O and DDEB in Appendix N (Figures 1 to 5, respectively).

B.4.5 Measurement and valuation of health effects

This section describes the HRQoL evidence available to inform utility values in the model. Utility data was available from several sources, primarily the pivotal EASE trial (OLP only) for adults and children, a time trade off (TTO) study performed in the general UK population, a cross-sectional study (CSS), and existing HRQoL/ utility data in the literature.

B.4.5.1 Health-related quality-of-life data from clinical trials

As discussed in section B.2.1, the pivotal EASE RCT is the only trial in DEB and JEB to have collected evidence relevant to the decision problem.(86)

HRQoL data were collected in the EASE OLP using iscorEB (patient completed section), EBDASI and the 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.(88) Of these measures, the EQ-5D is NICE's preferred measure of health-related quality of life in adults.

The choice of an appropriate utility measurement for children is a well-documented problem.(109) Development of a TTO with vignettes capturing child-related quality of life dimensions such as disruption to schooling offers an opportunity to test the sensitivity of EQ-5D-Y values against alternative derivations of utility in children. HRQoL data in EASE was obtained using the EQ-5D-5L for adults in the EASE 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 4 years were proxied by the parent or carer. The EQ-5D instruments were introduced as a protocol amendment in the OLP, hence no HRQoL data were collected in the DBP of EASE, and numbers of observations are limited as it was only collected in the OLP, and there were several missing observations where the EQ-5D was not completed.

To obtain utility scores, adult EQ-5D-5L domain scores collected in EASE were mapped to the EQ-5D-3L using the Van Hout *et al.* (2012) mapping algorithm.(110) For HRQoL data collected among children and adolescents (using the EQ-5D-Y), the

adult EQ-5D-3L tariff was applied directly, in the absence of a validated value set specific to the youth version. This is a limitation but is considered the best valuation approach that could be adopted. The mean utility (SD) observed from 106 total observations in EASE is 0.511 (0.367). Utility values from the EQ-5D-5L (mapped to the EQ-5D-3L) and EQ-5D-Y were pooled and linearly regressed, summarised by model health state in Table 23, and in Appendix P. In line with the NICE reference case, these values were used in the base case economic analysis.

Table 23 Summary of Utility Values in EASE

Health State	Utility Value (Regressed)	Standard Error
Health state 1 (BSAP≤4%)	0.56	0.037
Health state 2 (BSAP 5-7%)	0.51	0.034
Health state 3 (BSAP 8-10%)	0.46	0.037
Health state 4 (BSAP 11-18%)	0.35	0.570
Health state 5 (BSAP 19-24%)	0.23	0.088
Health state 6 (BSAP ≥25%)	0.08	0.130
Abbreviations: BSAP, body surface area percentage.		

B.4.5.2 Mapping

No mapping algorithms currently exist to map EB specific instruments, such as the EBDASI and iscorEB, to the EQ-5D to obtain utility values. If the iscorEB is included in future clinical trials for EB this could potentially be developed as a preference-based utility instrument and/ or be mapped to the EQ-5D to provide disease specific utility estimates. However, the only mapping performed, as detailed in section B.4.5.1, involved mapping the EQ-5D-5L to the EQ-5D-3L using the Van Hout *et al*. (2012) mapping algorithm to obtain utility values for EASE OLP adult respondents.(110)

B.4.5.3 Health-related quality-of-life studies

In line with NICE guidance to the methods of technology appraisal, an SLR was conducted to identify relevant studies reporting utility values, or studies which included HRQoL data that could be mapped using published algorithms to the EQ-5D. As discussed in Section B.4.2, an SLR was conducted to identify relevant studies in published literature relating to prior economic evaluations, cost, and resource use data, and HRQoL in EB. Due to the rare nature of DEB and JEB, the inclusion criteria

relating to population were widened to include all EB types. The SLR search strategy used to identify all relevant economic evidence, including HRQoL data, is detailed in Appendix G. An overview of the methodology used to identify HRQoL evidence, identification of studies, description of studies and quality assessment of studies identified is detailed in Appendix H.

This section focuses on existing HRQoL data associated with EB to support utility data inputs for patients and carers into the economic model.

B.4.5.3.1 Studies identified by the SLR

Following a review of all records, three studies/ sources were identified that reported HRQoL data for patients and (in some instances) carers relevant to the decision problem - one published study (Angelis *et al*., 2016), and two unpublished sources (the EASE trial, and the CSS). Data in the form of EQ-5D (the NICE preferred measure) was identified: EQ-5D-5L included in a CSS sponsored by Amryt Pharmaceuticals, Angelis *et al.* 2016*,* and the EASE RCT.(50, 60, 86)

Following completion of the SLR, an additional record for the Angelis *et al*. 2016 study was recently updated and published, Angelis *et al*. 2022. This was identified in routine hand searching following completion of the SLR and has been separately considered for use in the economic model.(37, 50, 58, 73)

The EASE OLP EQ-5D data has been discussed above (Section B.4.5.1). The two other evidence sources identified as relevant to providing inputs for the economic model in the SLR, and the 2022 update to the Angelis *et al*. study, are discussed below.

Angelis *et al*. (2016, 2022)

The 2016 Angelis *et al.* study identified in the SLR, reported a mean EQ-5D index (TTO tariff) across patients with a mix of EB subtypes (34.9% DEB, 62.8% EBS, 2.3% JEB) as well as for carers of EB patients. Utility values were provided for EB patients from eight European countries (Spain, France, UK, Bulgaria, Hungary, Germany, Sweden, Italy) as well as by individual country, including the UK. Mean EQ-5D utility (TTO tariff) was higher for carers than patients in both the combined and UK populations and was slightly lower for both patients and carers in the UK compared to

the combined European values (EQ-5D TTO tariff utility values: UK patients: 0.563; UK carers: 0.675; European (eight countries) patients: 0.579; European (eight countries) carers: 0.696).

The recently published 2022 Angelis *et al.* update, identified after completion of the SLR, provided an analysis of the DEB-only population from the same data source as the earlier Angelis publication. This new analysis provided EQ-5D-3L utilities across five European countries (France, Germany, Italy, Spain, UK) as well as by individual country. This showed a substantially lower mean EQ-5D-3L utility score among DEB patients (mean: 0.304, SD = 0.449) relative to the overall EB study population in the UK. Carers of DEB were shown to have a slightly higher mean EQ-5D-3L (mean: 0.713, SD= 0.071), compared to all EB subtypes combined (Angelis *et al*. 2016). The mean UK patient EQ-5D-3L score in the UK was considerably lower than the average across five European countries for the DEB only population (mean: 0.456, SD=0.328).

Cross-sectional study on EB Burden

A cross-sectional study (CSS) commissioned by Amryt Pharmaceuticals investigated the HRQoL of patients and carers in the population relevant to the decision problem, living in the UK, Republic of Ireland and the US. “Utility Elicitation in Epidermolysis Bullosa: Cross-Sectional Survey”.(60) The main objectives of the study were to elicit patient and carer HRQoL and utility outcomes using validated generic and disease specific instruments; including iscorEB and CHU9D, to analyse the consequences of EB that have the greatest impact on both patients and carer HRQoL; and, to better understand the impact of EB and EB management for patients and carers. The CHU9D is a paediatric generic preference-based measure of health-related quality of life recommended for use in people up to the age of 18 years. It was completed as a proxy by 11 carers of children aged ≤15 years.

Both patient and carer HRQoL data were collected in the study using the EQ-5D-5L directly from patients or via a proxy respondent in the form of a patient carer or parent where the patient was unable to complete the EQ-5D-5L directly. The study also collected information on patient estimated BSAP, which was then categorised using two approaches as follows:

- Self-reported BSAP – Split into 6 categories (<=4%, >4% to <=7%, >7% to <=10%, >10% to <=18%, >18% to <=24%, >24%)
- BSAP calculated from Lund & Browder Diagram – Split into 6 categories (<=4%, >4% to <=7%, >7% to <=10%, >10% to <=18%, >18% to <=24%, >24%)

The Lund & Browder diagram has limitations in the way in which it has been implemented in this study. The Lund and Browder chart is designed to be completed by clinicians who can physically assess patients in a clinic, whereas the CSS was conducted online, and the Lund and Browder chart was completed by patients. Patients were given a diagram and if they marked one area as having wounds (one or many) the whole area was reported as a wound, which led to a much higher BSAP than expected. Hence, the economic model utility estimates from the EQ-5D were generated according to the self-reported BSAP categories (corresponding to the economic model states) and used in scenario analysis as an alternative source of values to those from the EASE OLP EQ-5D data.

In total, 78 participants responded to the questionnaire during the data collection period of September 2021 to February 2022. Of these, 59 (75.6%) were self-completions by patients aged ≥16 years, eight (10.3%) were completions by patients aged ≥16 years who required some assistance from parents/ carers with self-completion, and 11 (14.1%) were proxy completions by parents/ carers on behalf of young people/ children under 16 years of age. The majority of respondents were from the US (84.6%), with 12.8% from the UK, and 2.6% from RoI. Of the self-completers (n=67), the majority of patients had DEB (44.8% DDEB, 44.8% RDEB), with lower numbers of JEB (9.0%) and KEB (1.5%), and the mean age was 26.2 years (SD: 9.00). In the proxy completions (n=11), the majority had JEB (72.7%), with the rest having RDEB (27.3%), and the mean age was 7.9 years (SD: 5.07). The overall sample has been used as there are too small numbers for just the UK subgroup, or for DEB and JEB separately. Data from the survey were reported separately for self-reported and proxy-reported completions.(60)

In the self-reported completions, the mean EQ-5D was 0.52 (SD: 0.29), ranging from 0.87 (SD: NR) in participants in the ≤4% BSAP health state to 0.41 (SD: 0.32) in those in the ≥25% BSAP health state. In the proxy-reported completions, the mean EQ-5D

was marginally lower, 0.50 (SD: 0.37), and the mean for participants in different BSAP health states ranged between 0.74 (SD: 0.07) in participants with a BSAP health state between 11% and 18%, to 0.26 (SD: 0.64) for those with a BSAP health state of ≥25% (Table 24).

Carer HRQoL data was reported by 11 participants, with mean and range values reported for all carers and by BSAP category of the patient they care for. In this group the mean EQ-5D utility value was 0.88 (SD: 0.14) and ranged from 0.98 in participants with a BSAP health state of 19% to 24%, to 0.69 in participants with a BSAP health state of ≥25% (Table 24). However, the carer HRQoL data has not been used in the economic model due to too low numbers in each of the health states to give meaningful or robust estimates. Instead, carer values from a TTO study sponsored by Amryt Pharmaceuticals have been used in the economic analysis (see Section B.4.5.3.2).

The EQ-5D values from the CSS have been used in a scenario analysis in the economic evaluation. For this, the patient (n=67) and proxy (n=11) values have been combined to give the full study set of participants, excluding one kindler EB patient (total n=77). Table 24 reports the combined regressed values used in model scenario analysis, alongside the carer values (n=11). EQ-VAS was also reported in the cross-sectional study for patient, proxy and carer; however, this has not been extracted for input in the economic model due to availability of EQ-5D derived utility data.

Table 24 Summary of utility values in DEB/ JEB populations reported by wound burden/ severity (BSAP categories)

Study	**Cross-Sectional Study (Morgan *et al.* (2022))**	
Patient population	**Combined patient and proxy regressed (n=77) [a]**	**Observed Carer data (n=11)**
Utility Measure	**EQ-5D-5L**	**EQ-5D-5L**
Utility data		
Mean (SD)	0.57	0.88 (0.14)
Range	NA	0.56 – 1
Mean (SD) by BSAP health state		
Health state 1 (BSAP ≤4%)	0.69	NA
Health state 2 (BSAP 5-7%)	0.64	0.94 (NR)
Health state 3 (BSAP 8-10%)	0.59	NA
Health state 4 (BSAP 11-18%)	0.54	0.96 (0.03)
Health state 5 (BSAP 19-24%)	0.49	0.98 (0.03)
Health state 6 (BSAP ≥25%)	0.44	0.69 (0.12)

Abbreviations: BSAP, body surface area percentage; EQ-5D-5L, Euroqol 5-dimension 5 level; n, number; NA, not applicable; NR, not reported; SD, standard deviation
[a] Patient and proxy data was combined for use in the economic model; one Kindler EB patient has been excluded from the data.

B.4.5.3.2 Time trade-off study to derive patient and carer utilities

To supplement EQ-5D results collected in the EASE trial and the cross-sectional study, a TTO exercise in the UK general public was sponsored by Amryt to elicit utility valuations specific to BSAP health state descriptions. TTO is a widely used and accepted method of eliciting utility values and, (in the absence of directly observed utility values), an accepted method of utility elicitation according to NICE guidelines.(97, 111) The use of vignettes and TTO is a frequently used approach within the rare disease and HST context. The main advantage of the TTO study is that it provides data on caregiver utilities that was not available from EASE or the CSS, for use in the base case of the economic model, with the patient utilities used in scenario analysis.

The TTO exercise involved a series of choice tasks based around health states, which are representative of the multi-dimensional burden of EB on daily lives of patients and carers. Based on the stated preferences and value that members of the UK general population assign to each health state, health state utility values (HSUV) are estimated.

Health state descriptions (vignettes) for six patient health states were developed to represent quality of life reflective of different EB severities associated with wound burden categories (as measured by BSAP). These were constructed using the iscorEB patient components and EQ-5D-5L domains as the framework for the descriptors included in each health state vignette. The quality-of-life burden of EB is portrayed via the health state descriptions, to ensure a multi-dimensional representation of living with the disease. Care was taken to ensure a balanced set of descriptors for each BSAP state so showing where EB has an impact and where less or no impact across states. Attention was also given to limiting the level of detail in the health state descriptions, to prevent response fatigue in participating individuals and to the wording of the health states, so as to minimise framing or labelling bias.

To quantify carer HRQoL burden where there is a lack of evidence in the literature, especially for EB, three carer health states were defined to depict quality of life associated with caring for people with differing severities of EB. For this exercise, participants were asked to imagine they were a carer of an EB patient in the described

health state to estimate the HRQoL of the carer. The patient and carer health state descriptors are summarised in Table 25 and Table 26.

The draft health state descriptors were rigorously reviewed by experts including EB clinical experts and representatives of EB patient advocacy groups (Section B.3.4). The final health state descriptions were then piloted with a small sample of the UK general population (n=10). Following piloting with 10 people, a representative cross-sectional sample of the UK general population (n=120) were recruited to participate in a composite TTO (cTTO) exercise conducted face-to-face with trained interviewers.(99) Full details of the methods of generating health state descriptions, and the piloting, recruitment, and interview process for the TTO are detailed in the report.(112)

Table 25 Patient health state descriptions (vignettes) relating to BSAP categories

Health state 1 (≤4% BSAP)	
Wounds and other symptoms	You have a few **wounds on up to 4% of your body.** These wounds are on bony parts of your limbs i.e. hands, feet, ankles, elbows and knees (see diagram). You **develop blisters** easily and have a little **skin crusting, scabbing or erosions** on your body.
Disease management	You will need to **dress your wounds,** which takes < 1 hour **daily or every 2 days**.
Impact on your life	You have **low acute pain or discomfort** with **itching** due to your wound(s). You have **no** or **mild difficulty** in **eating and drinking**. Rarely, you have **difficulty with bowel movements**. You have **mild sleep disturbance** because of your skin. **Occasionally**, your symptoms and the number of visits to **medical specialists impact your school, work, daily activities**. Due to **a little difficulty** in **moving around** or **using your hands**, **learning progress, family time** and **leisure time** can be impacted**.** Sometimes, you experience **negative emotions (such as embarrassment, anxiety, or frustration)** due to EB. You find it **difficult to explain your disease** to others.
Health state 2 (5-7% BSAP)	
Wounds and other symptoms	You have **wounds over 5-7% of your body**. These wounds are on bony parts of your limbs i.e. hands, feet, ankles, elbows and knees (see diagram). You **develop blisters** easily and have a little **skin crusting, scabbing or erosion** on your body.
Disease management	You require caregiver help to **dress your wounds,** taking **<1 hour daily or every 2 days**. You **sometimes require painkillers**.
Impact on your life	You have **low acute pain or discomfort** with **itching** due to your wound(s). You have **mild difficulty** in **eating and drinking**. Rarely, you have **difficulty with bowel movements**. You have **mild sleep disturbance**. **Occasionally,** the number of visits to **medical specialists impact your school, work, daily activities**. Due **to a little difficulty in moving around or using your hands**, **learning progress** and **leisure time** are impacted**.** Sometimes, you experience **negative emotions (such as embarrassment, anxiety, or frustration)** due to EB. You find it **difficult to explain your disease** to others.
Health state 3 (8-10% BSAP)	
Wounds and other symptoms	You have **wounds over 8-10% of your body**. These wounds are mainly located on your hands, feet, ankles, elbows, knees and shins (see diagram). You **develop blisters** easily and have **skin crusting, scabbing or erosion** on your body. You have a low degree of **malnutrition** and **anaemia** from wounds. You can develop **osteopenia** (your bones become more fragile).

Disease management	You require caregiver **help to dress your wounds, taking ~2 hours daily.** You **sometimes require painkillers** and creams for your wounds.
Impact on your life	Your anaemia symptoms can leave you feeling **tired and weak**. You have **moderate acute skin pain or discomfort**, with **itching** due to your wound(s). Sometimes, you have **difficulty with bowel movements**. You have **moderate sleep disturbance**. Sometimes, the number of visits to **medical specialists impact your school, work, daily activities**. Due to some **pain and difficulty in moving around or using your hands**, **learning progress** and **leisure time** are impacted. Sometimes, you experience **negative emotions (such as embarrassment, anxiety, or frustration)** due to EB.
Health state 4 (11-18% BSAP)	
Wounds and other symptoms	You have **wounds over 11-18% of your body**. These wounds cover a significant area of your limbs, including hands and feet (see diagram). You **develop blisters** easily, including **mild eye blisters** and **rarely mouth erosions.** You have some **skin crusting, scabbing or erosions** on the affected parts of your body. You have a **moderate** degree of **malnutrition** and **anaemia** from wounds. You can develop **osteopenia** (your bones become more fragile).
Disease management	You require caregiver **help to dress your wounds, taking ~2 hours daily.** You are likely to require **painkillers and creams daily** for your wounds. You will need **1 or more throat stretches (dilations) per year** if you **cannot swallow**.
Impact on your life	Your anaemia symptoms can leave you feeling **tired and weak**. You have **moderate acute skin pain or discomfort**, with **itching** due to your wound(s). You have **moderate difficulty in eating and drinking**. Often, you have **difficulty with bowel movements**. You have **moderate sleep disturbance**. You will require screening for heart and kidney problems. Sometimes, the number of visits to **medical specialists impact your school, work, daily activities**. Due to moderate **pain and difficulty moving around or using your hands**, **learning progress and leisure time** are impacted; you **sometimes** require a **wheelchair.** Sometimes, you experience **negative emotions (such as embarrassment, anxiety, or frustration)** due to EB.
Health state 5 (19-24% BSAP)	
Wounds and other symptoms	You have **wounds over 19-24% of your body**. These wounds cover a significant area of your limbs and extend to your chest and abdomen (see diagram). You **develop blisters** easily, including **frequent eye blisters** and **sometimes mouth erosions.** You have a lot of open wounds, as well as **skin crusting, scabbing or erosion** on the affected parts of your body. You are at **high risk of infection** due to the severity and size of your wounds. You have a **moderate** degree of **malnutrition** and **anaemia** from wounds. Your throat is likely to **get narrower** from scar tissue. You have **osteoporosis** (your bones are more likely to break). Rarely, you can develop **kidney issues.**
Disease management	You require caregiver help to **dress your wounds, taking around 2-4 hours daily.** You require a **high dose** of **painkillers daily** and a number of other medicines to manage your symptoms related to EB. Often, **surgery** is needed to separate **fingers or toes,** if they get **fused together** by scar tissue. You will need **1 or more throat stretches (dilations) per year** if you **cannot swallow**.
Impact on your life	Your anaemia symptoms can leave you feeling **tired and weak**. You have **moderate acute skin pain or discomfort**, with **severe itching** due to your wound(s). You have **moderate difficulty in eating and drinking**. A lot of the time, you have **difficulty with bowel movements**. You have **moderate sleep disturbance** due to itch and pain. You will require regular screening for heart and kidney problems. **Frequently**, the number of visits to **medical specialists impact your school, work, daily activities**. Due to **joint pain** and high **difficulty in moving around or using your hands**, **learning progress and leisure time** are impacted; you **sometimes** require a **wheelchair**. Often, you experience **negative emotions (such as embarrassment, anxiety, or frustration)** due to EB.
Health state 6 (≥ 25% BSAP)	
Wounds and other symptoms	You have **wounds over more than 25% of your body**. These wounds cover a significant area of your limbs and a significant area of your chest and abdomen (see diagram). You **develop blisters** easily, and often have **extensive eye blisters** and **mouth erosions.** You have a lot of **skin crusting, scabbing or erosion** on the affected parts of your body. You are at **high risk of infection** due to the severity and size of your wounds. You have a **moderate** degree of **malnutrition** and **anaemia** from wounds. Your throat is likely to **get narrower** from scar tissue. You have **osteoporosis** (your bones are more likely to break). Rarely, you can develop **kidney issues.**
Disease management	You require caregiver help to **dress your wounds, taking 4 or more hours daily.**

	You require a **high dose** of **painkillers daily** for your wounds. Often, surgery is needed to **separate fingers or toes**, if they get fused together by scar tissue. You will need **2 or more surgeries/year** if you **cannot swallow**. A **feeding tube** will be inserted in your abdomen if you **cannot eat**.
Impact on your life	Your anaemia symptoms can leave you feeling **tired and weak**. You have **severe acute skin pain or discomfort**, with **severe itching** due to your wound(s). You are unable **eat and drink normally**. You are **unable** to have normal **bowel movements**. You are **mostly unable to sleep**. You will require regular screening for heart and kidney problems. **Frequently**, the number of visits to **medical specialists impact your school, work, or daily activities**. Due to **joint pains** and being unable to **move around or use your hands properly**, **learning progress and leisure time are severely impacted;** you **often** require a **wheelchair**. Often, you experience **negative emotions (such as embarrassment, anxiety, or frustration)** due to EB. You have to take a number of medications, which have **side effects** and have a significant impact on your daily life and activities.
Abbreviations: BSAP, body surface area percentage; EB, epidermolysis bullosa.	

Table 26 Carer health state descriptions (vignettes)

Health state A (5-7% BSAP)	
Wounds and other symptoms	**You are the main caregiver of a person with wounds covering 5-7% of their body.** These wounds are on bony parts of their limbs i.e. hands, feet, ankles, elbows and knees (see diagram). The person **develops blisters** easily and has **skin crusting, scabbing or erosions** on their body.
Disease management	You help **dress the person's wounds**, so that they heal. The process takes **less than 1 hour daily**. The person with EB has **low acute (temporary) skin pain or discomfort** with **itching**, especially when dressings are changed.
Impact on your life	You accompany the person with EB to their **medical visits**; **sometimes** this **impacts your work life.** Due **to a little difficulty in moving around or using their hands**, you **sometimes** aid the person with EB to **adjust to their daily activities**. Sometimes, you experience **negative emotions (such as anxiety or frustration)** due to the nature and burden of the condition.
Health state B (11-18% BSAP)	
Wounds and other symptoms	**You are the main caregiver of a person with wounds covering 11-18% of their body.** These wounds cover a significant area of their limbs, including hands and feet (see diagram). The person **develops blisters** easily and has a lot of **skin crusting, scabbing or erosions** on their body.
Disease management	You help **dress their wounds daily**, so that they heal. The process takes **2 or more hours daily**. The person with EB has **moderate acute (temporary) skin pain or discomfort** with **itching**, especially when dressings are changed. You regularly **administer treatment** for pain, itch and nutritional supplements to the person with EB.
Impact on your life	The person with EB has **moderate difficulty** with **eating and drinking normally**– you **aid their feeding daily.** They will develop **moderate sleep disturbance**; your **sleep** will be **somewhat impacted**. You accompany the person with EB to their frequent **medical visits** and in-hospital treatment for **anaemia**; **you are unable to work full-time.** Due **to moderate difficulty in moving around or using their hands**, you **often** aid the person with EB to **adjust to their daily activities**, including washing**.** Often, you experience **negative emotions (such as anxiety or frustration)** due to the nature and burden of the condition.
Health state C (≥ 25% BSAP)	
Wounds and other symptoms	**You are the main caregiver of a person with wounds covering 25% or more of their body**. These wounds cover a significant area of their limbs and a significant area of their chest and abdomen (see diagram). The person **develops blisters** easily and has a lot of **skin crusting, scabbing or erosions** on their body.
Disease management	You **dress the person's wounds daily**, so that they heal. The process takes 4 **or more hours daily**. The person with EB has **severe acute (temporary) skin pain or discomfort** with **itching**, especially when dressings are changed. You regularly **administer treatment** for pain, itch and nutritional supplements to the person with EB. They require a **high dose** of painkillers (daily) for their wounds.
Impact on your life	The person with EB is **unable to eat or drink normally**– you **aid their feeding** multiple times a day. They are **unable to sleep well** and your **sleep** will be **very impacted**.

	You accompany the person with EB to their frequent **medical visits** and in-hospital treatment for **anaemia**; **you are unable to work.** Due **to their inability to move around or use their hands**, you **must always** aid the person with EB to **adjust to their daily activities.** Often, you experience **negative emotions (such as anxiety or frustration)** due to the nature and burden of the condition.
Abbreviations: BSAP, body surface area percentage; EB, epidermolysis bullosa.	

The TTO exercise was performed with 120 members of the UK public. After removing non-traders (n=5), i.e., respondents that did not trade any time or provided the same response to all of the health states, the viable sample was n=115. The mean age of respondents was 48.0 years, with 51.3% male, and 47.8% female. Health problems were reported by 29.6% of respondents, and 2.6% lived in a rural rather than urban area. Full patient characteristics are reported in Appendix H and the TTO report.(99)

The mean utility score provided by respondents across all states was 0.63 (SD; 0.2). This is higher than the mean utility values of 0.57 and 0.511 reported in the CSS and EASE OLP, respectively, and also the mean utility score reported in Angelis *et al.* 2022. Table 27 reports the results per BSAP health state. The results for patient utilities by BSAP health state were used in the economic model as a scenario analysis, and the carer results by BSAP health state were used in the base case.

Table 27 Summary of TTO results by wound burden/severity (BSAP categories) for patient and caregiver health states

Health state (BSAP%) (N=115)	**Utility values mean (SD)**
Patient	
Health state 1 (BSAP ≤4%)	0.82 (0.2)
Health state 2 (BSAP 5-7%)	0.79 (0.2)
Health state 3 (BSAP 8-10%)	0.76 (0.2)
Health state 4 (BSAP 11-18%)	0.61 (0.3)
Health state 5 (BSAP 19-24%)	0.53 (0.3)
Health state 6 (BSAP ≥25%)	0.54 (0.3)
Carer	
Health state CG A (BSAP 5-7%)	0.85 (0.2)
Health state CG B (BSAP 11-18%)	0.76 (0.2)
Health state CG- C (BSAP ≥25%)	0.64 (0.3)
Abbreviations: BSAP, body surface area percentage; CG, caregiver; HS, health state; SD, standard deviation.	

B.4.5.4 Utility decrements of adverse reactions

Utility decrements and costs associated with specific adverse events have not been included in the economic analysis. It is believed that EQ-5D assessments will reflect the disease complications (treatment-emergent) experienced by patients with DEB and JEB. As detailed in section B.2.10, adverse events associated with Filsuvez gel usage were mostly of low severity and associated with disease complications (treatment-emergent) rather than being directly associated with Filsuvez gel or current clinical management (treatment-related).

B.4.5.5 Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of the patient utility values applied in the model for base case settings and as scenario analyses are presented in Table 28.

B.4.5.5.1 Patient utilities

Despite some data limitations the EQ-5D data collected in the OLP of the EASE trial has been applied in the base case. These values were deemed clinically representative of DEB and JEB disease burden by clinicians and patient representatives present at the multi-stakeholder panel (MSP) meeting (as described in Section B.2.3.3) and are closest to the mean EQ-5D value (0.304) for EB patients in the UK reported in Angelis *et al.* (2022).(58) The choice of base case utility values to implement into the model were a key point of discussion at the MSP meeting (Section B.3.3). The EQ-5D utility values collected in the OLP of the EASE trial were overall considered representative of the HRQoL of DEB and JEB patients by advisors on the panel. It was highlighted that the EASE trial utility values, compared with TTO and CSS values, were more applicable for quantifying HRQoL of patients in higher severity health states whilst also demonstrating the burden of the disease through differences between the least severe and most severe health states.

Although selected for the base case, limitations with the EASE EQ-5D data are acknowledged. No published value set currently exists for the EQ-5D-Y in the UK, and consequently the UK adult EQ-5D-3L tariff has been applied, generating additional uncertainty around utility values generated for children based on data from the trial. As discussed in Section B.4.5.1, both the EQ-5D-Y and the EQ-5D-5L were collected

in the OLP of the EASE trial as a protocol amendment, meaning that there are only utility values collected for patients being treated with Filsuvez gel, and there are overall limited observations associated with high proportions of missing values. Given that EQ-5D data is available from the pivotal trial (albeit with some data limitations) this has been used in the base case, pooling all EASE utilities together and applying the same values for both and adults and children. Appendix P provides an overview of EASE-derived EQ-5D data and associated analyses.

The TTO and CSS utility values have been considered as scenario analyses in the economic evaluation. The TTO offers a useful alternative source of utility estimates, where heath state descriptions were designed based on carefully constructed and clear PRO (including the iscorEB) alongside having patient/ carer input and clinical validation. The descriptions in the vignettes are based on robust patient/ carer and clinical experience evidence and are useful for understanding the differences in wound burden and disease severity states in DEB and JEB from the patient/ carer perspective therefore complement the evidence derived from the generic EQ-5D.

Both the TTO and CSS generate similar utility estimates per health state when compared with each other although the absolute values are considerably higher than the EASE EQ-5D utility values for each health state. The absolute utility values in the TTO and CSS were discussed at the multi-stakeholder panel meeting (section B.3.3) and considered by the experts attending this as potential overestimations of the HRQoL experienced by EB patients. They are also higher than values published in Angelis *et al.* 2022.(58) However, as shown in Table 28, the relative values are not dis-similar across the sources, but the EQ-5D values appear to better reflect the severity and HRQoL impact of DEB and JEB, and better reflect reality in that patients experiencing relatively low wound burden and BSAP have a significantly compromised HRQoL (e.g. 0.56 at 0-4% BSAP), with higher wound burden demonstrating a very poor HRQoL (0.08 [close to death] at ≥25% BSAP). This supports that DEB and JEB is a severe and chronically disabling disease.

Table 28 Summary of utility values for cost-effectiveness analysis

BSAP Health State	Base Case (Regressed EASE)	Scenario (TTO)	Scenario (Regressed CSS combined patient and proxy)
Health state 1 (BSAP ≤4%)	0.56	0.82	0.69
Health state 2 (BSAP 5-7%)	0.51	0.79	0.64
Health state 3 (BSAP 8-10%)	0.46	0.76	0.59
Health state 4 (BSAP 11-18%)	0.35	0.61	0.54
Health state 5 (BSAP 19-24%)	0.23	0.53	0.49
Health state 6 (BSAP ≥25%)	0.08	0.54	0.44
Abbreviations: BSAP, body surface area percentage; CSS, cross sectional study; TTO, time trade off			

B.4.5.5.2 Carer utilities

A summary of the carer utility values applied in the model for base case settings and as scenario analyses are presented in Table 30. The number of carers per patient was also explored in the model; members of the MSP validated that DEB and JEB patients in higher severity health states would require more carers, where it was discussed that most severe patients would ideally have two full-time carers.(98)

This notion has also been explored in the literature and applied in previous technology appraisals. (113) On this basis, an estimate of 1.78 carers per patient was considered appropriate in the DEB and JEB context, and it was noted that appraisals HST17 and HST11 included this (114, 115); hence this was adopted as representative of the average number of parents per household (minus the patient).(113) In the base case, 1.78 was the number of carers assumed for the two most severe BSAP states, with lower numbers of carers per patient assumed for relatively less severe BSAP states (based on MSP feedback).(98) A scenario is also explored where one carer is assumed for each patient, regardless of severity (Table 29).

The TTO is a key source of data for estimating caregiver utilities for the economic evaluation, detailed in Section B.4.5.3.2. Given limited carer utility values in EB stratified by disease severity, base case caregiver utility values are sourced from the TTO study. Health states 1 and 2, 3 and 4, and 5 and 6 are assumed to be respectively equal in terms of carer HRQoL, with estimates for utility values ranging from 0.85 in the least severe health state, to 0.64 in the most severe health state (Table 30). These values are, as expected, higher than those for patients, and maybe higher than those

that would be generated by use of an EQ-5D instrument if that were completed by carers of EB patients in the UK, but the relative differences across disease severity states appear to have face validity. It is assumed there are no differences in carer utilities by adult or children.

Table 29 Number of Carers

State	Base Case (Scaling per health state)	Same number per health state
Health state 1 (BSAP ≤4%)	0.5	1
Health state 2 (BSAP 5-7%)	0.5	1
Health state 3 (BSAP 8-10%)	1	1
Health state 4 (BSAP 11-18%)	1	1
Health state 5 (BSAP 19-24%)	1.78	1
Health state 6 (BSAP ≥25%)	1.78	1
Abbreviations: BSAP; body surface area percentage		

A scenario analysis has been included that explores caregiver utility applied as observed in the CSS (described in B.4.5.3). The EQ-5D was administered to caregivers (n=11) online, to self-complete, assessing their own HRQoL, and categories by patient BSAP category. Mean CSS carer utility results per health state are reported in Table 30.

Table 30 Summary of carer utility values

State	Base Case (TTO)[a]	Scenario (HST 8)
Health state 1 (BSAP ≤4%)	0.85 (0.21)	0.94
Health state 2 (BSAP 5-7%)	0.85 (0.21)	0.94
Health state 3 (BSAP 8-10%)	0.76 (0.23)	0.96
Health state 4 (BSAP 11-18%)	0.76 (0.23)	0.96
Health state 5 (BSAP 19-24%)	0.64 (0.27)	0.84
Health state 6 (BSAP ≥25%)	0.64 (0.27)	0.84
Abbreviations: BSAP; body surface area percentage; TTO, time trade off *[a] Values were elicited for three health states, using groupings of health state 1 and 2, 3 and 4, and 5 and 6.*		

B.4.6 Cost and healthcare resource use identification, measurement, and valuation

B.4.6.1 Cost and healthcare resource use identified in the SLR

As outlined in section B.4.3, an SLR was conducted to identify relevant studies reporting prior economic evaluations, cost and resource use data, and HRQoL/ utility data in EB. Due to the rare nature of DEB and JEB, the inclusion criteria relating to population were widened in the SLR to include all EB subtypes. The SLR search strategy and study selection methods used to identify all relevant economic evidence, including HRQoL data, is detailed in Appendix G. This section summarises the key sources of cost and healthcare resource use data associated with EB, identified as relevant to supporting model development and data inputs for assessing the cost-effectiveness of Filsuvez gel. A more detailed overview of the studies identified reporting cost and healthcare resource evidence is detailed in Appendix I.

Cost and resource use data relevant to the decision problem and appropriate for use in the economic model, were identified from three main sources: publications reporting data from the PEBLES registry, a multinational, bottom-up costing study (Angelis *et al. 2016*), and the Amryt Pharmaceuticals-sponsored CSS.(50, 52, 60, 116, 117)

One additional publication was identified outside of the lifecycle of the SLR (Angelis *et al*. 2022). This was a reanalysis of the data collection reported in Angelis *et al*. in 2016, and is included as a data source for the economic model, as it updates and expands upon evidence provided in the earlier publication.(50, 58)

B.4.6.1.1 Angelis et al. (2016, 2022)

Angelis *et al.* 2016 reported cost estimates (cost year 2012) for drugs, carers, hospitalisation, transport, social care service, medical tests, medical visits, health material, early retirement, and productivity loss, for patients with EBS, JEB, and DEB, but did not report the associated resource use data.(50) Data were reported for EB patients as aggregate values from eight European countries (Spain, France, UK, Bulgaria, Hungary, Germany, Sweden, Italy) as well as by individual country. Most UK patients in the study (62.8%) had EBS which lies outside of the population defined in the decision problem. For this reason, Angelis *et al.* 2022, which reported data for only

the DEB population from the study, offered a more appropriate estimation of costs for use in the economic model.

Angelis *et al. 2022* reported aggregate data for DEB patients separately from five countries (France, Germany, Italy, Spain, UK). UK cost estimates (n=15) were mostly driven by high direct non-medical costs (UK mean €26,415 (£23,177 equivalent), SD: €39,526 (£34,680 equivalent)), with patients requiring support from carers at home. Total direct medical costs for the UK were a mean of €8,201 (£7,196 equivalent) (SD €7,169 (£6,290 equivalent)), and indirect costs a mean of €9,930 (£8,713 equivalent) (SD €16,893 (£14,822 equivalent)). The total mean UK cost, including wider societal costs, was reported to be €44,546 (£39,085 equivalent) (SD €48,392 (£42,459 equivalent)). Full itemised costs from this study (converted and inflated to 2021 GBP for inclusion in the cost effectiveness analysis), are shown in Table 31.(50, 58, 118, 119)

Table 31 Summary of Angelis *et al.* 2022 itemised costs for the UK

Cost component	Euros (2020 prices)		GBP (2021 prices) [a]	
	Mean (EUR)	SD (EUR)	Mean (GBP)	SD (GBP)
Direct health and social care costs:				
Prescription drugs	€ 66.00	€ 76.00	£59.02	£67.97
Medical tests	€ 446.00	€ 719.00	£398.86	£643.00
Medical visits	€ 3,825.00	€ 5,172.00	£3,420.68	£4,625.30
Hospital admissions	€ 1,326.00	€ 4,102.00	£1,185.84	£3,668.40
Health material	€ 2,502.00	€ 992.00	£2,237.53	£887.14
HC transport	€ 35.00	€ 135.00	£31.30	£120.73
Professional care	€ 2,323.00	€ 8,996.00	£2,077.45	£8,045.09
Indirect costs:				
Non-HC transport	€ 57.00	€ 96.00	£50.97	£85.85
Main informal Carer (non-professional carers, who are often relatives)	€ 21,246.00	€ 35,264.00	£19,000.21	£31,536.45
Other Informal Carers (non-professional carers, who are often relatives)	€ 2,790.00	€ 7,666.00	£2,495.09	£6,855.67
Other societal costs:				
Patient's productivity loss	€ 66.00	€ 255.00	£59.02	£228.05
Patient's early retirement	€ 9,864.00	€ 16,932.00	£8,821.34	£15,142.22

Abbreviations: HC; health care, SD; standard deviation;
[a] Bank of England conversion rate used and inflated to 2021 prices

Across both Angelis *et al.* 2016 and Angelis *et al.* 2022, it is unclear which resource items are included (or excluded) within each of the cost categories reported.*(50, 58)* For example, the definition of "materials" is not reported, and therefore it is unclear as to what this category includes. Angelis *et al.* 2022 acknowledges, as a limitation of the study, that bandage costs were not assessed, however whether materials include items such as dressings and/ or emollients is not reported. Furthermore, it is unclear whether hospital visits correspond to inpatient, outpatient or accident and emergency visits, however with knowledge of the disease environment we can make assumptions on what falls under each category, and it is a useful source to give a full picture of the costs of EB.

B.4.6.1.2 PEBLES registry

The PEBLES study collected cost estimates for RDEB patients only, disaggregated by RDEB subtype.(52, 116, 117) The study reported annual dressing costs and limited formal carer costs. Annual costs for bandages and dressings ranged from £93 and £542,543 amongst n=55 patients with recessive dystrophic EB (RDEB), and from £487 to £76,567 amongst n=17 patients with RDEB Generalised Severe (RDEB-GS). Pillay *et al.* 2020 reported a formal carer cost of £12.50 per hour for all RDEB patients (n=53) at 2017 prices.(52) Limited data were reported in the three publications; however, it is useful data on the average cost of dressings for patients.(52, 116, 117)

B.4.6.1.3 Cross-sectional survey of EB burden (resource use)

As a secondary objective, the CSS provided estimates of resource utilisation relating to patient wound care and skin characteristics, medical care, and the personal financial impact associated with EB (Section B.4.5.3.1).(60) Cost estimates derived from the CSS are presented by self-reported BSAP health state (Section B.4.5.3.1), with the one KEB patient removed to represent the licensed indication.

Resource use associated with dressing change, an important element of wound care, was also identified in the form of time spent to perform dressing changes and number of dressing changes per week. The mean time to perform dressing changes for self-reported patients was 4.54 hours (SD: 2.16) with a mean range of 1 hour for patients with BSAP Health State 1 (category of ≤4%), to 3.75 hours for patients with a BSAP Health State 6 (category of ≥25%). The mean number of dressing changes per week was 4.83 (SD: 2.19) with a mean range of 1 for patients with a BSAP Health State 1

(category of ≤4%), to 5.5 for patients with a BSAP Health State 6 (category of ≥25%). For respondents who proxy-reported for EB patients (n=11), the mean time to perform dressing changes was 1.73 hours (SD: 0.9) and the mean number of dressing changes per week was 4.54 (SD: 2.16). Full resource use by BSAP is reported in the Cross-Sectional Study report.(60)

The frequency of outpatient visits, emergency room visits, inpatient stays, physician visits, and nurse visits over the past 12 months was reported for patients and proxy based on their BSAP health state, reporting how key secondary care medical resource items vary by severity.(60) The main finding is that key secondary medical resource usage increases, as severity increases. Findings relating to these secondary care medical resource items are summarised in Appendix I by self-reported patients and proxy respondents.

The CSS collected a range of resource use observations directly from EB patients, highlighting the increased use of healthcare services as EB wound severity increases. Although most of the participants in the CSS were from the US, the general findings demonstrate clearly that EB patients require extensive care, including regular hospital and specialist centre visits with this likely to be the case also in the UK (as supported by experts at the MSP). However, the specific values elicited for healthcare resource use are unlikely to be generalisable to a cost effectiveness analysis performed from a UK healthcare payer perspective. For carer time spent changing dressings and frequency of dressing changes, this data is limited by the number of observations to certain health states, resulting in unexpected non-linear results. Given more robust UK focussed values from the SEE, the resource use values from the CSS have not been applied in the economic model, although the study does support the findings from the SEE, which reflect the wide-ranging cost impact of DEB and JEB associated with wound burden/ disease severity.(60, 97)

B.4.6.2 Use of Structured Expert Elicitation to support resource use estimates

An SEE exercise with EB experts was performed to supplement the cost and resource use data identified in the SLR (Section B.4.6.1), amongst other objectives (B.3.2). Resource use assumptions, in particular the use of dressings and bandages, were explored at Stage 2 of the SEE (Section B.3.2).(97)

Participants in the SEE recommended that the number of dressings applied per visit should be assumed to increase in line with total BSAP. The estimates from the SEE were that for patients aged 0 to 4 there are, on average, no dressings applied in the least severe health state (BSAP ≤4%) to an estimated 6 dressings in the most severe health state (BSAP ≥25%). For patients aged 5 to 14, it was estimated that there are, on average, 2 dressings applied in the least severe health state (BSAP ≤4%) and up to 30 dressings in the most severe health state (BSAP ≥25%). For patients aged ≥15 there are estimated to be, on average, 5 dressings applied in the least severe health state (BSAP ≤4%) up to 35 dressings in the most severe health state (BSAP ≥25%). For further details of elicited values see Appendix N.(97)

Results from the SEE, supported by data analysis from EASE and the CSS, suggested that hours spent (per month) changing dressings ranged, on average, from 21 in the least severe health state (BSAP ≤4%) to 84 in the most severe health state (BSAP ≥25%). For further details of elicited values see Table 32. There was general agreement that, even if severity remained unchanged, then dressing changes would become more frequent as patients grow older (applies to children and adults). Results from the SEE suggested that the need for professional assistance with dressing changes increases with increasing severity of EB, as data was elicited as to who performs dressing changes (self, family or professional).

The SEE results also confirmed the CSS results that the number of annual visits to specialist (outpatient) clinics increases with increasing severity of EB, Table 32. The pattern and volume of visits is similar for all EB sub-types, although it is noted that DDEB patients attend much less frequently than patients in other subtypes.(60, 97)

Table 32 SEE dressing changes and outpatient visits outputs

	Health state 1 (BSAP ≤4%)	Health state 2 (BSAP 5-7%)	Health state 3 (BSAP 8-10%)	Health state 4 (BSAP 11-18%)	Health state 5 (BSAP 19-24%)	Health state 6 (BSAP ≥25%)
Dressing changes						
Monthly carer time (formal and informal carer hours)	21	27	30	36	54	84
Patients who require no assistance with dressing changes*	55%	55%	34%	34%	14%	14%

	Health state 1 (BSAP ≤4%)	Health state 2 (BSAP 5-7%)	Health state 3 (BSAP 8-10%)	Health state 4 (BSAP 11-18%)	Health state 5 (BSAP 19-24%)	Health state 6 (BSAP ≥25%)
Patients who require family member assistance with dressing changes	46%	46%	50%	50%	51%	51%
Patients who require professional assistance with dressing changes	1%	1%	16%	16%	36%	36%
Outpatient visits						
Monthly outpatient visits (hospital)[a]	0.28	0.32	0.40	0.50	0.68	0.83

Abbreviations: BSAP. Body surface area percentage
[a] SEE elicited these values as an annual rate, these have been divided by 12 to calculate a monthly rate for consistency and use in the model.

The estimates from the SEE were used to provide base case resource use and cost estimates by BSAP health state, and alternate values from Angelis *et al*. (2022) were applied as a scenario analysis.(58)

B.4.6.3 Intervention and comparator costs and resource use

An acquisition cost of £275.33 per [23.4g] tube (list price) of Filsuvez gel is applied in the model. Filsuvez gel usage was observed in the EASE DBP and OLP. The mean tube usage per month observed across the DBP and 24-month OLE was [redacted] tubes.(87) This is applied in all health states in the base case to calculate costs associated with Filsuvez gel usage.

As Filsuvez gel is a topical treatment, there are no additional healthcare professional costs assumed to be associated with administration or monitoring.

Amryt Pharmaceuticals have submitted a patient access scheme (PAS) application to PASLU, which consists of a [redacted]

Outside of the “drug” category reported in Angelis *et al.* (2022),(58) accounting for painkillers, emollients etc., no other drug acquisition costs are associated with the CCM comparator arm.

B.4.6.4 Health-state unit costs and resource use

B.4.6.4.1 Base case

Background health state costs applied in the model have been estimated using itemised costs from published bottom-up costing studies, supplemented with values elicited from the SEE study to apply divergent levels of resource use according to patient health state. The SEE provided mean frequencies for number of dressings, dressing times and outpatient visits.(97)

Costs associated with wound dressings were derived from PEBLES (Pillay *et al.* 2020), which reported a mean annual cost of £45,884 per patient.(52)

To reflect the clinical expert assumption that dressing usage would vary in line with the total BSAP covered by wounds, variation around this mean by health states was applied according to the distribution of estimated mean dressing changes per visit, elicited as part of the SEE.(97) Expert responses suggested a ten-fold difference in the expected levels of resource use between the highest and lowest severity health states (Table 33). Mean estimated numbers of dressing changes per visit aligned well with the BSAP ranges associated with each of the six model health states, supporting the face validity of these estimates. These ratios were applied as adjustment factors relative to the PEBLES mean annual dressing cost of £45,884, by assuming a uniform distribution of patients across health states.(52)

Table 33 SEE number of dressings applied per visit combined with PEBLES annual dressing cost

	Health state 1 (BSAP ≤4%)	Health state 2 (BSAP 5-7%)	Health state 3 (BSAP 8-10%)	Health state 4 (BSAP 11-18%)	Health state 5 (BSAP 19-24%)	Health state 6 (BSAP ≥25%)
SEE: number of dressings applied per visit (mean estimate) [a]	2.33	4.00	7.33	11.67	17.00	23.67
SEE: Ratio of dressings per visit relative to health state 1	1.0	1.7	3.1	5.0	7.3	10.1
PEBLES mean dressing cost per patient per year, scaled by SEE distribution [b]	£9,733	£16,685	£30,589	£48,665	£70,911	£98,720
PEBLES mean dressing cost per patient per year, weighted using SEE number of dressings, inflated to 2021 [c]	£10,122	£17,352	£31,813	£50,611	£73,748	£102,669

Abbreviations: BSAP, Body surface area percentage; PEBLES, Prospective Epidermolysis Bullosa Longitudinal Evaluation Study; SEE, structured expert elicitation

[a] N=2 experts

[b] Weightings applied to PEBLES mean of £45,883.85 (Pillay et al., 2020), assuming Pillay patients are distributed equally across health states

[c] Inflated using PSSRU 2021(120)

The data elicited from the SEE as to who performs dressing changes (self, family or professional), were combined with the times elicited to create a separate time per BSAP for formal (professional assisting with dressing changes), and informal (family assisting with dressing changes) carers. The number of informal and formal hours per month by BSAP health state, has been combined with the PEBLES carer cost per hour (Pillay *et al.* 2020), to calculate the base case of carer costs per month, detailed in Table 34.(52)

The number of outpatient visits and the time spent changing dressings have been used in combination with a unit cost to provide a cost per health state. For outpatient visits, the elicited times have been combined with a unit cost of £137.00 of outpatient visits (PSSRU 2021) to calculate a monthly cost that was used in the base case in the economic model, detailed in Table 34.(120)

Table 34 Dressing time and outpatient costs (SEE-derived)

	Health state 1 (BSAP ≤4%)	Health state 2 (BSAP 5-7%)	Health state 3 (BSAP 8-10%)	Health state 4 (BSAP 11-18%)	Health state 5 (BSAP 19-24%)	Health state 6 (BSAP ≥25%)
Dressing changes						
Monthly informal carer hours spent changing dressings [d]	9.66	12.42	15	18	27.54	42.84
Monthly formal carer hours spent changing dressings [d]	0.21	0.27	4.8	5.76	19.44	30.24
Monthly informal carer hours spent changing dressing, costed [a]	£128.28	£164.94	£199.20	£239.04	£365.73	£568.92
Monthly formal carer hours spent changing dressing, costed [a]	£2.79	£3.59	£63.74	£76.49	£258.16	£401.59
Outpatient visits						
Monthly outpatient visits (hospital) [c]	0.28	0.32	0.40	0.50	0.68	0.83
Monthly outpatient visit costed (hospital) [b]	£38.36	£43.84	£54.80	£68.50	£93.16	£113.71

Abbreviations: BSAP, Body surface area percentage
[a] Costed using unit cost of carer from PEBLES (Pillay et al. 2020) of £12.50 an hour, inflated to 2021 costs using PSSRU
[b] Costed using unit cost of outpatient visit (PSSRU Unit costs of health and social care 2021: Weighted average of all outpatient attendance) of £137.00
[c] SEE elicited these values as an annual rate, these have been divided by 12 to calculate a monthly rate for consistency and use in the model.
[d] Calculated using the proportions of who performs dressing changes, combined with the hours spent on dressing changes, both elicited in the SEE.

Costs for dressings, time spent on dressing changes and outpatient visits, elicited from the SEE, have been applied to each health state to create a total cost applied to both arms, detailed in Table 35. Other background costs associated with the disease (e.g. inpatient treatments) are assumed to be equal across the health states, so do not result in differences in incremental costs. This is expected to be a conservative assumption in the absence of data to the contrary.

Table 35 Base Case background costs (annual, per patient)

Health State	Base Case Costs (Applied to both arms)
Health state 1 (BSAP ≤4%)	£10,614.08
Health state 2 (BSAP 5-7%)	£17,919.02
Health state 3 (BSAP 8-10%)	£33,190.40
Health state 4 (BSAP 11-18%)	£52,297.28
Health state 5 (BSAP 19-24%)	£77,781.78
Health state 6 (BSAP ≥25%)	£108,569.11
Abbreviations: BSAP, body surface area percentage	

B.4.6.4.2 Scenario analysis

To explore sensitivity to alternative costing approaches, Angelis *et al.* 2022 UK cost estimates, reported in Table 31, are used as a comprehensive cost of the disease in a scenario analysis.(58) These costs have been applied in additional scenarios.

Two scenarios were developed to explore the impact that SEE-derived assumptions on resource use had on the ICER. An extreme scenario is that use of Filsuvez gel has no impact on resource use even when patients spend longer in lower severity health states than they would in receipt of CCM alone. A further scenario tests the impact that would be observed if those in the most severe health states (HS 5 & 6) received three times as many resources as those in the least severe health states (HS1 & 2)

with those in intermediate health states (HS 3 &4) receiving twice as many dressings as those in the least severe health states (HS 1 & 2). This portrays an arbitrary 3:1 HS-modifier, exploring a positive correlation between health state and resource use that is less pronounced than that applied in the base case. Both analyses are explorative scenarios designed to test the influence of SEE-derived assumptions on the ICER rather than reflecting alternative evidence sources. Weightings were applied to the mean cost in Angelis *et al.* (2022) to apply the costs relevant to each severity health state

A further scenario analysis was conducted including the addition of productivity loss and early retirements costs (see Table 31) to assess the impact on cost-effectiveness of Filsuvez gel when considering a wider societal perspective.

Given more robust, UK-focussed values from the SEE, the resource use values from the CSS have not been applied in the economic model, although the study does support the findings in the SEE that there is likely to be a wide-ranging cost impact for management of DEB and JEB patients' wound burden/ disease severity.

B.4.6.5 Adverse reaction unit costs and resource use

As described in Section B.2.10, the rate of adverse events observed in the EASE trial were considered to predominantly related to the underlying EB disease and existing comorbidities recorded at baseline, and few were considered related to treatment with Filsuvez gel. There were minimal between-arm differences in safety and tolerability data collected in the 90-day DBP, and this was supported by the 24-month data collected in the OLP when all participants were treated with Filsuvez gel. Consequently, no utility decrements or resource use/ costs associated with adverse events have been estimated or included in the cost-effectiveness modelling.

B.4.6.6 Miscellaneous unit costs and resource use

No further miscellaneous costs or resource use items have been identified as being relevant to include in the cost effectiveness analysis.

B.4.7 Uncertainty

There are several areas of uncertainty associated with the nature of this rare disease and the evidence available in order to develop a *de novo* economic model (as there

are no prior economic evaluations in EB) and evaluate the cost-effectiveness of Flisuvez gel in the treatment of DEB and JEB. EB is a heterogeneous disease that can present differently between patients, and particularly between disease subtypes. Furthermore, severity and wound burden can fluctuate substantially at the individual patient level over time since EB partial-thickness wounds are dynamic in nature (as described in Section B.1.3). This makes performing clinical trials in EB and the subsequent development of an economic model to capture such heterogeneity particularly challenging. The challenges are typical of rare diseases seen at HST where there are also data limitations, and the approach taken to the economic modelling is a pragmatic one based on data availability. One advantage of EASE is that a relatively high number of patients were enrolled in the RCT, considering EB is an rare disease with orphan status (N=223 participants, from 28 countries). The selected model structure focuses on how best to capture the impact of varying DEB and JEB disease severity with the data available and translates this into HRQoL/ utility outcomes to quantify the QALY benefits for Filsuvez gel over a lifetime time horizon. In terms of strengths there is a strong body of utility data available from several sources (EQ-5D in EASE, cross-sectional study, and utility data from a TTO study that is particularly useful for providing carer utility data) to assess the utility outcomes associated with wound burden/ disease severity states. The CSS also provides rich data on disease burden especially carer burden (HRQoL and informal care time/ personal costs), and resource use, and provides a good base for further burden and PRO/ utility data collection especially in the UK (as most participants in the CSS are from the US). The SEE, and MSP meeting, has also been useful for addressing potential uncertainties in the economic model.

B.4.7.1 BSAP

There are uncertainties associated with the use of BSAP (wound burden) as the measure of outcome used in the economic model as it is a surrogate for wound burden/ disease severity and HRQoL impact, but not a direct measure of HRQoL (no suitable HRQoL measures were included in the DBP). However, comprehensive data exist in significant patient numbers from the DBP for this outcome, and clinical experts were in general agreement that it represents a reliable and objective surrogate for disease severity and consequent HRQoL impact associated with EB (Section B.4.3.2), hence suitable as a basis for health states in the economic model. The EBDASI is another

measure of disease severity that was included in the DBP, but as only one section of this instrument was used, which constrained the scoring system in order to categorise patient severity, meant there were limitations in using it as a basis for health state categorisation in the economic model (Section B.4.3.2). The vignettes developed as part of the TTO study, detailed in Section B.4.5.3.2, with patient and expert input, describe well the differences in burden that patients (and carers) face across different levels of wound burden/ disease severity, but also depicts that even with treatment that can reduce wound burden and severity, the impact on HRQoL can still be considerable.

B.4.7.2 EASE DBP follow-up and extrapolation beyond the trial

The short follow-up period of the 90-day DBP of EASE offers additional challenges for modelling HRQoL as EB is a lifelong and chronically disabling disease with variable life expectancy dependent on the type and severity of EB. Modelling the progression of BSAP over time for the Filsuvez gel arm in the economic model is assisted by the availability of EASE OLP data to 24 months with which to validate progression assumptions/ extrapolation, whereas there is only the 90-day DBP data available for the comparator arm which represents the proxy for outcomes associated with CCM assumed in the model. In the base case, the assumption is that there is no further change in BSAP over time apart from a natural disease progression rate (supported by expert opinion, DM, Table 17) and a number of scenarios have been explored for different assumptions regarding BSAP progression for the CCM comparator.

B.4.7.3 Comparator arm in EASE, control gel

The EASE study was considered the best and only relevant evidence for the economic analysis of Filsuvez gel *versus* CCM alone. The clinical SLR did not identify any other relevant RCT data for Filsuvez gel or the CCM comparator for estimating relative treatment effect, and hence an indirect treatment comparison was neither feasible nor required. However, a further uncertainty associated with using the EASE study relates to assuming the control gel arm of EASE represents an accurate proxy for the outcomes associated with CCM in clinical practice. There is uncertainty over this as there may be some control gel effect due to its excipients having wound healing properties individually (Section B.2.12). However, it may also be considered that if there is some control gel effect then that may translate at least partially to the benefit

that could be expected from following best practice in CCM for DEB and JEB in actual clinical practice. Therefore, it is unlikely that all the benefit in EASE seen for the control gel arm is a control gel effect that would not be seen with CCM in clinical practice. However, it is possible that there is some overestimation of CCM benefit by using this proxy, and to account for this, exploratory scenarios have been performed assuming some degree of control effect.

B.4.7.4 Limited data for JEB

There is uncertainty relating to composition of EB subtypes in the EASE study population. Whilst subjects from both DEB and JEB populations are represented, the proportion of the EASE sample with RDEB-S was substantially higher than expected in the overall population. This has been explored in the analysis through alternative weightings of patient groups. Additionally, the small number of JEB patients raises some uncertainties around generalisability to a real-world population. EASE data have been pooled to represent a DEB/ JEB population which increases the statistical power of analysis (a particularly important aspect when considering a rare disease like EB). However, there remains a degree of uncertainty as to whether pooled results are applicable to a JEB population where numbers of patients in the EASE trial were low. A scenario analysis has also been performed for the RDEB-S patient population alone, to explore whether the results are different from the base case using all the data.

B.4.7.5 Impact on long term complications

A further aspect of uncertainty is around the impact of treatment on longer-term complications such as SCC (see premise introduced in section B4.1). EB is a life-long condition, with a substantial impact on morbidity and mortality that are typically spread across a patient's lifetime. Over the (relatively short) time horizon of a clinical trial, there is limited capacity to observe the likely impact of treatment on complication rates. As a result of the SEE (B.3.2), it was agreed that development of sepsis, amputations, and incidence of cardiac events were not major complicating factors of EB. This implied that special provision for these would not be required as part of an economic model for Filsuvez gel. However, the true potential impact of Filsuvez gel on incidence of SCC can only be studied with longer term data collection. If it can be demonstrated that Filsuvez gel is successful in keeping individuals in less severe health states for longer periods of time, then it is possible that incidence of SCC (and other

complications) could, at least, be delayed resulting in life year, HRQoL, and so additional QALY benefits. However, whilst a theoretical possibility, this premise has not been included in the economic analysis. This remains an uncertainty which could be addressed by further prospective data collection and research.

B.4.7.6 Further data collection to reduce uncertainty

To address some of the uncertainties above, further data on outcomes associated with CCM and on disease progression (BSAP and other outcomes) associated with CCM in actual clinical practice would help to reduce uncertainty over outcomes associated with CCM of DEB and JEB. In particular, access to data collected in established sources such as the PEBLES registry, selected output from which has already been reported in Pillay *et al.* 2020, Mellerio 2020, and Mellerio 2017, are likely to provide valuable insight.(52, 116, 117) As this database matures, it is expected that further analysis will capture important aspects of CCM and EB outcomes, including PRO and HRQoL outcomes, not yet been fully explored.

PEBLES data is captured as part of patients' regular clinical care, to provide longitudinal record of the EB progression. The data collected on natural history of the disease, if accessible, could provide useful insights and a base to collect data on the risk of complications of the disease including SCC, and disease progression. These are areas that have been explored in the SEE, therefore individual real world prospective data would help to reduce uncertainties in this area.

The PEBLES data identified in the economic SLR in terms of cost and resource use, as detailed in B.4.6.1, was in the form of two abstracts and one slide set, therefore provides limited information for use in the economic model.(116) The three records identified provided annual dressing costs as a mean and a range for the RDEB population and RDEB subtypes, with various data collection time points recorded. The range of annual dressing costs reported was vast but this represents the true range between the RDEB population, reflective of heterogeneity in wound care.

Due to the large range and extreme minimum and maximum values, this data could not be separated into the BSAP health states for use in the economic model. Therefore, the SEE elicited values were used to provide weightings to estimate the costs per health state. Access to the PEBLES registry data and further real-world

prospective data collection would be extremely beneficial and would allow more certainty in current clinical management costs between the BSAP health states. This should help reduce the impact of uncertainties in the model relating to health state costs.

In addition, as mentioned above, the CSS provides a useful source of burden data in EB and could be used (working with patient bodies) as a base also for prospective data collection in the UK on patient/ carer burden, PRO/ HRQoL data, and resource use data relating to current management, and impact of the introduction of Filsuvez gel.

B.4.8 Managed access proposal

Amryt Pharmaceuticals would be willing to discuss commercial arrangements and managed access arrangements, especially regarding further data collection prospects of the sort outlined above in B.4.7, to address areas of evidence uncertainty.

B.4.9 Summary of base-case analysis inputs and assumptions

B.4.9.1 Summary of base-case analysis inputs

The base case for the economic analysis is driven by the premise that Filsuvez gel used as part of the routine care of partial-thickness wounds in patients with DEB and JEB, will accelerate wound healing and reduce total body wound burden (BSAP). Through continued use, this reduction in wound burden is estimated to be maintained at a lower level than with CCM alone, and hence contribute to meaningful improvements in patient (and carer) HRQoL, over a lifetime horizon (Section B.2.12).

The base case settings applied in the economic model are summarised in Table 36.

Table 36 Summary of base case variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Age	6 months at model baseline, to reflect intended license.	Alternate values of 0.06 years (21 days old) as per youngest eligible patient in EASE protocol and 16.67 years (average	B.2.3.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
		age at EASE baseline) explored in scenario analyses	
Time Horizon	Lifetime (50 years)	Alternate time horizons explored from 30-90 years	B.4
Cycle Length	30 days	No alternate cycle lengths explored in scenario analyses	B.4
Half Cycle Correction	Applied	No half cycle correction applied as a scenario	B.4
Annual Discount Rate (Costs)	3.5%	Scenario exploring annual discount rates of 0%, 1.5%, and 6% are explored	NA
Annual Discount Rate (QALYs)	3.5%	Scenario exploring annual discount rates of 0%, 1.5%, and 6% are explored	NA
Transitions	Base Case transitions based on mean distribution method	EASE observed transitions tested in a scenario	B.4.4.1
Long Term Extrapolations	CCM transitions only for a 90 period (as per EASE), Filsuvez gel patients transition for 12 months in the model, based on EASE 12-month OLP data and validated with the aggregate 24-month OLP data.	Alternate transition periods explored in scenario analysis	B.4.4.1
EB Subtype Distribution	As per EASE Baseline	A scenario exploring subtype distributions reported in Petrof *et al.* 2022(7) is explored. Alternate scenarios weighting each subtype to 100% of patients have also been explored.	B.2.3.2
Mortality Estimates	Long term mortality estimates per EB subtype derived from Petrof *et al.* 2022	Alternate mortality estimates elicited from SEE explored in scenario analysis	B.4.4
Monthly Tube Usage	[redacted] tubes per month, reflecting mean usage across EASE DBP and 24-month OLP visits, where received	Regressed tubes per health state, increasing with health state severity explored in scenario analysis	B.4.6.3

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Patient Utility Values	Regressed EQ-5D values elicited from EASE	Alternate values for patient utility values include the TTO and CSS utility values. Utility values are varied in probabilistic sensitivity analyses, randomly sampling values using a beta distribution.	B.4.5.5
Carer Utility Values	Included from TTO study. The number of carers varied by severity of patient from 0.5 in the lower severity health states to 1.78 in the higher severity health states (upper carer number based on previous HST precedence and expert opinion).	Carer utilities not applied in scenario analysis	B.4.5.5
Costs	SEE-derived resource estimates for dressings, time spent on dressings and outpatient visits – combined with relevant unit cost estimates	Costs are varied in probabilistic sensitivity analyses, randomly sampling values using a gamma distribution. Hypothetical cost weights (e.g. a 3:1 HS-modifier) by health state have been applied to resource estimates including tests, hospitals, materials etc. as per Angelis *et al*. 2022.These have been explored in scenario analysis. A further scenario analysis was conducted including the addition of productivity loss and early retirements costs (see Table 27) to assess the impact on cost-effectiveness of Filsuvez gel when considering a wider societal perspective	B.4.6.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Abbreviations: CSS, cross sectional study; EB, epidermolysis bullosa; EQ-5D, EuroQol 5 dimension.			

B.4.9.2 Assumptions

B.4.9.2.1 Disease progression

Assumption: Under current clinical management, estimated changes in BSAP across a cohort of patients by EB subtype are as follows:

- RDEB-S [1.3% increase in BSAP per year]
- RDEB-O [0% increase in BSAP per year]
- DDEB [0% increase in BSAP per year]
- JEB-O [0% increase in BSAP per year]

Justification: As part of the SEE process (Section B.3.2) experts were asked to estimate disease progression in terms of BSAP over time, for each EB subtype included in the model (RDEB-S, RDEB-O, DDEB, JEB-O).

Appendix N highlights the aggregated results, combining individual clinician responses into a mean estimate. For RDEB-O, DDEB, and JEB-O, it was agreed that BSAP progression in these patients would be relatively flat over a lifetime horizon, therefore for simplicity, a 0% increase per year in terms of BSAP has been applied.

For RDEB-S patients, clinician responses were aggregated and the mean trendline (Appendix N), demonstrates a linear 1.3% increase in BSAP per year. All clinicians agreed that this is a good estimate of RDEB-S patient trajectory, however this increase would likely plateau around age 40 (50%). Therefore, in the model, a 1.3% increase per year is applied for RDEB-S patients up until age 40, where BSAP flattens.

B.4.9.2.2 Clinical effectiveness

Assumption: The clinical effectiveness of Filsuvez gel is generalisable across EB types (JEB, DDEB, RDEB)

Justification: There is limited capacity for subgroup analysis based on EASE due to low patient numbers (JEB, DDEB). However, no statistical significance was found

between groups when assessing hazard ratios. This assumption was tested during expert engagement in the MSP (Section B.3.3), and there was consensus that there is no clinical rationale as to why wound healing should be different across EB subtypes.

Scenario analyses (e.g. restricting CE analysis to RDEB-S) were undertaken to explore the impact of this assumption.

B.4.9.2.3 Mortality

Assumption: Complications associated with EB lead to premature death in a majority of patients with RDEB-S. Overall survival rates associated with patients receiving standard of care are consistent with survival analyses based on retrospective registry data published by Petrof *et al.,* 2022*.(7)*

Justification: Premature death is rarely observed in DDEB, JEB non-severe, and RDEB non-severe patients. These assumptions were tested during expert engagement in the MSP (Section B.3.3) and SEE (section B.3). Experts agreed that DDEB and RDEB non-severe patients would broadly follow general population mortality rates. For JEB non-severe, it was highlighted that the mortality profile would be slightly worse than the general population. For simplicity, general population mortality figures are assumed for DDEB, JEB non-severe, and RDEB non-severe. The uncertainty surround JEB non-severe mortality is explored in a scenario analysis, allowing JEB non-severe patients to follow a mortality profile slightly worse than the general population.

B.4.9.2.4 Health-related Quality of Life

Assumption: Carer quality of life is captured in the model, using elicited carer utility values for each health state, as per the time trade off study. Base case Total QALYs to estimate cost effectiveness are calculated by summing the total patient QALYs and the total carer QALYs. The number of carers required for patients scales per health state, ranging from an assumption of 0.5 carers in the least severe health state to two carers in the most severe health state. Carer costs and QALYs per health state are weighted accordingly.

Justification: There is a lack of evidence from the EASE trial and wider literature estimating the number of carers required per child and adult EB patient dependent on EB disease severity (BSAP). A patient representative present at the multi-stakeholder panel (described in section B.3.3) suggested that patients with severe disease would ideally be monitored by two full time carers, usually parents or close family members. Based on this and given the lack of a set precedent in prior NICE STAs/ HSTs, assumptions have been made ranging the number of carers with DEB and JEB disease severity.

B.4.10 Base-case results

B.4.10.1 Base-case incremental cost-effectiveness analysis results

Base case cost effectiveness results are reported in Table 37, as per the base case model settings highlighted in section B.4.9, Table 36.

Applying a [redacted] to the Filsuvez gel list price (£275.33 per 23.4g tube) results in a [redacted] over a lifetime horizon, results in total discounted costs associated with Filsuvez gel of £1,155,726 compared to £939,290 for current clinical management, with incremental costs of £216,436. Filsuvez gel is associated with a discounted QALY gain of 2.3 versus current clinical management. The base case ICER applying the PAS discount is £95,980/ QALY for Filsuvez gel versus CCM.

As described in section B.4.1, the primary premise behind the economic evaluation of Filsuvez gel is that it leads to improvements in quality of life in DEB and JEB patients, and their carers. This is achieved in the economic model through a reduction in wound burden (as proxied by BSAP) and hence relative disease severity. Total undiscounted QALY gains of 4.6 for Filsuvez gel are observed *versus* CCM applying base case settings. Whilst this is a meaningful health benefit *per se*, very high QALY gains are not to be expected in such a disease which remains chronic, recurring, and disabling, and especially for a treatment that does not influence mortality risks (premise 1, detailed in B.4.1). These base case results demonstrate a step–change in terms of improving QoL where there is no current treatment, aside from CCM including standard management of wounds.

Table 37 Base-case results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Without PAS ICER incremental (£/QALY)	PAS Discount	ICER with PAS
Filsuvez gel	£1,155,726	48.3	£216,436	2.3	[redacted]	[redacted]	£95,980
CCM	£939,290	46.0	-				

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 38 Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at £100,000
Filsuvez gel	£1,155,726	48.3	£216,436	2.3	0.09
CCM	£939,290	46.0	-		

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit.

B.4.11 Exploring uncertainty

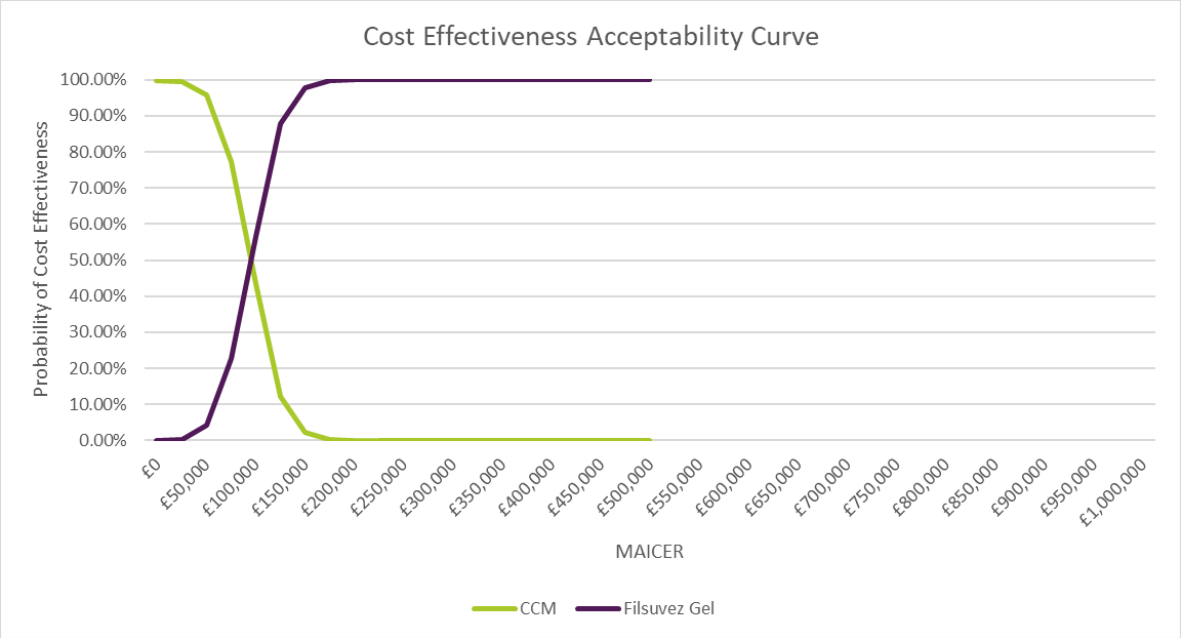
B.4.11.1 Probabilistic sensitivity analysis

Parameter uncertainty was assessed in the model through probabilistic sensitivity analysis (PSA). Parameters were assigned relevant probability distributions and varied over 1000 Monte Carlo simulations. PSA Cost effectiveness results are summarised in Table 39.

Similar to the base case, the PSA ICER is cost effective at the £100,000 per QALY gained threshold (£94,345). The cost-effectiveness acceptability curve (Figure 17) shows that Filsuvez gel has a 50% probability of cost effectiveness at the £100,000 threshold, increasing to 100% probability of cost effectiveness at the £150,000/ QALY gained threshold.

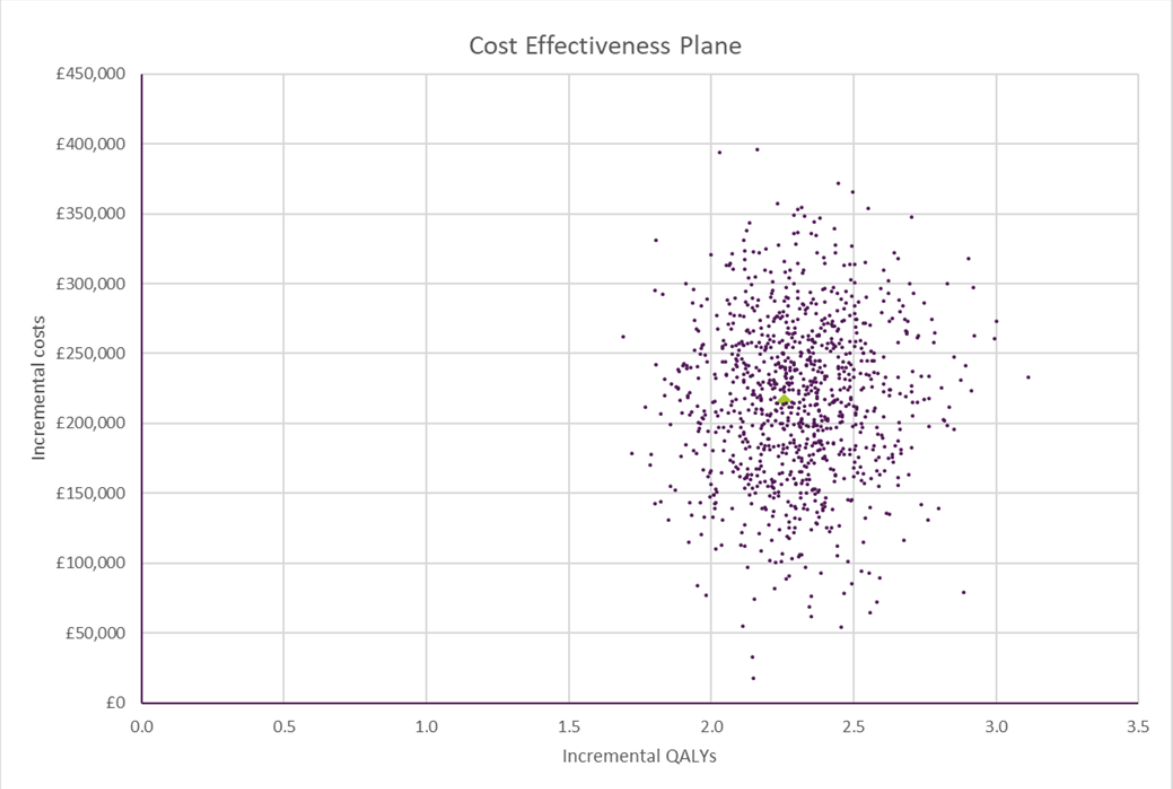
Total costs, QALYs and the ICER are similar in PSA to the base case, highlighting that parameter uncertainty in the model (standard deviations and confidence intervals), especially regarding base case costs and utility values, is not a key driver of results.

Figure 17 Cost-effectiveness acceptability curve



Abbreviations: CCM, current clinical management, MAICER, Maximum acceptability incremental cost-effectiveness ratio

Figure 18 Cost-effectiveness plane



Abbreviations: QALYs, quality-adjusted life years.

Table 39 Summary of PSA results (PAS Applied)

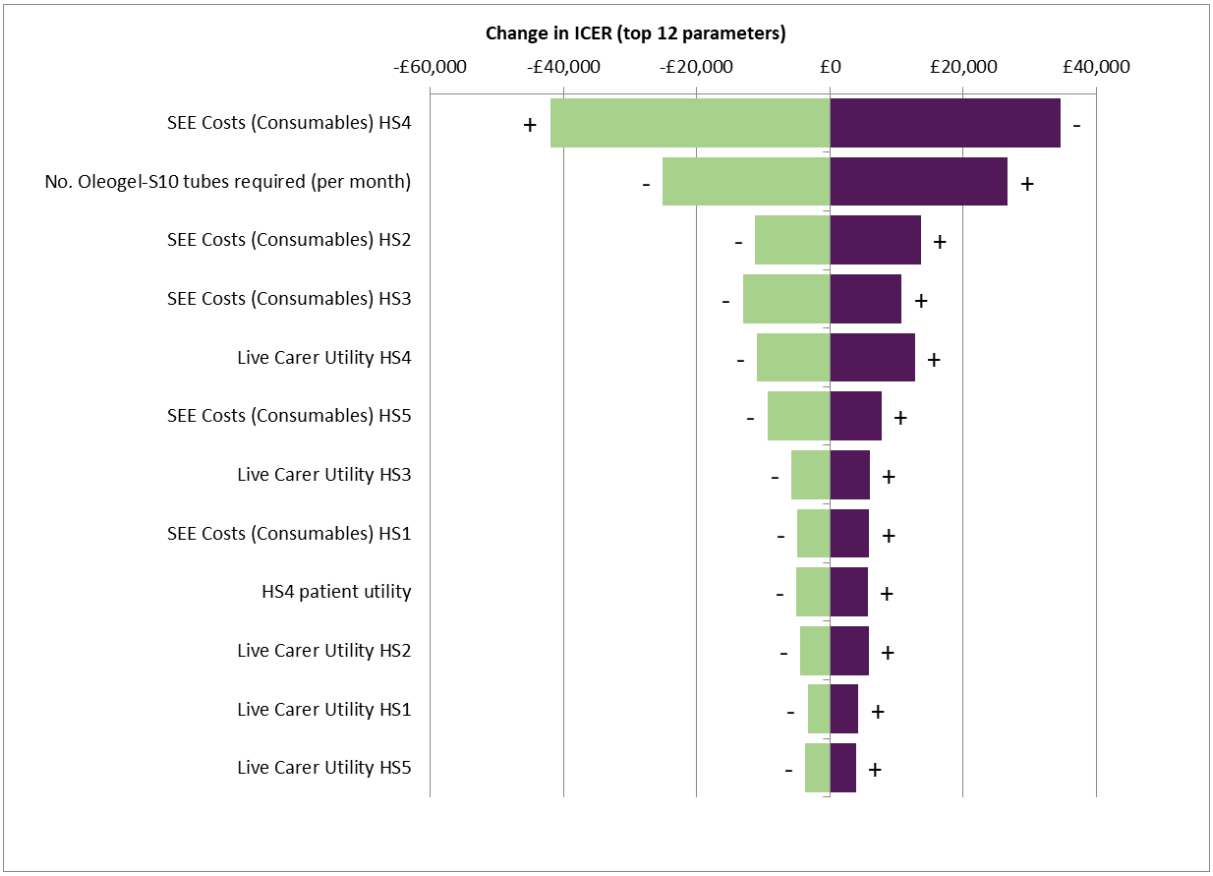
Treatment Arm	Total Costs	Total QALYs	ICER
Filsuvez gel	£1,152,657	48.11	£94,345
CCM	£935,336	45.80	-
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.			

B.4.11.2 One Way Sensitivity Analysis

One way sensitivity analysis (OWSA) was conducted, altering base case parameters in the model to plausible extreme high/low values, calculating 95% confidence intervals for each parameter using relevant probability distributions, to assess the impact on cost effectiveness results of the uncertainty associated with each model parameter. For parameters where 95% confidence intervals were not calculable, i.e. missing standard deviation/ error values, an arbitrary standard deviation of 20% of the mean value was applied. The tornado diagram (Figure 19), highlights the top 12 most influential parameters on the ICER. Consumables costs in the base case sourced from PEBLES and weighted by health state as per the SEE results (Section B.4.6.4.1) are a large driver of cost effectiveness, making up a large proportion of background costs. Varying these consumables costs to extreme high and low values has an impact on the cost effectiveness results, especially for the health state 4, consumables costs where ranging the values impacts the ICER around £40,000/ QALY in either direction. Another key driver of costs in the model is the assumption on number of tubes per health state, where increasing or decreasing the number of Filsuvez gel tubes used impacts results.

Carer utility values are also prominent in the influential parameters that impact the ICER. Given the large background costs associated with DEB and JEB, any minor movements in QALY gains for Filsuvez gel will have considerable impact on the ICER. Carer QALY gains account for 47% of incremental QALYs in the base case analysis and given assumptions surrounding number of carers per health state, this seems to have considerable impact on the ICER when varying utility values.

Figure 19 OWSA Tornado Diagram



Abbreviations: HS, health state; ICER, incremental cost-effectiveness ratio; OWSA, one way sensitivity analysis

B.4.11.3 Scenario analysis

A range of scenario analyses have been conducted, setting parameters in the model to alternate plausible values (Table 40). Key scenarios included altering standard model settings (time horizon, discount rates etc.), using alternate values for cost and utility (patient and carer) parameters, and making changes to the long-term assumptions associated with the transition period for Filsuvez gel patients. ICER results range from Filsuvez gel dominating CCM to £273k/ QALY with PAS for a pessimistic scenario relating to Filsuvez gel transition probabilities and benefit based on 90-day DBP trial data, alone.

Table 40 Scenario Analysis

Scenario (Changes from base case)	Incremental Costs (With PAS)	Incremental Costs (Without PAS)	Incremental QALYs	ICER (With PAS)	ICER (Without PAS)
Base Case	**£216,436**	[redacted]	**2.3**	**£95,980**	[redacted]
Time horizon – 30 years	£171,634	[redacted]	1.8	£96,772	[redacted]
Time Horizon – 90 years	£244,549	[redacted]	2.6	£95,651	[redacted]
Half cycle correction not applied	£216,853	[redacted]	2.3	£96,329	[redacted]
Annual Discount rate (costs) – 0%	£438,254	[redacted]	2.3	£194,347	[redacted]
Annual Discount rate (costs) – 1.5%	£313,588	[redacted]	2.3	£139,063	[redacted]
Annual Discount rate (costs) – 6%	£150,825	[redacted]	2.3	£66,885	[redacted]
Annual Discount rate (QALYs) – 0%	£216,436	[redacted]	4.6	£46,660	[redacted]
Annual Discount Rate (QALYs) – 1.5%	£216,436	[redacted]	3.3	£65,607	[redacted]
Annual Discount rate (QALYs) – 6%	£216,436	[redacted]	1.5	£139,639	[redacted]
Patient Baseline Start Age – 0.06 years	£216,150	[redacted]	2.3	£95,984	[redacted]
Patient Baseline Start Age – 16.67 years	£214,221	[redacted]	2.2	£96,023	[redacted]
Transition Approach – EASE Observed Transitions	£250,597	[redacted]	2.0	£128,044	[redacted]
Utility Source - TTO	£216,436	[redacted]	2.2	£99,000	[redacted]
Utility Source - CSS	£216,436	[redacted]	1.9	£115,906	[redacted]
Cost Source – Angelis *et al.* 2022(58) (costs weighted 3:1 instead of 10:1 between most	£425,009	[redacted]	2.3	£188,474	[redacted]

Scenario (Changes from base case)	Incremental Costs (With PAS)	Incremental Costs (Without PAS)	Incremental QALYs	ICER (With PAS)	ICER (Without PAS)
and least severe health state)					
Cost Source – Angelis *et al.* 2022(58) (same costs for each HS)	£462,281	[redacted]	2.3	£205,002	[redacted]
No caregiver utility values applied	£216,436	[redacted]	1.2	£182,385	[redacted]
Caregiver utility source – CSS	£216,436	[redacted]	1.0	£209,452	[redacted]
Number of caregivers – assume the same number per health state (1)	£216,436	[redacted]	1.9	£112,973	[redacted]
Number of caregivers – 2 caregivers for health state 5 and 6	£216,436	[redacted]	2.3	£94,338	[redacted]
Filsuvez Transition Period – 90 Days	£345,661	[redacted]	1.3	£272,944	[redacted]
Filsuvez Transition Period – 6 months	£297,074	[redacted]	1.6	£182,419	[redacted]
Filsuvez Transition Period – 2 years	£106,678	[redacted]	3.2	£33,640	[redacted]
Filsuvez Transition Period – All time points	-£73,293	[redacted]	4.2	-£17,328	[redacted]
Health States – 6 health states reduced to 3 (cost and utility inputs)	£223,199	[redacted]	2.2	£101,354	[redacted]
Population – RDEB-S patients only	£132,820	[redacted]	1.4	£98,164	[redacted]

Abbreviations: CSS; cross-sectional study; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; TTO; time trade off; QALYs, quality-adjusted life years

B.4.12 Subgroup analysis

No subgroup analyses have been carried out, although assumptions around the inclusion and relative prevalence of different EB types are explored in the scenario analyses.

B.4.13 Benefits not captured in the QALY calculation

As outlined throughout, EB presents a significant emotional and financial burden on patients and their families. The volume of care required for dressing changes alone, which for many patients takes several hours per day, presents a substantial level of impact on the primary caregiver, with opportunity costs beyond those captured in the QALY calculation. Significant productivity losses for both patients and carers arise from the impact of disease on education, workforce and other social engagement. As identified in Angelis *et al.*, 2022, there are considerable indirect costs associated with early retirement of patients (and their carers) with DEB (and by inference other EB subtypes).(58) Indeed, for UK patients, on average, this represented the largest cost item of those studied, being 52% higher than all direct medical costs. Costs associated with privately purchased formal care, where afforded, may also be borne by patients and their families.

PEBLES data are captured as part of patients' regular clinical care, to provide a longitudinal record of EB progression. The data collected on natural history of the disease, if accessible, could provide useful insights and further future data to improve knowledge and reduce uncertainty in terms of the impact of wound burden, disease severity and complications of the disease, and on disease progression in terms of wound burden and other outcomes. The PEBLES data identified in the economic SLR in terms of cost and resource use, as detailed in Section B.4.6.1, was in the form of two abstracts and one slide set, therefore providing only limited information for use in the economic model. Access to the PEBLES registry data would be extremely beneficial and would allow more certainty in current clinical management costs between the BSAP health states. This would mitigate the impact of some uncertainties in the model, and potentially allow disease complications to be included in the model. Currently, the QALY calculations in the model base case and scenario analyses are based on HRQoL gains alone from reducing wound burden/ disease severity with Filsuvez gel. If an association between BSAP or other wound burden measures could

be established in the future there may be other QALY gains not currently captured in the model, from additional utility, cost and mortality benefits of reduced complications such as SCC .

Following advice at the MSP, it was decided to incorporate informal carer costs (specifically time spent on dressing changes) within the economic model. Informal carers can be regarded as providing services that would otherwise be provided by the NHS. Inclusion of such costs is in line with the NICE health technology evaluations manual. The unit cost per hour of a formal care worker was used applied to informal carer time but it is entirely possible that this fails to account for opportunity costs of higher paid alternative employment. Impact on early retirement or lost workdays experienced by informal carers was, however, not captured in base case QALY calculations as discussed above.

Research on the incorporation of carer disutility in previous NICE HST appraisals suggests there is a strong precedence for including carer disutility, regardless of disease indication, which indicates it is an important consideration in cost-effectiveness evaluations performed for decision making purposes in the UK.(113) Due to the nature of EB, and the high level of associated wound care, carers are expected to have a high level of impact on their daily lives and quality of life.

Although EQ-5D is NICE's preferred measure of utility, there are potential limitations with its applicability in this submission. The absence of a robust measure of utility in children (partly through lack of numbers of children in studies and partly because of issues of face validity of results, where presented) creates some uncertainty as to whether full health effects have been adequately captured. Additionally, it is not clear whether EQ-5D fully captures the health impact of an incurable congenital disorder of uncommon severity. Patients may "normalise" their experiences which can result in EQ-5D values that an objective observer may consider to be unrealistically high. However, the absolute values from the EQ-5D in EASE OLP of 0.08 to 0.56 are a reasonable representation of the absolute HRQoL impact of DEB and JEB.

There are uncertainties as to whether the cost profile provided in Angelis *et al.* 2022 which relate to a UK DEB population (n=15) are representative of the costs for a DEB/ JEB population.(58) A further source of uncertainty relates to a lack of clarity as to

which resource items are included (or excluded) within each of the categories reported. For example, there is no detail as to whether ‘materials’ include bandages, dressings and emollients (this limitation was highlighted by authors of the study) nor is it clear whether hospital visits correspond to inpatient, outpatient or accident and emergency visits. This being said, Angelis *et al*. is useful in providing a comprehensive data-based average cost of the disease, with categories of direct, indirect and societal costs, and has been used as a stand-alone input for cost and resource use as part of scenario analysis.(50, 58) Further research and interrogation of emerging databases (e.g PEBLES) would provide greater clarity into the true costs of care in the target population to reduce uncertainty.

Filsuvez gel represents the first active licensed treatment for DEB and JEB for a chronically disabling and severe disease where there is high unmet need and high patient and family impact. It is also a step change in improving the current standard of care.

Uncertainties regarding existing treatment patterns, associated costs, HRQoL and complications associated with EB can undoubtedly be informed by further research, including interrogation of real-world evidence (e.g., access to PEBLES). This is particularly important in a condition with considerable unmet needs, which has no cure or, until Filsuvez gel, no licenced treatment designed to alleviate debilitating wound burden. Ongoing review of such evidence is of paramount importance to the community affected by EB in all its forms.

B.4.14 Validation

B.4.14.1 Validation of cost-effectiveness analysis

The SEE process (Section B.3.2) and the MSP (Section B.3.3) provided validation of several aspects of the cost-effectiveness analysis.(97, 98)

Prior to the SEE exercise, a clinical expert in the UK (JM) was engaged to discuss the use of BSAP as a key element within health state descriptors and consider the appropriateness and validity of alternative outcome measures to depict potential effectiveness of Filsuvez gel (Section B.3.5). As a result of these discussions, it was felt that BSAP was the most useful measure, in that it was well populated in the EASE

trial and could be directly related to accelerated wound healing (an extension of the trial's primary endpoint [proportion of patients with first complete target wound closure within 45 +/-7] days of treatment based on investigator assessment). Through further discussion, a six-way classification of BSAP categories was felt to broadly reflect an even mix of differing levels of severity as experienced by patients over the course of the EASE trial. In the absence of any validated method of capturing different severities of BSAP, these categories were also regarded as a reasonable reflection of severity across all sub types. The advantage of a six-way classification was that it enabled detection of clinically significant BSAP changes at a granular level. The disadvantage was that it inevitably meant that patient numbers in each health state are lower than would be the case with fewer health states. It was therefore considered important to consider three health states as an alternative structure (to which costs and utilities could be attached in an economic model). Discussion with the same clinical expert (JM) and further validated at the MSP, considered it would be appropriate to combine health states 1 and 2, 3 and 4, 5 and 6 when considering patient utilities and costs. However, it was recognised that clinically significant improvements in the EASE trial detected across 6 health states were somewhat masked when a 3-state configuration was applied.

Health economic modelling assumptions for natural disease progression, mortality profiles, disease complications and resource use profiles were all validated through the SEE and MSP. In each instance, the potential influence of EB type, age and health state was considered, and consensus reached.

The underlying structural aspects of the health economic model were conceived throughout a model conceptualisation process. The approach was then validated at a MSP meeting, with six experts (JM, AM, AW, SP, SN, SH, Table 17).

B.4.15 Interpretation and conclusions of economic evidence

The economic analysis presented in this review and the de novo cost-effectiveness model on which it is based represents the first such analysis performed or published in DEB and JEB, or in EB overall. With the simple [redacted] the list price for Filsuvez gel, the evidence suggests that the intervention (Filsuvez gel plus CCM) would be cost effective versus CCM alone for treatment of DEB and JEB, at the NICE HST willingness to pay threshold of £100,000 per QALY gained.

BSAP was selected as the most direct measure of overall clinical effectiveness as the measure of total body wound burden and surrogate for disease severity, and following consultation with clinical experts, specific BSAP categories were developed to reflect the varying severity of EB across six discrete health states. The transitions between these six BSAP health states in the Filsuvez gel arm and the CCM arm are the drivers of clinical effectiveness and HRQoL outcomes in the economic model.

Following a late protocol amendment, EQ-5D data were collected for adults and children subjects during the EASE OLP. but was not collected in the DBP. It is unclear whether EQ-5D fully captures the health impact of lifelong, chronic diseases such as DEB and JEB, where patients may “normalise” their experiences over time which can result in values that may underestimate the impact on HRQoL. To account for this, alternative methods of identifying patient utilities (EQ-5D in CSS- and TTO-derived utilities) were considered in scenario analyses. Economic modelling results are sensitive to the method of measuring patient utility. Regressed EQ-5D utilities are used in the base case (regressed values were used to smooth out undue influence of outliers in a small dataset). Overall, although absolute utility values from the different sources differed, the relative utility values for patients across BSAP states was reasonably consistent.

Carer HRQoL values from the TTO exercise are included in the base case as the best source of data for these utilities, by BSAP state. Based on HST precedence, the number of carers required for patients has been scaled by disease severity in the base case, from 0.5 carers in the least severe health state to 1.78 carers in the most severe health state, with carer QALYs per health state weighted accordingly. As demonstrated in scenario analyses, the ICER is sensitive to assumptions relating to the number of carers and their disutility. There are limited data relating to costs and healthcare resource use in EB, in particular relating to estimates by wound burden/ disease severity (i.e. BSAP) health state for use in the economic model. Hence, estimates derived from the SEE exercise combined with unit cost estimates from PSSRU and the PEBLES registry data are used in the base case. Clinical experts consulted confirmed that healthcare resource usage in terms of dressing changes, carer time required and outpatient visits, would increase as disease severity increases. This infers that as Filsuvez gel keeps patients in lower severity disease states for

longer, there will be a decrease in resource usage compared to CCM, and this represents a driver of cost-effectiveness in the economic analysis.

A range of scenarios were developed to explore uncertainty relating to the transition period for each treatment arm. Scenarios address the potential control gel effect in EASE and explore long term extrapolations of BSAP outcomes, for Filsuvez gel. In the base case, Filsuvez gel patients transition for up to 12 months. During the MSP meeting, clinical and patient experts thought it unlikely that there would be treatment waning effects with continued use of Filsuvez gel. Therefore, scenarios were explored, allowing patients receiving Filsuvez gel to transition for longer periods of time, but keeping CCM patients in a steady state after 90 days of treatment. For the most optimistic scenario, patients on Filsuvez gel are assumed to transition during the whole time-horizon (i.e. improvement continues over a lifetime). In this scenario Filsuvez gel becomes a dominant treatment (more QALYs, less costs), compared with CCM.

Results for the whole DEB and JEB combined population are considered a reasonable estimate of clinical benefit in both EB subtypes. The ICER, in a scenario when considering RDEB-S alone population (the majority of patients in EASE informing the model), shows similarity to the ICER relating to the whole DEB and JEB population. More real-world data on Filsuvez gel impact on JEB patient outcomes in the future would be useful to confirm this.

The approach adopted in the economic model base case is potentially conservative. As Filsuvez gel has proven potential to maintain patients in lower severity health states for longer periods of time (than would be the case with CCM alone), it is plausible that incidence of complications might be delayed in the longer term. Specifically in regard of SCC, it is possible that this may lead to increased life expectancy indirectly related to the wound burden reduction benefits of Filsuvez gel. However, there was insufficient verification within the structured expert elicitation (SEE) exercise, based on evidence available, of an association of BSAP level and complications such as SCC to support inclusion in the modelling of this. Hence, potential benefits relating to reductions in complications in terms of quality of life, costs of care and patient longevity have not been modelled (even within scenario analysis). Further research and/or interrogation of emerging data (e.g., PEBLES) and future real-world evidence might enable more informed assessment of these potential effects.

There are several important aspects of patient and carer QoL that can be impacted by use of Filsuvez gel but are not captured in the QALY, detailed in Sections B.4.13. Patients with EB have considerable life-impacting and currently unmet needs, with a substantial impact of the disease on carers and family. An undiscounted QALY gain of 4.6 has been estimated for Filsuvez gel, which in the context of DEB/ JEB being a severely disabling chronic disease with significant burden for patients and carers, and with no previous licensed or effective therapies, represents a significant health benefit for a disease where sizeable QALY benefits are difficult to achieve. There are data uncertainties typical of rare disease evaluations undergoing the HST appraisal. However, the economic analysis performed shows that Filsuvez gel represents an important breakthrough for the entire EB community, improving the HRQoL of patients and their carers/ family members, and with the PAS discount, can be considered a cost-effective use of NHS resources.

B.4.16 Cost to the NHS and Personal Social Services

B.4.16.1 Annual treated patient numbers

For the EB subtypes corresponding to the licenced indication of Filsuvez gel, assuming constant prevalence across the constituent countries of the UK, adjustment according to ONS mid-2021 population estimates suggest patient numbers in England of 56 and 604 JEB and DEB patients, respectively (Table 4). Therefore, the upper estimate of current eligible patients covered by the anticipated marketing authorisation is 660 being an upper estimate as it also includes those 6 months and younger (not covered by the licenced indication). The population estimates of DEB and JEB rise to 671, 681, 691 and 701 over years 2 to 5 respectively.

Clinical experts covering the four specialist EB treatment centres were consulted on the number of patients expected to be eligible for treatment with Filsuvez gel. They estimated that most DEB and JEB patients would be eligible for treatment, therefore anticipating that up to 701 patients across the four treatment centres would be eligible for treatment with Filsuvez gel at any one time. The four specialist centres consist of: Birmingham Women's and Children's NHS Foundation Trust, University Hospitals Birmingham NHS Foundation Trust, Great Ormond Street Hospital (GOSH) for Children NHS Foundation Trust, and Guy's and St Thomas' (GST) Hospital NHS Foundation Trust.

The eligible population for Filsuvez gel in the budget impact has been calculated using Office of National Statistics (ONS) population statistics for England from 2021. Applying the prevalence of JEB and DEB patients as reported by Petrof *et al*. 2022 (11.7 per 1 million live births), and assuming 100% of patients are eligible for treatment with Filsuvez gel, it is estimated that there are up to 661 patients in year 1. Over the next five years, the number rises to 671, 681, 691 and 701 over years 2, 3, 4 and 5, respectively. Filsuvez gel will be administered alongside CCM and will be used each time a patient changes dressing. It is assumed no additional supportive medicines are required alongside the use of Filsuvez gel, as well as no medicines (other than some emollients) displaced with its use.

The uptake rate is estimated to be 25% in years 1 to 5. This is based on clinical expert opinion that whilst eligible, the potential population of 660 is an upper estimate of current eligible patients covered by the anticipated marketing authorisation, since it also includes those 6 months and younger (not covered by the licenced indication). In addition, clinical experts, from University Hospitals Birmingham NHS Foundation Trust and Guy's and St Thomas' (GST) Hospital NHS Foundation Trust, when consulted, thought that at any one time up to 150-175 patients will be using Filsuvez gel. The number of eligible patients that is estimated to be treated with Filsuvez gel is 165 in year 1. Over the next five years, the number rises to 168, 170, 173, and 175 over year 2, 3, 4 and 5, respectively.

The total number of patients treated with Filsuvez gel is expected to be further adjusted compared with the anticipated uptake due to discontinuation and mortality, included at a rate of 8.3% and 2.33%, respectively (discussed in section 3). Hence, the number of patients treated with Filsuvez gel is estimated as 152 in year 1, rising to 154, 156, 158 and 161 over Year 2, 3, 4 and 5, respectively.

B.4.16.2 Costs to the NHS

The medicinal form of Filsuvez gel is a 23.4g tube containing 250cm^2 area. The medicine acquisition cost per patient is derived from a price per tube of £275.33 with a usage of [redacted] tubes per month, based on the mean utilisation in EASE overall study (both DBP and OLP), detailed in B.2.10.1.

The average acquisition cost per annum per patient is estimated as [redacted] using the list price, and [redacted] per annum using the PAS price.

CCM includes dressing changes, which includes both time costs, and dressing consumables costs, and emollients and topical treatments on wounds. Use of emollients and topical treatments for daily wound care is not available for EB patients. In absence of this, an alternative source on open wound data was used.(121) The BIM accounts for an arbitrary assumption that 50% of these topical treatments will be displaced by Filsuvez gel, due to the gel nature of the treatment. However, emollients are a minor cost item and make little difference in the budget impact.

Some cost savings relating to overall dressing changes are anticipated for patients who use Filsuvez gel. Time spent on dressing changes when treated with Filsuvez gel has been evidenced to have a 15% reduction when compared to treatment with CCM alone per annum per patient; calculated from number of dressing changes per week recorded in EASE combined with the time spent per dressing change recorded in the CSS (detailed in the Company budget impact analysis submission document). A unit cost per hour of £12.50 from the average unit cost of a formal carer, PEBLES data, has been inflated to 2021 costs and applied to time estimates spent on dressing changes, resulting in a cost saving of £1,250.26 per annum, per patient with the use of Filsuvez gel.

It is, however, expected that whilst the time spent changing dressings is evidenced to reduce during the use of Filsuvez gel, there will also be a reduction in the number of dressings used during dressing changes. This reduction in the number of dressings is assumed to proportionately be the same of the reduction in time spent changing dressings, 15%. Average annual cost of dressings is reported in PEBLES, identified in B.4.6.1, in which the BIM allows a proportional saving of 15% in dressing consumables to be applied to patients using Filsuvez gel.

There is not expected to be any significant impact on service structures in Years 1-5 of introducing Filsuvez gel. Patients with Filsuvez gel are currently managed with CCM at specialist centres, and no structural changes are envisaged following the introduction of Filsuvez gel. No additional tests or procedures are required prior to patients being approved to commence treatment with Filsuvez gel (Table 2).

B.4.16.3 Estimated budget impact

The expected net budget impact (without PAS) is £11,220,966 in year 1, £11,368,610 in year 2, £11,516,255 in year 3, £11,663,899 in year 4 and £11,885,365 in year 5, detailed in Table 41.

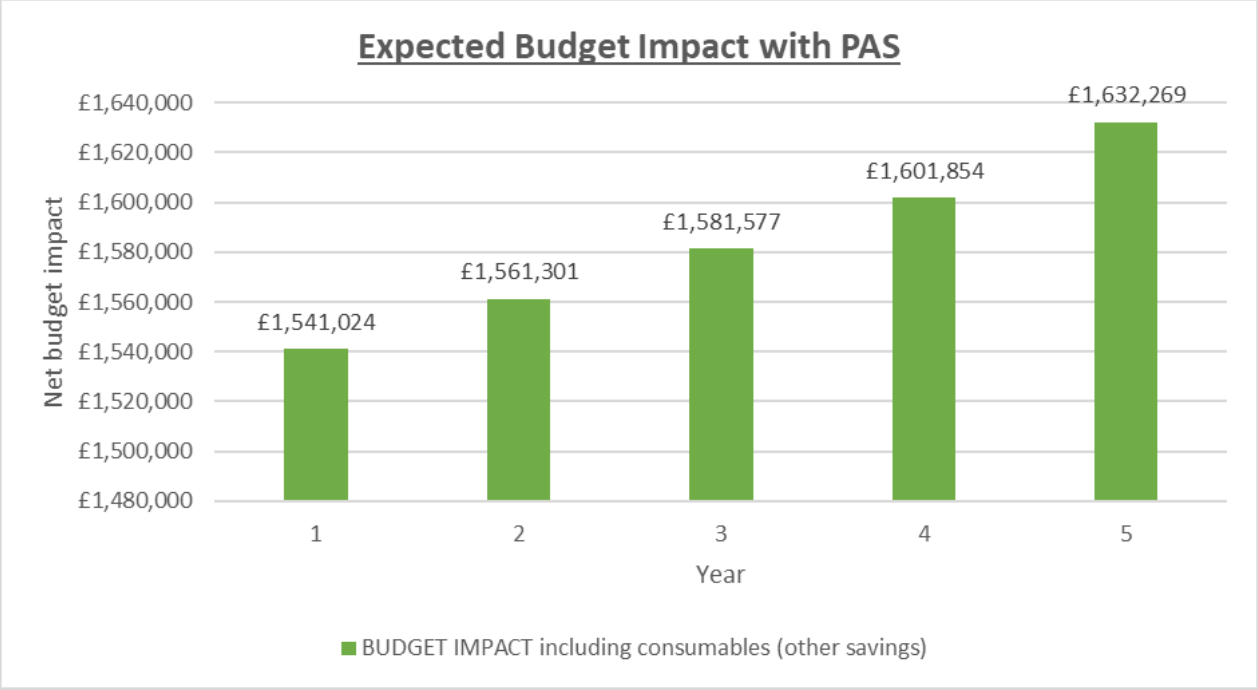
With the PAS, the expected net budget impact is [redacted] in year 1, [redacted], in year 2, [redacted] in year 3, [redacted] in year 4 and [redacted] in year 5, detailed in Table 41 and Figure 20. Therefore, it is clear that the expected net budget impact based on list price and with a PAS, remains below £20 million, in each of the first three years.

Table 41 Expected budget impact (list price and PAS price)

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible population for treatment with Filsuvez gel (birch bark extract)	661	671	681	691	701
Population expected to receive Filsuvez gel (birch bark extract)	152	154	156	158	161
Net budget impact (list price)	£11,220,966	£11,368,610	£11,516,255	£11,663,899	£11,885,365
Net budget impact (PAS price)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PAS, patient access scheme

Figure 20 Expected budget impact (PAS price)



Abbreviations: PAS, patient access scheme

B.4.16.4 Limitations of the budget impact assessment

Due to the rarity of DEB and JEB, there is a paucity of data to inform some parameters. Where data have been unavailable from published sources and trial evidence, clinical opinion has been sought (Section B.3). Data on time spent undertaking dressing changes was derived from a number of sources, principally the EASE trial and SEE. Use of these data was validated at the MSP. Assumptions relating to time savings relating to dressing changes have been incorporated within the model. This lack of supporting data led us to exclude any effects on consumable medical products (other than emollients in line with the SmPC) and accordingly, a conservative budget impact assessment has resulted which sees the same levels of CCM being administered to patients (whether using Filsuvez gel or not). However, we have assumed that use of Filsuvez gel can reduce the amount of time spent administering CCM.

There is some evidence in the EASE trial that, as patients become more familiar with using Filsuvez gel, they start to use less of it. The reasons for this are, however, not fully understood. A cautious approach has been adopted in the budget impact assessment, using the mean overall usage (EASE DBP and OLP for all patients using Filsuvez gel), which sees constant rather than declining use over time.

A cautious assumption on uptake rates has been assumed, based on feedback from clinical experts (section B.4.16.1).

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B.6 Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: EASE EB-specific measures

Appendix N: Structured expert elicitation exercise – key results

Appendix O: Interim 12-month efficacy data from EASE OLP

Appendix P: EASE HRQoL analysis

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly specialised technology

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

Summary of Information for Patients (SIP)

April 2023

File name	Version	Contains confidential information	Date
Summary of Information for Patients (SIP)	1.0	No	15 April 2022

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) name of the medicine (generic and brand name):

Response:
Filsuvez® gel (birch bark extract)/Oleogel-S10

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Response:
Children and adults with dystrophic and junctional epidermolysis bullosa, aged six months and older.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response:
On 21 June 2022, Filsuvez gel received marketing authorisation in the EU for treating partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients aged six months and older, followed by MHRA approval on 11 August 2022, for the same indication. (1, 2)

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response:
Amryt has provided the following financial support to relevant patient organisations:

1. CURE EB - EB Family and Butterfly Run - £5,000.00
2. DEBRA UK – Annual Members Weekend - £15,990.00
3. DEBRA UK – Patient and Carer Insight study - £56,000.00

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Response:
Epidermolysis Bullosa (EB) is the name for a group of painful genetic skin conditions that cause the skin to become very fragile and tear or blister at the slightest touch. The name comes from 'epiderm' - the outer layer of skin, 'lysis' - the breakdown of cells and 'bullosa' - blisters.

There are many different types of EB, all classified under four main types ranging from the mildest, in which only the hands and feet are affected, to the most severe, which can have a devastating effect on any part of the body, causing lifelong disability and pain. In severe cases, EB can sadly be fatal.

The types of EB that are being assessed as part of this appraisal are the more severe types – dystrophic (DEB) and junctional epidermolysis bullosa (JEB), which substantially impact the quality of life of patients and their families/caregivers.

EB patients (both children and adults) have a lower quality of life than those without EB, an impact that increases with disease severity. (3, 4, 5) Itch and pain linked to wound management severely limit patients' lives and are ranked as the most challenging aspects of EB that compromise Health-

Related Quality of Life (HRQoL). (6, 7, 8) Survey data also indicate that EB places a significant emotional and financial burden on patients and their families. (9, 10, 11).

Children with EB often spend much time during their early years in hospital, particularly children with JEB, where they are often hospitalised for long periods due to failure to thrive. (12) Care at home can also be traumatic for patients with a high wound burden and the carers who assist them, as daily bathing, blister lancing/draining, and dressing changes can be extremely time-consuming (up to four hours per day), painful, and anxiety-provoking particularly for parents caring for young children. (4, 13) Patients may struggle to cope with learning to live with disfigurement, physical impairment, loneliness, and low self-esteem, particularly given the unpredictable disease progression. (14)

As with many rare diseases, few studies focus on how EB impacts the family's quality of life. Having a child with EB carries a substantial physical and emotional toll, potentially affecting every aspect of their lives, including but not limited to relationships, emotional/mental well-being, and financial stability. (15, 16) The impact on siblings is often overlooked. However, they may experience difficult emotions, including guilt, sadness, embarrassment, and resentment. The frequency and duration of required hospital stays can impact the sibling relationship, and the sibling may spend less quality time with the parents than they otherwise would. (15)

Global epidemiological data for EB varies across studies, but the incidence is estimated to be between 19 and 41 per million live births. (3, 17) The most recent published prevalence and incidence data from the NHS national EB service based on data from 2,594 individuals in England and Wales with EB who were enrolled prospectively in the database between 2002 and 2021, including 1,200 live-born babies, are summarised in the table below for the population relevant to this submission.

EB type	Subtype	Estimated prevalence based on the population for England of 56,489,800
DEB	Recessive	186
	Dominant	384
	DEB (NOS)	34
	All DEB	604
JEB	Severe	3
	Intermediate	19
	Other subtypes	34
	All JEB	56
All DEB/JEB		660

Source: calculated from figures published in Petrof 2022 and adjusted using ONS mid-2021 population estimates.(18, 19)

Abbreviations: DEB, dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; JEB, junctional epidermolysis bullosa; NOS, not otherwise specified

However, the eligible patient population of 660 is an upper estimate of current eligible patients covered by the marketing authorisation since it also includes those six months and younger (not covered by the licenced indication). In addition, when consulted, clinical experts thought that up to 150-175, patients would be treatment eligible.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?
Response: Laboratory diagnosis is essential to identify and locate the faulty gene, which will determine the type of EB. Skin sample analysis can be done initially and is often the first step with new borns. Prenatal testing is also possible. Neonatal teams, GPs, Dermatologists, or the EB specialist healthcare teams will be able to advise which method of diagnosis is most suitable in individual circumstances. Sometimes, it's possible to test an unborn baby for EB using amniocentesis and chorionic villus sampling at about 11 weeks into pregnancy. This may be offered if either parent is known to carry the faulty gene(s) associated with DEB and JEB. If there is no history of EB in the family, the first sign is often when a baby is born with skin missing on one or more parts of the body. EB can be diagnosed or flagged as a possibility by the neonatal team, but further laboratory testing is required to confirm the diagnosis and EB type.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed: • What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP. • Please also consider: o if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data. o are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.
Response: The mainstay of treatment of DEB and JEB is the management of wounds, reducing the potential for new injury, minimising complications, and improving quality of life. (20, 21, 22, 23, 24). Various clinical guideline recommendations and expert consensus statements exist for different aspects of EB; however, none were written for a specific country or healthcare system. Despite these recommendations for wound care and other elements of EB, no guidelines have been published that are specific to UK clinical practice, and the unmet need for improving patient and carer outcomes with new treatments remains significant. EB patients are generally cared for in a multidisciplinary team (MDT) setting. As a rare disease, very few dermatologists or other specialists will have had much exposure to EB. Therefore, since 2002, the nationally commissioned EB service has managed clinical care for DEB and JEB patients in England, Wales, Scotland, and Northern Ireland. (18, 25, 26) Due to its lifelong nature, it is recognised that EB patients and their carers become experts in managing wounds, and their involvement in any disease management choices is paramount. (20, 23, 27). This results in highly heterogenous clinical management strategies that may not only vary between patients with different subtypes of DEB and JEB but also on an intra-patient level between

wounds in different locations, sizes, and chronicity, and also over time, both seasonally and over a patient's lifetime as their disease enters different phases.

Therefore, the standard of care for EB partial-thickness wounds is heterogenous and includes a variety of non-adhesive dressings and bandages, topical antimicrobials, topical steroids, and a variety of topical agents not 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. (23)

Additional recommendations for the management of skin manifestations may include: lancing and draining of intact blisters since EB blisters are not self-limiting,(21, 22, 23, 24) action to address colonisation (germs on the skin) and infection 9germs within the body) of wounds, such as the use of antiseptics and topical/systemic antimicrobials mentioned above,(21, 24, 28) efforts to treat intense pruritus (itching),(8, 20, 22, 23, 24) and protection from further skin trauma. (28, 29)

Pain management, including pharmacological (treatment with drugs) and non-pharmacological (non-drug treatment) interventions, is also crucial to tackling both background pain and procedural pain experienced during wound management practices such as bathing, dressing changes and blister lancing, and other clinical procedures. (21, 24, 28, 30)

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:

EB patients (both children and adults) have a lower quality of life than those without EB, an impact that increases with disease severity. (3, 4, 5) Itch and pain linked to wound management severely limit patients' lives and are ranked as the most challenging aspects of EB that compromise HRQoL.(6, 7, 8). Survey data also indicate that EB places a significant emotional and financial burden on patients and their families. (9, 10, 11)

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Filsuvez gel is a non-aqueous gel. 1g of gel contains refined bark extracts from a range of sliver birch-type trees, namely Betula pendula Roth and Betula pubescens Ehrh, as well as hybrids of both species, triterpenes (a class of chemical compounds found in leaves, stem bark, fruits and roots), which are mixed with an extraction solvent to create the gel. (31, 32)

Laboratory studies show that the extract modulates inflammatory mediators and is associated with activating intracellular pathways involved in wound healing and closure. (32) However, the precise mechanism of action of Filsuvez gel in wound healing is unknown. (32)

Filsuvez is neither innovative nor novel. However, DEB and JEB are debilitating, rare, severe and chronically disabling lifelong conditions with a devastating effect on both paediatric and adult patient quality of life and having a significant impact on the well-being and quality of life of their parents/ carers and family members, including siblings.

There is currently no cure, and until the licensing of Filsuvez gel in 2022, there had been no approved treatments for EB or any subtype. The overall disease burden for this small and clinically distinct EB population is substantial. New treatment options are urgently required to address significant unmet needs for improving quality of life and potentially reducing mortality.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Response:

Filsuvez will not be used in combination with any other treatment.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Filsuvez should be applied to the wound surface at a thickness of approximately 1mm 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.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Response:

The pivotal phase III EASE trial represents the most robust source of clinical effectiveness and safety data for Filsuvez gel. It is therefore used exclusively as the primary source of evidence in the evidence submission to NICE. The EASE trial was a randomised controlled phase III trial providing a direct head-to-head comparison of the safety and efficacy of Filsuvez gel compared to a control gel arm. It was designed to investigate whether Filsuvez gel is effective for treating EB wounds and for long-term safety.

The trial was a two-phase study: a 90-day randomised, double-blind (Explain) phase of Filsuvez gel *versus* control gel, followed by a 24-month single-arm open-label phase, during which all participants received Filsuvez gel. (33, 34)

The control gel was an identical-looking sunflower oil gel containing no active substance. Patients received either Oleogel-S10 or control gel for a double-blind (neither group knew which gel they were receiving) study phase of 90 days.

The probability that patients would receive Filsuvez gel was 50%, meaning they had a 1 in 2 chance of receiving Oleogel-S10. However, in the follow-up phase of the Study, all patients were treated with Filsuvez gel for 24 months.

The inclusion and exclusion criteria were as follows:

Inclusion criteria (patients considered suitable to be included in the trial)	Exclusion criteria (patients considered unsuitable to be included in this trial)
• Male and female patients with DEB, JEB, or KEB • Patients aged 4 years and above **(reduced to > 21 days following an IDMC safety review in 2019)** • EB target wound 10–50 cm^2 in size aged ≥ 21 days and < 9 months outside of the anogenital region	• EBS • EB target wound with clinical signs of local infection • Use of systemic antibiotics for wound-related infections within 7 days • Administration of systemic or topical steroids within 30 days • immunosuppressive or cytotoxic chemotherapy within 60 days • Previous stem cell transplant or gene therapy for EB • Current and/or former malignancy

The EASE was performed in several countries, including the UK. In total, about 250 patients participated.

The EASE trial was completed on 1 July 2022.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others, and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in-confidence information, but where necessary reference the section of the company submission where this can be found.

Response:

The information regarding the efficacy of Filsuvez gel can be found in section B2.

Filsuvez gel received marketing authorisation from the MHRA on 11 August 2022. To be approved, the MHRA must be satisfied that the potential benefits of a new treatment outweigh its potential risks.

As mentioned above, the EASE trial comprised two components, a randomised, double-blind phase and an open-label single-arm phase in which all patients received Filsuvez gel. Below is a summary of the efficacy data for both parts of the Study.

Double-blind study phase (neither group knew which gel they were receiving):

- Filsuvez gel was found to accelerate wound healing in EB patients. By Day 45, 41.3% of the group receiving Filsuvez gel had first complete wound closure compared to 28.9% of the control gel group (34, 35).
- At the end of the 90 days, the percentage of the body surface area that was covered in wounds was less with the Filsuvez gel group compared to the control group (34, 35)
- There was a slight improvement in itching symptoms in both groups. (34)
- Filsuvez gel patients had less pain when changing dressings, and a reduction in the number of dressing changes was noted in those receiving Filsuvez gel compared to those in the control gel group (34)
- The number of wound infections was lower in those receiving Filsuvez gel (1.8%) compared with the control gel group (4.4%). (34)
- The proportion of patients who reported having missed work or school because of problems associated with EB was slightly lower in the Filsuvez gel group (61.1%) compared to the control gel group (64.9%).

Follow-up phase (all patients were treated with Filsuvez gel for 24 months):

- The results from this follow-up phase show a reduction in the overall body wound coverage and disease progression over two years.
- The reduction in itching was maintained from the first phase of the Study, as was the reduction in pain when changing dressings.

The outcomes deemed most important to patients and carers include faster wound closure and overall wounds on the body, less pain, reduced itch and less time off of school or work.

There are limitations to the data. Whilst patients with DEB and JEB are represented in the trial, a smaller number of JEB patients raises some uncertainty around real-world representation (section B.4.7.4). There are also limited data relating to costs and healthcare resource use in EB. Therefore, unit cost estimates are used in the base case (B.4.15). Limited data were collected on the measure of the health-related quality of life and clinical outcomes as the EQ-5D and iscorEB scores were only collected in the OLP phase of the trial (B.2.12)

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Response:

The quality-of-life measure used in the Study was the EQ-5D, a standardised measure of health-related quality of life tool in the form of a questionnaire. The patient's quality of life was assessed using the EQ-5D at months 12 and 24 of the OLP phase. The Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa (iscorEB) was also assessed in the OLP phase to provide further information. The results from the EQ-5D and iscorEB on the quality-of-life impact were minimal due to them being added during the Study's later phase, resulting in fewer baseline comparisons. Only a small number of patients and clinicians completed these assessments at the end of the trial.

Filsuvez was found to reduce total body wound burden, which, in turn, can reduce the required frequency of painful and often traumatic dressing changes. It also produced a faster time to wound closure. A reduction in disease severity and subsequent quality of life benefit would have a substantial impact on the patient, their families and clinicians.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Response:

The EASE trial collects information on both side effects and adverse events. Side effects are a direct consequence of the medicine being used, and adverse events are any other events that happen because of the disease or other events. The number of patients experiencing a side effect was similar between those receiving Filsuvez gel and those receiving the control gel. It is worth noting that the side effects captured in the trial data are also consistent with the course of the disease and are more likely to be adverse events. With that in mind, we are unaware of any side effects directly with Filsuvez gel. However, the table below shows the most common adverse events that may occur as part of the disease:

Adverse Events	Symptoms	% of patients who have had this adverse event (number out of 100)	How adverse events could be managed
Wound complication	In studies with EB patients, wound complications comprised different local complications such as increased size, re-opening, and pain. (*)	41%	Daily blister management and dressing changes, along with specific treatment from a specialised EB team
Anaemia	Tiredness, pale skin, cold hands and feet, shortness of breath	18%	Increasing iron in the diet, iron supplements and giving iron intravenously
Wound infection	Warm, red and painful at the wound site, fever, bad odour	10.2%	Antiseptic and antibiotic creams and lotions, antibiotic tablets, the specific dressings to help THE healing process
Fever	Body temperature above 38C, chest or back feel hotter than usual, shivering, sweating	9.8%	Plenty of fluids, rest, paracetamol or ibuprofen, keep an eye on the patient
Itchy skin	Uncomfortable, irritating feeling that makes you want to scratch your skin	6.8%	Antihistamine tablets
Difficulty swallowing	Difficulty swallowing food or drink	6.3%	Change in diet, swallowing therapy, feeding tubes

* Filsuvez Gel - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Of the 223 patients that received at least one dose of Filsuvez gel, 5 discontinued the Study due to an adverse event (3 in the Filsuvez gel group and 2 in the control gel group). (34)

A total of 205 (91.9%) patients continued into the 24-month phase of the Study, where all participants received open-label Filsuvez gel. (36)

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Response:

The key benefits of Filsuvez gel to patients, carers and their communities include the following:

- Filsuvez gel helps wounds to close more quickly
- The percentage of the body surface area that was covered in wounds decreased
- The number of wound infections decreased
- The number of daily wound dressing changes was reduced, as was the pain related to these dressing changes
- Filsuvez gel is relatively easy to administer as it can be applied to the wound or directly to the dressing and does not have to be used sparingly

All of the above contribute to a less painful and time-consuming daily regime for EB patients and their carers.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

While the treatment aims to accelerate wound healing and slow the progression of the disease, it is not disease-modifying or curative.

It often takes patients and their carers several weeks and months to find the right mix of existing treatments. Finding this balance can often lead to entrenched behaviour where there is often resistance to trying any new approach.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Response:

The bullets below give a suggestion of structure, subheadings and key points to give the context of how the cost effectiveness of the treatment has been modelled. Addressing each of the bulleted points below should be kept to a few sentences.

How the model reflects the condition

- What is the structure of the model? Explain how the model reflects the experience of having the condition over time.

Modelling how much a treatment extends life

- Does the treatment extend life? If so, please explain how (for example. by delaying disease progression, reducing disease severity or complications, reducing disease relapses or life-limiting side effects).
- Describe briefly which trial outcomes feed into the economic model. If trial data used for a certain length of time followed by extrapolation, please note how long the trial data was used for and briefly how the data has been extrapolated.

Modelling how much a treatment improves quality of life

- How is the treatment modelled to change a person's quality of life compared with the treatments already in use? This should include after stopping treatment if relevant. For example, say if the treatment improves quality of life because of improving symptoms or decreases quality of life because of side effects.
- Which quality of life measure(s) did you use to estimate a person's quality of life over time and on treatments? Are there any aspects of the condition or its treatments affecting quality of life which may not have been fully captured by the methods used to estimate quality of life?

Modelling how the costs of treatment differ with the new treatment

- Does the medicine lead to any cost implications (positive or negative) for the health service (e.g., drug costs, number of days in hospital)?
- Are there any important differences in the way the medicine is given compared with those already in use that will affect the experience of the patient or costs to the health service or patients (e.g., where it is given or the monitoring that is needed)?

Uncertainty

- Are there any key assumptions you have made in your model about the medicine's benefits or costs because of lack of data?
- Did you test using alternative assumptions or data in your model? Which had the largest effect on your cost effectiveness estimates?

- Are there any data you have presented to support your modelled outcomes being plausible?

Cost effectiveness results

- What is the modelled benefit in overall survival, quality adjusted life years and the incremental cost effectiveness ratio?

Additional factors

- Have you made a case for a severity modifier being relevant for this condition? If so, please summarise the data presented

Are there any benefits or disadvantages of the treatment not captured in the modelling

Health economic models

Health economic models are developed to evaluate the health and cost outcomes regarding a new healthcare intervention or technology. Usually, this implies developing a cost-effectiveness model that estimates "value for money" and a budget impact model that estimates the financial impact on the healthcare system.

Health economic models are tools developed to demonstrate value for money and the budget impact of a new healthcare intervention or technology. They are essential for payer and health system reimbursement within markets with mature and developing Health Technology Assessment (HTA) bodies, such as NICE.

Health economic models help to extrapolate outcomes of interest beyond those captured in a clinical trial. They are also designed to capture and accumulate all health and cost consequences of a healthcare intervention or technology over a time horizon.

It's important to understand that neither a trial nor a health economic model perfectly represents a disease in the real world, so patient and clinical expert input into NICE appraisals is essential.

The cost-effectiveness assessment of a new treatment

To determine the cost-effectiveness of a new treatment and its value to the health system compared to the current standard of care, NICE uses the Incremental Cost Effectiveness Ratio or ICER for short and the Quality Adjusted Life Year or QALY for short.

The ICER gives a monetary value to how much it costs to achieve one QALY. The QALY measures disease burden and includes both length and quality of life. A new treatment can increase the number of QALYs a patient can achieve by improving both the length and quality of life, where one QALY is perfect health and 0.5 of a QALY means a 50% reduction in health quality.

These measures enable NICE to compare the ICER level to its willingness to pay QALY threshold to determine if a new treatment brings more value to the health system than the current standard of care.

The EB Health Economic Model

With the input of health economists, statisticians, EB clinicians, nurses and patient experts, the company developed a health economic model which was submitted to NICE as part of its overall evidence submission.

A cost-effectiveness analysis was developed to estimate the overall cost and health-related quality of life (HRQoL) impact of Filsuvez gel for treating partial-thickness wounds, relative to the standard of care, for EB patients and their carers over a patient's lifetime.

At a patient level, EB wounds are dynamic and overall wound burden will typically fluctuate over time as new wounds develop and others heal. Increasing the rate at which wounds heal when treated with Filsuvez gel (demonstrated via the primary endpoint of the EASE DBP), however, reductions can be achieved in patients' overall wound burden at a given time relative to treatment with current clinical management (CCM) alone.

The cost-effectiveness model aims to quantify this reduction based on total body wound burden as proxied by body surface area percentage (BSAP), an endpoint of the pivotal EASE trial that serves as a surrogate measure for severity and consequent HRQoL impact.

The model base case considers the impacts of reductions in wound burden regarding resource needs (notably the costs associated with dressing changes and wider primary and secondary care needs) and patient and carer HRQoL as captured in the EASE trial and wider sources.

The base cost-effectiveness does not make claims around the potential impact of Filsuvez gel in reducing clinical complications associated with DEB and JEB, in particular risks of complications such as Squamous Cell Carcinoma (SCC), which tend to be related to the presence of longer-term chronic wounds. By reducing overall wound burden and disease severity, the likelihood of chronic wounds occurring is reduced, and hence the risk of SCC and other complications might also plausibly be reduced.

The economic model is structured as a cohort-level state transition model including seven distinct health states: six ordinal health states representing differing levels of EB total wound burden, defined as discrete ranges of the BSAP covered by partial-thickness wounds and death.

As with almost all economic models, there are several uncertainties, assumptions and limitations, including around disease progression and the risk of SCC.

Cost-effectiveness

Filsuvez gel is associated with a discounted QALY gain of 2.3 *versus* current clinical management.

As described in section **Error! Reference source not found.**, the primary premise behind the economic evaluation of Filsuvez gel is that it leads to improvements in quality of life in DEB and JEB patients, and their carers. This is achieved in the economic model through a reduction in wound burden (as proxied by BSAP) and hence relative disease severity.

Whilst this is a meaningful health benefit *per se*, very high QALY gains are not to be expected in such a disease which remains chronic, recurring, and disabling, and especially for a treatment that does not influence mortality risks.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Response:

The company does not consider the treatment to be innovative. However, it could represent a step-change in treatment as no other licensed treatment currently exists. The hope is that a positive NICE outcome will signal to other companies working in the EB space that getting a new treatment approved for use in the NHS in EB is possible.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Response:

The company are not aware of any potential inequalities.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Response:
Information on EB can be found on the follow websites:

www.debra.org.uk

https://www.nhs.uk/conditions/epidermolysis-bullosa/

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS)

organisations | Public involvement | NICE and the public | NICE Communities | About | NICE

- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

Term	Definition
BSA	Body surface area
BSAP	Body surface area percentage
BSC	Best supportive care
CCM	Current clinical management
DDEB	Dominant dystrophic epidermolysis bullosa
DEB	Dystrophic epidermolysis bullosa
EB	Epidermolysis bullosa
EBDASI	Epidermolysis Bullosa Disease Activity and Scarring Index
EBS	Epidermolysis bullosa simplex
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
iscorEB	Instrument for Scoring Clinical Outcomes of Research for Epidermolysis Bullosa
ITT	Intention to treat
JEB	Junctional epidermolysis bullosa - other
JEB-O	Junctional epidermolysis bullosa -severe
JEB-S	Junctional epidermolysis bullosa
KEB	Kindler epidermolysis bullosa
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PRO	Patient-reported outcome

PTW	Partial-thickness wounds
QALY	Quality adjusted life year
RCT	Randomised controlled trial
SCC	Squamous cell carcinoma
SoC	Standard of care
TBSA	Total body surface area
TBWB	Total body wound burden

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

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16. Wu YH, Sun FK, Lee PY. Family caregivers' lived experiences of caring for epidermolysis bullosa patients: A phenomenological study. Journal of Clinical Nursing. 2020;29(9-10):1552-60.
17. Fine JD. Epidemiology of Inherited Epidermolysis Bullosa Based on Incidence and Prevalence Estimates From the National Epidermolysis Bullosa Registry. JAMA Dermatol. 2016;152(11):1231-8.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

Clarification questions

27th January 2023

File name	Version	Contains confidential information	Date
ID1505 birch bark extract clarification questions [AICno CIC]	1	Yes	27/01/23

Response notes

Following a call with NICE and the EAG on 24th January 2023, we have provided further clarifications at the end of Section B (page 51). For clarity, this document summarises these clarifications alongside the original responses provided on 12th January 2023 (12-month data cut) and 20th January 2023 (24-month data cut).

An updated model version (Filsuvez UK CEM v1.3) has also been provided, and includes an updated log sheet documenting changes made since the submission model (Version 1.0).

Abbreviations table

AE	Adverse effect
AIC	Akaike information criterion
ANCOVA	Analysis of covariance
BIC	Bayesian information criterion
BSAP	Body surface area percentage
CADTH	Canadian Drug and Health Technology Agency
CCM	Current Clinical Management
CCT	Controlled clinical trial
CEM	Cost-effectiveness model
CS	Company submission
CSR	Clinical study report
CSS	Cross-sectional study
DBP	Double-blind phase
DDEB	Dominant dystrophic epidermolysis bullosa
DEB	Dystrophic epidermolysis bullosa
EAG	External Assessment Group
EB	Epidermolysis bullosa
EB PTW	Epidermolysis bullosa partial thickness wounds
EBDASI	Epidermolysis Bullosa Disease Activity and Scarring Index
EQ-5D	EuroQol 5-dimension
FAS	Full analysis set
GLM	Generalised linear model
HRQoL	Health-related quality of life
HST	Highly Specialised Technology
ICER	Incremental cost effectiveness ratio
ISSG	Information Specialist Sub-Group
JEB	Junctional epidermolysis bullosa
LS	Least squares

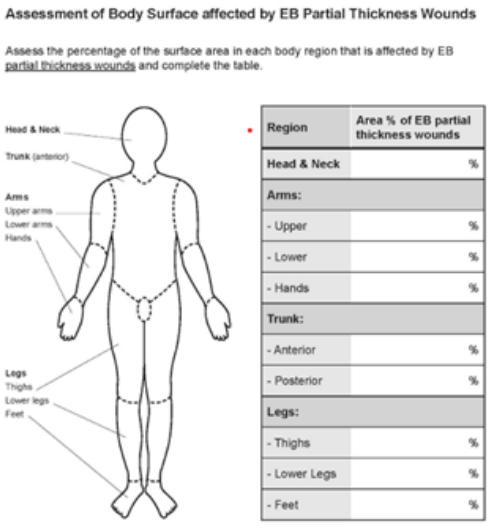
N	Number
NA	Not applicable
NHS	National Health Service
NHS CRD	National Health Service Centre for Reviews and Dissemination
NHS EED	National Health Service Economic Evaluation Database
NI	No information
NICE	National Institute for Health and Care Excellence
NR	Not reported
OLP	Open-label phase
OLS	Ordinary least squares
PAS	Patient Access Scheme
PICOS	Population, intervention(s), comparator(s), outcome(s), study design
PSA	Probabilistic sensitivity analysis
PSSRU	Personal social services research unit
PT	Preferred term
QALY	Quality adjusted life years
RCT	Random controlled trial
RDEB	Recessive dystrophic epidermolysis bullosa
RDEB-O	Recessive dystrophic epidermolysis bullosa - other
RDEB-S	Recessive dystrophic epidermolysis bullosa - severe
ROBINS-I	Risk Of Bias in Non-Randomized Studies of Interventions
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SEE	Structured expert elicitation
SMR	Standardised mortality ratio
TBSA	Total body surface area
TSOP	Topic Selection Oversight Panel
TSQM	Treatment satisfaction questionnaire for medication
TTO	Time trade-off
UK	United Kingdom

Section A: Clarification on effectiveness data – All responses provided 12 January 2023

A1. Priority: CS B.2.2, page 33: Please clarify the nine anatomical regions assessed for the BSAP outcome measure (and clarify if these were the same for all patients).

Company response: The nine anatomical regions assessed for the BSAP outcome using the Lund and Browder method are presented in the Figure below, and were the same for all patients.

Figure 1: Assessment of BSAP of total body surface area affected by EB partial thickness wounds



Assessment of Body Surface affected by EB Partial Thickness Wounds

Assess the percentage of the surface area in each body region that is affected by EB partial thickness wounds and complete the table.

Region	Area % of EB partial thickness wounds
Head & Neck	%
Arms:	
- Upper	%
- Lower	%
- Hands	%
Trunk:	
- Anterior	%
- Posterior	%
Legs:	
- Thighs	%
- Lower Legs	%
- Feet	%

Source: EASE Study protocol v6.0. (1)

A2. Priority: CS B.2.3.1, Table 8 reports that the intervention was applied 'to all areas on the subject's body that were affected by EB partial-thickness wounds' and that 'Liquid antiseptics at each dressing change to clean and/ or reduce microbial colonisation of target wounds and additional wounds matching target wound criteria prior to study treatment'. Table 9 reports that, 'All other wounds that matched target wound criteria were to be photo-documented similarly' and 'the investigator will photograph the EB target wound and all other wounds that match target wound criteria'. The Amryt SAP V.6.0 section 3.6 reports, 'Study medication is administered to the EB target wound and to all areas on the patient's body that are affected by EB partial thickness wounds'.

Please clarify if all wounds that satisfied the target wound criteria, but were not designated the target wound, were also treated with the intervention and, if so:

Please clarify how many such wounds were treated per patient (mean and range) in each arm.

Please clarify what proportion of the BSAP percentage was accounted for by treated wounds.

Please clarify if the outcomes '*Time to first wound closure up to 90±7 days of treatment*', '*Incidence of wound infection*', '*Maximum severity of wound infection*' (key secondary efficacy outcomes) and '*Dressing change frequency*' (post hoc

analyses) relate to the target wound only or all treated wounds (CS B.2.3.1, Table 8, page 39) and, if the latter, please provide these data.

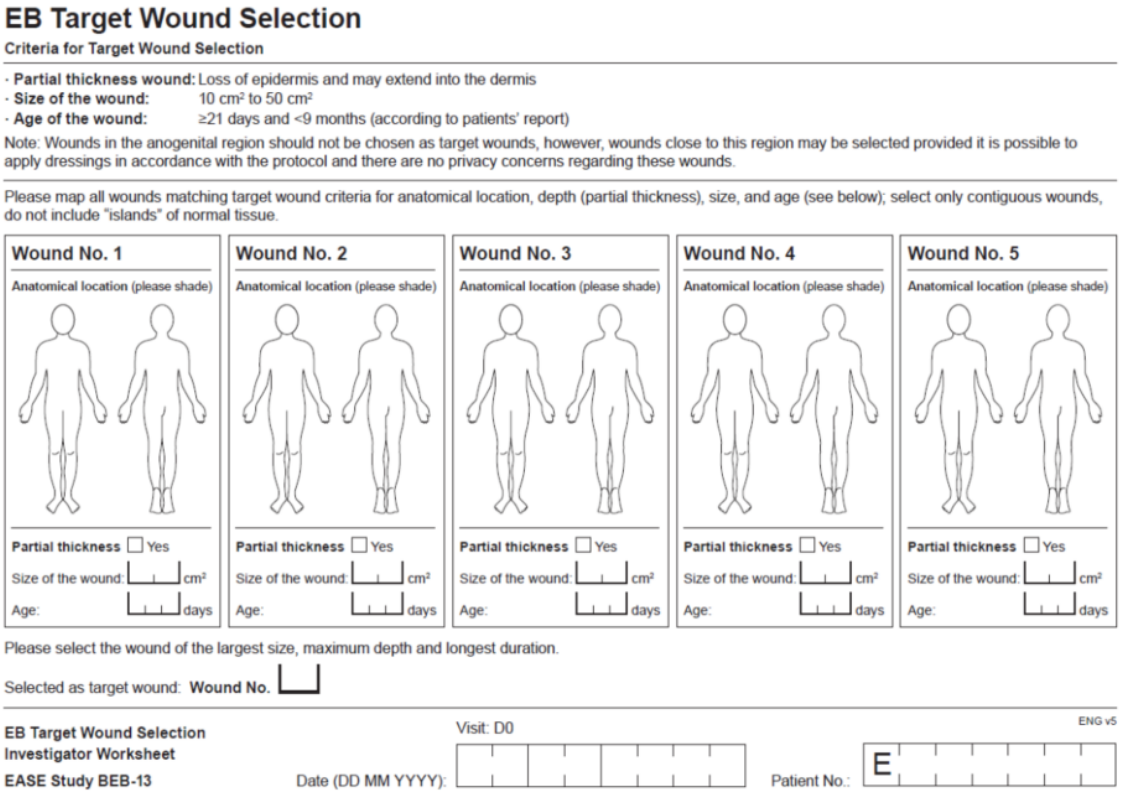
If only the designated target wound was treated:

Please clarify what proportion of the BSAP percentage was accounted for by the treated wound.

Company response: In EB, the wound healing process is altered and therefore the associated partial-thickness wounds are dynamic, reoccurring, and sometimes chronic.(2) Individual wound trajectory is highly variable and therefore at any one time a patient may present with multiple wounds that are in different stages of the wound healing and breakdown cycle. This presented a challenge in EASE, to measure wound healing in such a heterogeneous population.

In EASE, all wounds were treated which is why secondary endpoints such as BSAP and EBDASI were included, since they capture an overview of the wound-healing process across the whole body. Additionally, from all the partial-thickness wounds, target wounds, meeting predefined criteria, were selected for assessment of the primary endpoint (Figure 2).(1)

Figure 2: EASE EB target wound selection investigator worksheet



EB Target Wound Selection

Criteria for Target Wound Selection

- **Partial thickness wound:** Loss of epidermis and may extend into the dermis
- **Size of the wound:** 10 cm² to 50 cm²
- **Age of the wound:** ≥21 days and <9 months (according to patients' report)

Note: Wounds in the anogenital region should not be chosen as target wounds, however, wounds close to this region may be selected provided it is possible to apply dressings in accordance with the protocol and there are no privacy concerns regarding these wounds.

Please map all wounds matching target wound criteria for anatomical location, depth (partial thickness), size, and age (see below); select only contiguous wounds, do not include "islands" of normal tissue.

Wound No. 1	Wound No. 2	Wound No. 3	Wound No. 4	Wound No. 5
Anatomical location (please shade)	Anatomical location (please shade)	Anatomical location (please shade)	Anatomical location (please shade)	Anatomical location (please shade)
Partial thickness ☐ Yes	Partial thickness ☐ Yes	Partial thickness ☐ Yes	Partial thickness ☐ Yes	Partial thickness ☐ Yes
Size of the wound: ___ cm²	Size of the wound: ___ cm²	Size of the wound: ___ cm²	Size of the wound: ___ cm²	Size of the wound: ___ cm²
Age: ___ days	Age: ___ days	Age: ___ days	Age: ___ days	Age: ___ days

Please select the wound of the largest size, maximum depth and longest duration.

Selected as target wound: **Wound No.** ___

EB Target Wound Selection
Investigator Worksheet
EASE Study BEB-13

Visit: D0

Date (DD MM YYYY): ___

Patient No.: E ___

ENG v5

In EASE, wound definitions were as follows:

- **Target wound**: On Day 0, the investigator selected a single EB target wound that met the target wound criteria. In the event that several EB partial-thickness wounds matched the target wound criteria, the wound of the largest size, maximum depth and longest duration was selected as the EB target wound, based on the investigator's clinical judgement.

- **Additional wounds**: In addition to the EB target wound, the investigator could have selected up to 4 other wounds that met the target wound criteria. These wounds are referred to as "additional wounds" that met the target wound criteria and were evaluated for closure, along with the EB target wounds, based on clinical assessment and photography.

- **Other wounds**: All other EB partial-thickness wounds that did not meet target wound criteria are referred to as "other" wounds. Some of the efficacy assessments (e.g., total body surface area, wound infections) were based on all wounds, including the EB target wound, additional wounds that met

the target wound criteria, and all other EB partial-thickness wounds that did not meet target wound criteria (i.e., other wounds). these are referred to as "other" wounds).

A total of 63 participants had at least one additional wound, other than the EB target wound, that met target wound criteria. Most of these subjects had no more than two additional wounds that met the criteria. The number of additional wounds per subject, that matched the target wound criteria, is summarised in Table 1.(3)

Table 1: Number of additional wounds per subject

	Filsuvez gel n=33	**Control gel n=30**	**All subjects n=63**
Number of additional wounds per subject matching the target criteria, n (%)			
One	25 (75.8)	17 (56.7)	42 (66.7)
Two	6 (18.2)	12 (40.0)	18 (28.6)
Three	1 (3.0)	0	1 (1.6)
Four	1 (3.0)	1 (3.3)	2 (3.2)

Participants were instructed to apply Filsuvez gel or control gel to all areas on their body that were affected by EB partial-thickness wounds. (inclusive of "target", "additional", and "other" partial thickness wounds [as defined above]). Therefore 100% of the BSAP percentage was accounted for by treated, EB partial-thickness wounds.

Time to first wound closure up to 90 ±7 days of treatment was reported for the target wound only. Since all partial-thickness wounds were treated and dressed during the trial, dressing change frequency relates to all wounds (inclusive of "target" wounds, "additional" wounds, and "other" wounds). Incidence and maximum severity of wound infection were collected for both target and additional wounds; data are summarised in Table 2 and Table 3.(3, 4)

Table 2: Data from the DBP of EASE for "additional" and "other" wounds

Intervention	**Filsuvez gel**	**Control gel**
Analysis set	Full analysis set	
n	109	114
Incidence of wound infection up to day 90 based on AE reported and/ or use of topical/ systemic antibiotics		
Additional wounds, n (%)	2 (1.8)	1 (0.9)
Other wounds, n (%)	12 (11.0)	18 (15.8)
Maximum severity of wound infection up to day 90 based on AE reporting of PTs only		
Additional wounds, n (%)	mild: 1 (0.9)	NA

Intervention	Filsuvez gel	Control gel
	moderate: 1 (0.9)	
Other wounds, n (%)	mild: 8 (7.3) moderate: 2 (1.8) severe: 1 (0.9)	mild: 6 (5.3) moderate: 6 (5.3) severe: 3 (2.6)
Abbreviations: AE, adverse event; NA, not applicable; PT, preferred term.		

Table 3: Data from the OLP of EASE for "additional" and "other" wounds

Intervention	Former Filsuvez gel	Former control gel
Analysis set	Full analysis set	
n	100	105
Incidence of wound infection up to month 24 based on AE reporting		
Additional wounds, n (%)	[redacted]	
Other wounds, n (%)		
Maximum severity of wound infection up to month 24 based on AE reporting		
Additional wounds, n (%)	[redacted]	
Other wounds, n (%)		
Abbreviations: AE, adverse event; NA, not applicable, NR, not reported.		

A3. Priority: CS B.2.5, page 53 reports 35% with a major protocol deviation based on compliance. Please clarify the source of this value and explain why this does not tally with numbers reported under Section B.2.10.1.

Company response: The figure 35% (reported in Section B.2.5) refers to the proportion of participants with a major protocol deviation regarding the investigational product. This data is for all participants in the safety analysis set (N=223) and is reported in Table 8 of the double-blind phase CSR.(3) As described in CS Section B.2.5, the majority of these deviations involved non-compliance with product administration (in terms of days between dressing changes, for example) and incorrect return of investigational product, where a conservative approach was taken for recording protocol deviations. Since the investigational product is topical, measuring treatment compliance in the EASE trial was more complex than could be expected with other administration methods, where measuring left over product may be more straightforward. The data reported under Section B.2.10.1, refers to treatment compliance which pertains to treatment duration (Treatment compliance overall [%] = Actual treatment duration overall / Treatment duration * 100).

A4. Priority: CS B.2.5, page 53: Please clarify the role of frequency of dressing changes as part of compliance (e.g., page 53: '*the majority involved non-compliance*

with product administration (in terms of days between dressing changes, for example)'; while reduced frequency of dressing changes is also reported as a positive outcome (CS B.2.6.1, page 58).

Company response: In the EASE trial, participants were instructed to topically apply study gel (Filsuvez gel or control gel), to all areas affected by EB partial-thickness wounds, during dressing changes.(1) The EASE trial protocol permitted participants to keep their usual schedule of wound dressing changes to acknowledge the significance of this to EB patients and their carers managing their burdensome wound care within their day-to-day life, only dictating that this interval could have been every day or every second, third, or fourth day, as long as they did not wait longer than 4 days until the next wound dressing change.(1, 3) Data collection on the frequency of dressing changes provided support for the assessment of drug accountability, therefore in the context of protocol deviations, dressing changes taking place at a frequency of greater than 4 days were considered non-compliant.

Clinical expert input suggests that EB patients are generally reluctant to modify their usual dressing change routine, however, there was a reduced frequency of dressing changes observed and explored in post-hoc analyses. Care at home can be traumatic for patients with a high wound burden, and for the carers who assist them, as daily bathing, blister lancing/ draining, and dressing changes can be extremely time-consuming (up to four hours per day), painful, and anxiety-provoking particularly for parents caring for young children, hence any reduction in frequency (within the trial-based compliant window of ≤ every 4 days) was deemed worthy of exploration since the dressing change process is burdensome to patients and carers.(5)

A5. Priority: CS B.2.10.1: Please define '*compliance*' as reported in this section.

Company response: Treatment compliance overall [%] = Actual treatment duration overall / treatment duration * 100.

A6. Priority: CS B.2.10.1: Please provide data for compliance/tube usage for each arm during the OLP at 12 and at 24 months.

Company response: As stated in the previous question, treatment compliance was assessed based on treatment duration rather than tube usage (Treatment compliance overall [%] = Actual treatment duration overall / Treatment duration * 100).

Treatment compliance was [redacted] in the former Filsuvez gel arm at 24-months, and [redacted] in the former control gel arm at 24-months.(4) At the interim 12-month analysis (as of 15th of July 2021), treatment compliance was [redacted] in the former Filsuvez gel arm, and [redacted] in the former control gel arm.(6)

Tube usage data was not collected as an assessment of compliance. A post hoc analysis of tube usage was performed to provide useful information on how much product was being used. As reported in B.2.10.1 of the company submission, tube usage was found to be particularly high during the 90-day DBP when compared to the subsequent 24-month OLP. Amongst patients randomised to the Filsuvez gel arm, the 90-day DBP mean and median were 29.67 (SD: 23.486) and 23.27 (range: 6.0-165.0), tubes, respectively, [redacted] and [redacted] tubes, respectively, during the 24-month OLP. Further to this, Table 4 reports tube usage by arm at the end of the DBP (day 90) and at the end of the OLP (24 months).

Table 4: Summary of monthly tube usage data from the EASE DBP and OLP

DBP	**Filsuvez gel (n=109)**	**Control gel (n=114)**	**All participants (N=223)**
Mean monthly tube usage up to day 90 DBP (SD)	[redacted]	[redacted]	[redacted]
Median monthly tube usage up to day 90 DBP (range)	[redacted]	[redacted]	[redacted]
OLP	**Former Filsuvez gel (n=100)**	**Former control gel (n=105)**	**All participants (n=205)**
Mean monthly tube usage up to 24-months OLP (SD)	[redacted]	[redacted]	[redacted]
Median monthly tube usage up to 24-months OLP (range)	[redacted]	[redacted]	[redacted]

Abbreviations: DBP, double-blind phase; OLP, open-label phase; SD, standard deviation.

A7. CS Appendix D.1.2: Please clarify whether data extraction was conducted independently by two reviewers, and how and whether disagreements were resolved.

Company response: Eligible studies were data extracted independently by two reviewers. Where researchers disagreed, they discussed reasons for disagreement. If consensus was not reached, a third researcher would have been involved, however this was not necessary during this review.(7)

A8. CS Appendix D.1.2: Please clarify how and whether disagreements between reviewers were resolved concerning risk of bias assessments.

Company response: During data extraction, two researchers independently conducted quality assessment of each included study. Where researchers disagreed, they discussed reasons for disagreement. If consensus could not be reached on the quality of a study, then a third researcher would have been involved, however this was not necessary during this review.(7)

A9. CS Appendix D.1.2, Table 3: Please define the exclusion criterion '*ineligible intervention*'.

Company response: At the time of developing the review protocol, the precise nature of what is considered established clinical management of partial thickness wounds in DEB and JEB was unclear. Subsequent input gleaned from clinical experts in UK centres, detailed no licensed interventions and heterogenous, individualised practices in both wound care and management of complications. The review therefore considered in the first instance that established clinical wound management could include Filsuvez gel, or 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. It was planned that had the comparator been further clarified by NICE in a final scope, the PICOS may have been refined after primary screening, and full text screening conducted to the refined PICOS. However, the NICE final scope did not become available during the life cycle of this review but further searching of the literature, and input from clinical experts, 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 specifically for use in the management of EB wounds, with hygiene, blister management, and, pain and pruritis management advice, also provided.

During secondary screening it became apparent that the majority of interventions within otherwise eligible trial records could not be considered part of current established clinical management, mainly because they included investigational agents or techniques unlicensed in EB, that could not be considered established, current UK

clinical practice in relation to the care of partial thickness wounds associated with DEB and JEB. To that end the PICOS was applied as originally described and did not require further refinement. Thereby, the exclusion reason “ineligible intervention” refers to interventions not considered eligible in the pre-defined PICOS.

A10. CS Appendix D.1.3, Table 4: Please clarify if the risk of bias assessment concerns both the DBP and the OLP of the EASE trial. If it does so, please clarify why a separate risk of bias assessment was not conducted for the OLP, given the design of this phase was not an RCT? Would the ROBINS-I tool be more appropriate to assess this phase?

Company response: The risk of bias assessment was performed for both the EASE and OLP of the trial at the time that the clinical SLR was performed (i.e., prior to completion of the OLP). An additional assessment of the OLP, using ROBINS-I has been performed, the results of which are summarised in Table 5.(8)

Table 5: Risk of bias assessment of the EASE OLP using the ROBINS-I tool

Signalling question	**EASE OLP**
1: Bias due to confounding	
1.1 Is there potential for confounding of the effect of intervention in the study? (Y/ PY/ PN/ N) If N/PN to 1.1 the study can be considered low risk of bias due to confounding and no further signalling questions need be considered If Y/ PY to 1.1 determine whether there is a need to assess time-varying confounding	N – participants were instructed to continue with their usual wound care, with the addition of the intervention. All patients received Filsuvez gel during this phase.
1.2 Was the analysis based on splitting participants’ follow up time according to intervention received? (NA/ Y/ PY/ PN/ N/ NI) If N/ PN answer questions relating to baseline confounding (1.4 to 1.6) If Y/ PY, go to question 1.3	NA
1.3 Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? (NA/ Y/ PY/ PN/ N/ NI) If N/ PN answer questions relating to baseline confounding (1.4 to 1.6) If Y/ PY answer questions relating to both baseline and time-varying confounding (1.7 to 1.8)	NA
Questions relating to baseline confounding only	
1.4 Did authors use an appropriate analysis method that controlled for all the important confounding domains? (NA/ Y/ PY/ PN/ N/ NI)	NA
1.5 If Y/ PY to 1.4: were confounding domains that were controlled for measured validly and reliably by the variable available in this study? (NA/ Y/ PY/ PN/ N/ NI)	NA

1.6 Did the authors control for any post-intervention variable that could have been affected by the intervention? (NA/ Y/ PY/ PN/ N/ NI)	NA
Questions relating to baseline and time-varying confounding	
1.7 Did authors use an appropriate analysis method that controlled for all the confounding domains and for time-varying confounding? (NA/ Y/ PY/ PN/ N/ NI)	NA
1.8 If Y/ PY to 1.7: were confounding domains that were controlled for measured validly and reliably by the variables available in this study? (NA/ Y/ PY/ PN/ N/ NI)	NA
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	LOW
2: Bias in selection of participants into the study	
2.1 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? (Y/ PY/ N/ PN/ NI) If N/ PN go to 2.4	N - participants were randomised at the beginning of the DBP, before intervention was given. In the OLP, all participants were assessed within their prior allocation groups (prior Filsuvez gel or prior control gel) and no additional participants were recruited.
2.2 If Y/PY to 2.1: were the post-intervention variable that influenced selection likely to be associated with the intervention? (NA/ Y/ PY/ PN/ N/ NI)	NA
2.3 If Y/PY to 2.2: were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? (NA/ Y/ PY/ PN/ N/ NI)	NA
2.4 Do start of follow-up and start of intervention coincide for most participants? (Y/ PY/ N/ PN/ NI)	Y
2.5 If Y/ PY to 2.2 and 2.3, or N/ PN to 2.4: were adjustment techniques used that are likely to correct for the presence of selection biases? (NA/ Y/ PY/ PN/ N/ NI)	NA
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	LOW
3: Bias in classification of interventions	
3.1 Were intervention groups clearly defined? (Y/ PY/ N/ PN/ NI)	Y – based on prior allocation at DBP baseline
3.2 Was the information used to define intervention groups recorded at the start of the intervention? (Y/ PY/ N/ PN/ NI)	Y
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of outcome? (Y/ PY/ N/ PN/ NI)	N – allocation was randomly assigned ahead of the DBP, but open-label for all participants during OLP
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	LOW
4: Bias due to deviations from intended interventions	
4.1 Were there deviations from the intended intervention beyond what would be expected in usual practice? (Y/ PY/ N/ PN/ NI)	N
4.2 If Y/ PY to 4.1: were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome? (NA/ Y/ PY/ N/ PN/ NI)	NA

4.3 Were important co-interventions balanced across intervention groups? (Y/ PY/ N/ PN/ NI)	There were no important co-interventions
4.4 Was the intervention implemented successfully for most participants? (Y/ PY/ N/ PN/ NI)	Y – all patients in the OLP received the Filsuvez gel intervention
4.5 Did study participants adhere to the assigned intervention regimen? (Y/ PY/ N/ PN/ NI)	Y – high treatment compliance observed (99% in both groups)
4.6 If N/ PN to 4.3, 4.4, or 4.5: was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? (NA/ Y/ PY/ N/ PN/ NI)	NA
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	LOW
5: Bias due to missing data	
5.1 Were outcome data available for all, or nearly all, participants? (Y/ PY/ N/ PN/ NI)	N – due to discontinuations through the long OLP (2 years) not all participants were included analyses at each time point
5.2 Were participants excluded due to missing data or intervention status? (Y/ PY/ N/ PN/ NI)	Y – participants who had discontinued were not included in analyses
5.3 Were participants excluded due to missing data on other variables needed for the analysis? (Y/ PY/ N/ PN/ NI)	N
5.4 If PN/ N to 5.1, or Y/ PY to 5.2 or 5.3: are the proportion of participants and reasons for missing data similar across interventions? (NA/ Y/ PY/ N/ PN/ NI)	Y – discontinuation rates similar between arms (26% in prior control gel group and 31% in prior Filsuvez gel group).
5.5 If PN/ N to 5.1, or Y/ PY to 5.2 or 5.3: is there evidence that results were robust to the presence of missing data? (NA/ Y/ PY/ N/ PN/ NI)	NI
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	MODERATE – discontinuations consistent with the extended phase length means there is a risk of bias through missing data at the later endpoints
6: Bias in measurement of outcomes	
6.1 Could the outcomes measure have been influenced by knowledge of the intervention received? (Y/ PY/ N/ PN/ NI)	Y – this phase was open-label so participants and investigators knew that active intervention was being received
6.2 Were the outcomes assessors aware of the intervention received by study participants? (Y/ PY/ N/ PN/ NI)	Y – open-label
6.3 Were the methods of outcome assessment comparable across intervention groups? (Y/ PY/ N/ PN/ NI)	Y – methods were the same between groups
6.4 Were any systematic errors in measurement of the outcomes related to intervention received? (Y/ PY/ N/ PN/ NI)	N
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	MODERATE – owing this phase of the trial being open-label
7: Bias in selection of the reported result	
Is the reported effect estimate likely to be selected on the basis of the results, from…..	
7.1 …multiple outcome measurements within the outcome domain? (Y/ PY/ N/ PN/ NI)	N – order of analysis of endpoints predefined in SAP
7.2 …multiple analyses of the intervention-outcome relationships? (Y/ PY/ N/ PN/ NI)	N – analyses predefined
7.3 …different subgroups? (Y/ PY/ N/ PN/ NI)	N – both FAS and subgroup data presented

Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	LOW
Overall risk of bias	
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	MODERATE – open-label trial phase with a long follow-up period leading to discontinuations.
Abbreviations: DBP, double-blind phase; FAS, full analysis set; N, no; NA, not applicable; NI, no information; OLP, open-label phase; PN, probably no; PY, probably yes; ROBINS-I, Risk Of Bias In Non-Randomized Studies - of Interventions; SAP, statistical analysis plan; Y, yes.	

A11. Please clarify what value of the covariates were holding constant when calculating the LS mean in Table 12 and Table 13 of the CS**.**

Company response: The following reference groups for each stratum were held constant:

- For treatment group, Oleogel-S10 is the reference group to which control gel is being compared;
- For STRAT1V (EB Subtype), JEB/ Kindler is the reference group to which DEB is being compared;
- For STRAT2V (Wound Size at Baseline), 30 to 50 cm^2 is the reference group to which 10 to <20 cm^2 and 20 to <30 cm^2 respectively is being compared;
- The base variable is constant and no comparisons are available.

The estimates for each endpoint's covariates are presented in Table 6 to Table 10, below.

Table 6: For change from baseline to day 90 in total body wound burden (assessed using EBDASI)

Solution for Fixed Effects				
Effect	**Planned Treatment for Period 01**	**Verified Value of Stratum 1**	**Verified Value of Stratum 2**	**Estimate**
Intercept				9.0691
TRT01P	Control Gel			-0.1229
TRT01P	Oleogel-S10			0
STRAT1V		DEB		-5.5283
STRAT1V		JEB/Kindler		0
STRAT2V			10 to <20 cm2	-0.1058
STRAT2V			20 to <30 cm2	2.5909
STRAT2V			30 to 50 cm2	0
BASE				-0.3949

Table 7: For percentage change from baseline in EB target wound size at day 90:

Solution for Fixed Effects			
Effect	Planned Treatment for Period 01	Verified Value of Stratum 1	Estimate
Intercept			-60.4980
TRT01P	Control Gel		6.2828
TRT01P	Oleogel-S10		0
STRAT1V		DEB	10.4115
STRAT1V		JEB/Kindler	0
BASE			-0.1982

Table 8: For change from baseline to day 90 in BSAP (TBSA affected by EB PTW) assessed on the Lund and Browder chart

Solution for Fixed Effects				
Effect	Planned Treatment for Period 01	Verified Value of Stratum 1	Verified Value of Stratum 2	Estimate
Intercept				4.5554
TRT01P	Control Gel			1.2843
TRT01P	Oleogel-S10			0
STRAT1V		DEB		0.6468
STRAT1V		JEB/Kindler		0
STRAT2V			10 to <20 cm2	-3.4458
STRAT2V			20 to <30 cm2	-1.6018
STRAT2V			30 to 50 cm2	0
BASE				-0.5874

Table 9: For change from baseline in impact of wounds on sleep quality (Likert Scale) to Day 90

Solution for Fixed Effects			
Effect	Planned Treatment for Period 01	Verified Value of Stratum 1	Estimate
Intercept			0.7356
TRT01P	Control Gel		-0.3707
TRT01P	Oleogel-S10		0
STRAT1V		DEB	0.09879
STRAT1V		JEB/Kindler	0
BASE			-0.3698

Table 10: For response to treatment (TSQM) before wound dressing changes at day 90 in patients aged ≥14 years of age

Solution for Fixed Effects			
Effect	Planned Treatment for Period 01	Verified Value of Stratum 1	Estimate
Intercept			1.7447
TRT01P	Control Gel		-0.3022
TRT01P	Oleogel-S10		0
STRAT1V		DEB	-0.3970
STRAT1V		JEB/Kindler	0
D7AVAL			0.6688

A12. Please clarify how the median time to first complete closure of target wound by day 90 based on clinical assessment in Table 12 of the CS is greater than 90 days for both the intervention and control arm.

Company response: The median time based on the log rank test considers all 109 and 114 subjects, not just the 55 and 50 subjects who had closures. Subjects who did have closures have median time to closure of 33 and 39 days, respectively.

- For the log rank test, the subjects who did not show closures up to the end of the DBP are censored at the end of DBP visit, or last assessment date in case of early discontinuation.

- Therefore 54 and 64 subjects would contribute to the increased median time to closure in the log rank test calculation (the majority of these subjects would likely be censored sometime between 90 and 98 days, as EDBP has a 7-day window).

Literature searching:

A13. Please explain the rationale for using different population terms for the clinical (CS Appendix D) and economic (Appendix G) reviews.

Company response: The population for the clinical review was based on the anticipated licensed population and aligned with the EASE trial, while the economic review population was broader in case of predicted paucity of evidence.

Clinical review population: Adults or children (from birth) with DEB (RDEB or DDEB) or JEB.

Economic review population: Adults and children with epidermolysis bullosa (EB).

Whilst we acknowledge that there are differences in the presentation of the condition terms used between the searches, we also note that both searches focus on this core and key free-text line: (((epidermolysis or Junctional or Dystrophic) adj3 bullosa*). We are, accordingly, confident that key studies have been identified in both reviews.

A14. Please provide a source for the filters used to identify eligible studies for both the clinical and economic reviews, including a citation to published validation studies where available.

Company response: For clinical searches: The CADTH search filter for RCT/ CCT was used. This was modified at line 27 to increase sensitivity to single arm studies, to include the full P3 search filter proposed by Cooper *et al*. at line 37, and for a possible misspelling of trial at line 38.(9, 10) CADTH report that their filter has been validated twice, as follows: Validated using the gold standard database set from: Glanville J, Kotas E, Featherstone R, Dooley G. *Which are the most sensitive search filters to identify randomized controlled trials in MEDLINE?* J Med Libr Assoc. 2020 Oct 1;108(4):556-563.(11)

For economics searches: the unpublished NHS CRD NHS EED filter was used for costs (Lines 6-19 of the MEDALL search – see the ISSG website); the Paisley and Booth filter for HRQoL (Lines 21-47) of the MEDALL search); and a review specific search for specific utility questionaries which we developed through scoping (Lines 49-65 of the MEDALL search). We are not aware that these filters have been validated but they are well established filters developed by senior researchers.

We note that the filters used over each review have been modified from the original versions, in all cases, to increase sensitivity. The practice of modifying search filters is acknowledged by researchers. We note, too, that InterTASC's Information Specialist Sub-Group (ISSG) have been discussing when (and how) to cite search filters which have been amended since 2013. We continue to await this guidance with interest.

A15. In the grey literature searches for effectiveness evidence including those of trial registers and the NICE website (CS Appendix D, page 8-9 and 12-13) there is a recurrent spelling error "patrial thickness wounds" which presumably was intended to be "partial thickness wounds". Can the company confirm whether the searches that were run did not have this spelling error? If the error was incorporated, please clarify the additional number of hits that would be identified.

Company response: Thank you for picking this up. We have corrected the spelling to 'partial thickness wounds' following your suggestion and we have de-duplicated against our original searches to identify any unique items for screening. N=33 studies were identified following the correction, which resulted in n=24 to screen following

deduplication against the original searches, of which none were eligible for inclusion for the review. We therefore remain confident that key studies have been identified.

A16. The economic searches (CS Appendix G1.1) contain some unusual characters, specifically in relation to the spelling of the word "syndrome" which is variously reproduced as "2yndrome, 3yndrome, 4yndrome" (etc) throughout the database searches (MEDALL lines 3 and 22; EMBASE lines 3 and 18; Econlit line S2). Can the company clarify whether the searches were run as intended?

Company response: Thank you for your observation. This seems to be a formatting error in the submission template, and it is confirmed that the searches were run as intended with no 'unusual characters' relating to syndrome. The MEDALL, EMBASE and Econlit searches are shown below.

MEDALL

Database: MEDALL
Database host: Ovid
Data parameters: 1946 to March 01, 2022
Date of search: 2 March 2022

	Searches	Results
1	exp Epidermolysis Bullosa/	5345
2	Rothmund-Thomson Syndrome/	579
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.	6902
4	(partial* adj3 thick* adj3 wound*).ti,ab,ot,kf,kw.	611
5	1 or 2 or 3 or 4	8310
6	economics/	27425
7	exp "Costs and Cost Analysis"/	255609
8	economics, dental/	1920
9	exp Economics, Hospital/ or Financial management, hospital/	32782
10	Economics, Medical/	9189
11	economics, nursing/	4013
12	economics, pharmaceutical/	3056
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.	1015466
14	exp "fees and charges"/	31069
15	exp budgets/	13975
16	(resource*1 and (allocation or utili* or usage or use*1)).ti,ab,kf,kw.	226258
17	(expenditure* not energy).ti,ab,kw.	33728
18	(value adj1 money).ti,ab,kw.	37
19	(budget* or fiscal or funding or financial or finance*).ti,ab,kw.	205646
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	1453918
21	(15D or 15-D or 15 dimension).ti,ab,kw.	5743

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.	14556
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.	3143
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.	683
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.	150
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.	6827
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.	35
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.	425
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.	28414
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.	2049
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.	96
32	("time trade off" or "time tradeoff" or "time trade-off" or TTO).ti,ab,ot,hw,kw.	2109
33	(standard gamble* or SG).ti,ab,ot,hw,kw.	12584
34	("discrete choice" or DCE).ti,ab,ot,hw,kw.	8578
35	(AQoL or "Assessment of Quality of Life").ti,ab,ot,hw,kw.	2137
36	Quality-Adjusted Life Years/	14434
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.	405726
38	quality of life/	234230
39	value of life/	5782
40	uncertainty/	15469
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.	5046
42	(HSUV* or health state* value* or health state* preference* or HSPV*).ti,ab,ot,kw.	496
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.	314764
44	(utility* or disutili*).ti,ab,kw.	232570
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.	205062
46	(burden and (disease or illness or caregiver or home)).ti,ab,kw.	113945
47	(lost adj2 (productivity or work or employment or earnings)).ti,ab,kw.	3193
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	1174015
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.	2594
50	("Autoimmune Bullous Disease Quality of Life" or ABQOL or "Treatment of Autoimmune Bullous Disease Quality of Life" or TABQOL).ti,ab,kw.	20

51	("Children's Dermatology Life Quality Index" or CDLQI).ti,ab,kw.	248
52	("Dermatitis Family Impact Questionnaire" or DFIQ).ti,ab,kw.	31
53	("Dermatology Life Quality Index" or DLQI).ti,ab,kw.	2628
54	("EB Disease Activity and Scarring Index" or EBDASI).ti,ab,kw.	8
55	("Epidermolysis Bullosa Burden of Disease" or EB-BoD).ti,ab,kw.	3
56	("Infants and Toddlers Dermatology Quality of Life" or InToDermQoL).ti,ab,kw.	7
57	("Pediatric Quality of Life Inventory version 4" or PedsQL).ti,ab,kw.	1913
58	("Quality of Life Evaluation in Epidermolysis Bullosa" or "EB questionnaire" or "Quality of Life in EB" or QoLEB*).ti,ab,kw.	15
59	("Skindex-29" or "General Health Questionnaire-12" or GHQ-12).ti,ab,kw.	2083
60	("The Quality of Life in Epidermolysis Bullosa" or EB-QoL).ti,ab,kw.	9
61	("Birmingham Epidermolysis Bullosa severity score" or BEBS).ti,ab,ot,hw,kw,kf.	21
62	("Body Surface Area Percentage" or BSAP).ti,ab,ot,hw,kw,kf.	452
63	(iscorEB or iscorEB-c or iscorEB-p).ti,ab,ot,hw,kw,kf.	6
64	("The Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe" or BURQOL-RD).ti,ab,kw.	7
65	("Work Productivity and Activity Impairment Questionnaire" or WPAI).ti,ab,kw.	627
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	8374
67	48 or 66	1175737
68	20 or 67	2436637
69	5 and 68	452

Embase

Database: Embase
Database host: Ovid
Data parameters: 1980 to 2022 Week 08
Date of search: 2 March 2022

Search Strategy:

#	Searches	Results
1	exp epidermolysis bullosa/	8474
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4	(partial* adj3 thick* adj3 wound*).ti,ab,ot,kf,kw.	787
5	1 or 2 or 3 or 4	11180
6	exp economic evaluation/	327366
7	health economics/	30026
8	socioeconomics/	145510
9	exp health-care-cost/	311630
10	exp pharmacoeconomics/	211687
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.	1278329
12	(resource*1 and (allocation or utili* or usage or use*1)).ti,ab,kf,kw.	299058
13	(expenditure* not energy).ti,ab,kw.	44465
14	(value adj1 money).ti,ab,kw.	35

15	(budget* or fiscal or funding or financial or finance*).ti,ab,kw.	284468
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17	(15D or 15-D or 15 dimension).ti,ab,kw.	7172
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.	28258
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.	4038
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.	1244
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.	233
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.	13033
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.	65
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.	532
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.	54379
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.	3859
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.	138
28	("time trade off" or "time tradeoff" or "time trade-off" or TTO).ti,ab,ot,hw,kw.	3144
29	(standard gamble* or SG).ti,ab,ot,hw,kw.	18625
30	("discrete choice" or DCE).ti,ab,ot,hw,kw.	12530
31	(AQoL or "Assessment of Quality of Life").ti,ab,ot,hw,kw.	3482
32	quality adjusted life year/	30908
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.	703438
34	"quality of life"/	542582
35	uncertainty/	39649
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.	5995
37	(HSUV* or health state* value* or health state* preference* or HSPV*).ti,ab,ot,kw.	749
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.	398129
39	(utility* or disutili*).ti,ab,kw.	320250
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.	231651
41	(burden and (disease or illness or caregiver or home)).ti,ab,kw.	185916
42	(lost adj2 (productivity or work or employment or earnings)).ti,ab,kw.	4663
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	1695773
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	4641

	"Questionnaire for Adults Health- related Quality of Life" or "Coping with a Disease Questionnaire").ti,ab,kw.	
45	("Autoimmune Bullous Disease Quality of Life" or ABQOL or "Treatment of Autoimmune Bullous Disease Quality of Life" or TABQOL).ti,ab,kw.	38
46	("Children's Dermatology Life Quality Index" or CDLQI).ti,ab,kw.	480
47	("Dermatitis Family Impact Questionnaire" or DFIQ).ti,ab,kw.	61
48	("Dermatology Life Quality Index" or DLQI).ti,ab,kw.	5385
49	("EB Disease Activity and Scarring Index" or EBDASI).ti,ab,kw.	38
50	("Epidermolysis Bullosa Burden of Disease" or EB-BoD).ti,ab,kw.	6
51	("Infants and Toddlers Dermatology Quality of Life" or InToDermQoL).ti,ab,kw.	7
52	("Pediatric Quality of Life Inventory version 4" or PedsQL).ti,ab,kw.	3725
53	("Quality of Life Evaluation in Epidermolysis Bullosa" or "EB questionnaire" or "Quality of Life in EB" or QoLEB*).ti,ab,kw.	49
54	("Skindex-29" or "General Health Questionnaire-12" or GHQ-12).ti,ab,kw.	2677
55	("The Quality of Life in Epidermolysis Bullosa" or EB-QoL).ti,ab,kw.	20
56	("Birmingham Epidermolysis Bullosa severity score" or BEBS).ti,ab,ot,hw,kw,kf.	35
57	("Body Surface Area Percentage" or BSAP).ti,ab,ot,hw,kw,kf.	765
58	(iscorEB or iscorEB-c or iscorEB-p).ti,ab,ot,hw,kw,kf.	14
59	("The Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe" or BURQOL-RD).ti,ab,kw.	13
60	("Work Productivity and Activity Impairment Questionnaire" or WPAI).ti,ab,kw.	2264
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	15699
62	43 or 61	1698542
63	16 or 62	3493949
64	5 and 63	1004
65	(Conference abstract or Conference review or Conference paper).pt.	5099055
66	64 not 65	659

Econlit

Database: EconLit
Database host: EBSCOhost
Data parameters: 1886-current
Date of search: 2 March 2022

#	Query	Limiters/Expanders	Last Run Via	Results
S3	TI (partial* N3 thick* N3 wound*) OR AB (partial* N3 thick* N3 wound*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	0
S2	TI ((Kindler syndrom* or Kindler EB or Poikiloderma or Rothmund-Thomson Syndrome or butterfly	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced	0

	skin))) OR AB ((Kindler syndrom* or Kindler EB or Poikiloderma or Rothmund-Thomson Syndrome or butterfly skin)))		Search Database - EconLit	
S1	TI (((epidermolysis or Junctional or Dystrophic) N3 bullosa*)) OR AB (((epidermolysis or Junctional or Dystrophic) N3 bullosa*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit	1

Section B: Clarification on cost-effectiveness data

B1. Priority: Please provide a revised base case and supplementary analyses if there have been any amendments based on the clarification process. In addition to the pooled ICER, provide analyses using individual results for the four EB types as this may be informative to the committee.

Company response: Table 11 summarises model changes requested by the EAG, including impact on cost effectiveness results. Please note, the ordering in which model changes were applied in assessing impact on ICER. The CEM has been updated to report ICERs for each of the four groups in the results sheet (cells M39:M42). In the base case, ICER results are identical across groups other than RDEB-S.

Table 11: Summary table outlining model changes, chronology, and impact on ICER results

Question	Change order	Impact (Base case / scenario / PSA)	Change to base ICER (absolute)	ICER (with PAS)
B4	10	Scenario	-£14,591	£81,059
B5	14	Scenario	-£9,064	£76,988
B8	9	Scenario	-£25,772	£69,878
B13	11	Scenario	-£1,358	£94,292
B16	12	Scenario	+£316	£96,023
B17	8	Base Case	-£330.31	£95,650
B25	13	Scenario	-£4 (Weibull), -£9 (SMR)	£95,646 (Weibull), £95,641 (SMR)
B27	2	Base Case	£0	£95,980

Question	Change order	Impact (Base case / scenario / PSA)	Change to base ICER (absolute)	ICER (with PAS)
B28	3	Base Case	£0	£95,980
B29	4	Base Case	£0	£95,980
B30	7	Base Case	£0	£95,980
B34	5	Base Case	£0	£95,980
B35	6	Base Case	£0	£95,980
B36	1	Base Case	£0	£95,980
Addition of observed transition numbers (update following 24/01/2023 call)	15	Scenario	(variable according to steady state time point)	(variable according to steady state time point)
Revision of paid care unit cost (update following 24/01/2023 call)	16	Base Case	-£9,598	£86,052

B2. Priority: Please provide an updated model with a log of changes since the model initially submitted.

Company response 12 January 2023: Please see "Filsuvez UK CEM v1.3" uploaded separately, with a log of changes and impact on ICER result for each change.

B3. Priority: Please provide the following reference: 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 DEB and JEB 2022

Company response 12 January 2023: The final SEE report was provided by email on Monday 19th December 2022, by Eric Low of Eric Low Consulting, following discussions at the clarification meeting that day.

B4. Priority: The CS states that '*Regressed EQ-5D utilities are used in the base case*'. Please clarify why (as detailed in Appendix P) an OLS method was used. Looking at Figure 2 in Appendix P, it appears that for BSAP values >10 that the regression

equation overpredicts the utility of the majority (75%) of patients indicating that the fit may not be appropriate.

Company response 12 January 2023: The majority of EQ-5D values from EASE (n=89, 84.0%) were from patients in health states 1 and 2 (BSAP <8%), with only 17 observations corresponding to higher severity health states. Due to the distribution of patients with EQ-5D measurements across health states, the coefficient associated with BSAP is driven disproportionately by those in lower health states. However, potential underestimation of the utility decrement associated with more severe states was considered a conservative approach given the uncertainty associated with the small number of severe observations.

Feedback received from clinicians and patient representatives suggested that while patients may plausibly experience states worse than death at certain times, negative mean utility scores would not generally be expected for any of the health states considered, suggesting that OLS fitted estimates may not overestimate patient utilities even at more severe health states. Face validity of the OLS fitted estimates was also supported by the time trade off (TTO) study and cross-sectional study (CSS) EQ-5D utility estimates, both of which provided point estimate utility scores above zero in all six health states.

We have also explored use of non-linear approaches by using a generalised linear model (GLM) with a log-link function (Figure 3). This improves statistical fit in terms of AIC (0.709 *versus* 0.749), BIC (-472.86 *versus* -472.35) and R-squared (0.139 *versus* 0.104), although the utility estimates associated with the highest and lowest BSAP health states (0.57 to 0.10) remain comparable to those estimated in the OLS-based estimates used in the original submission (0.56 to 0.08), as shown in Table 12. GLM-based utility estimates have been added as a model scenario (selectable from dashboard cell E41). Using these utilities, the ICER (net of PAS) decreases by approximately £15,000 to £81,059.

Figure 3: EASE observed EQ-5D utility scores with GLM predictions for health state midpoints

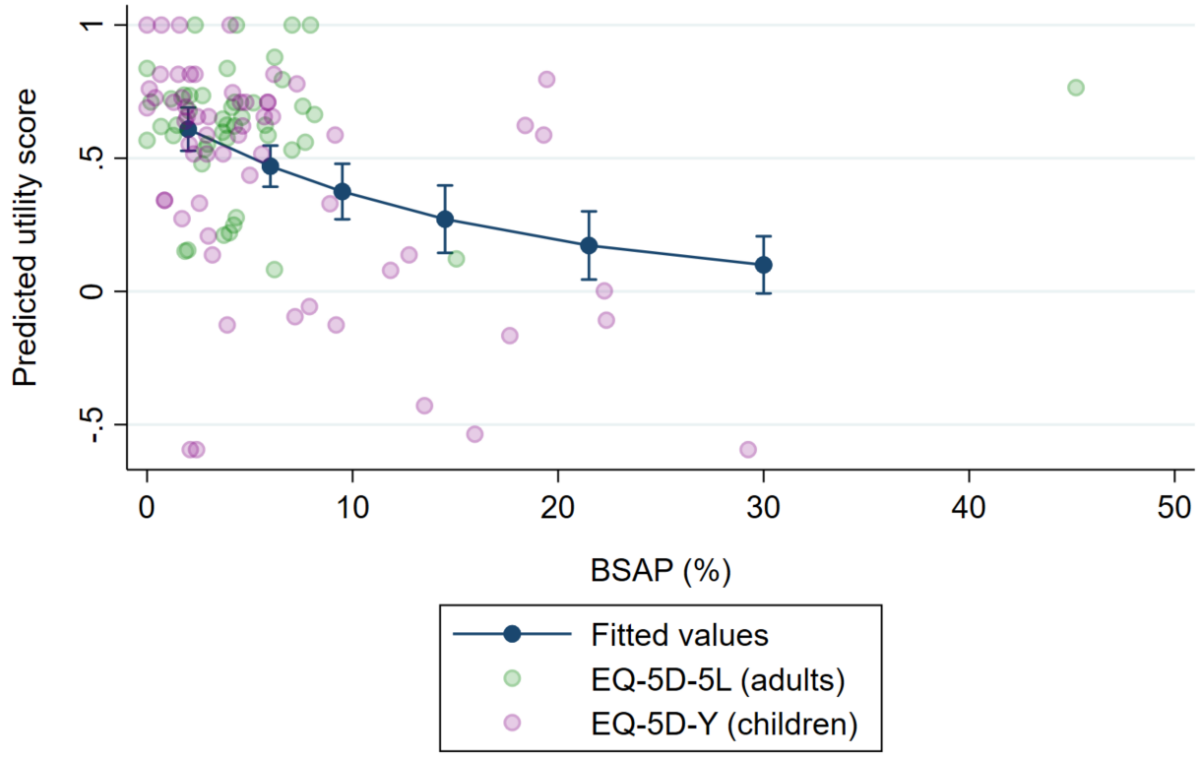


Table 12: Estimated utility scores and standard errors by model health state (GLM approach)

	Margin	Standard error	P>t	Lower 95% CI	Upper 95% CI
HS1 (BASP 0 to ≤4%)	0.571	0.036	0.000	0.500	0.641
HS 2 (BSAP 5-7%)	0.485	0.038	0.000	0.412	0.559
HS3 (BSAP 8-10%)	0.400	0.050	0.000	0.303	0.497
HS4 (BSAP 11-18%)	0.271	0.065	0.000	0.145	0.398
HS5 (BSAP 19-24%)	0.172	0.065	0.008	0.045	0.300
HS6 (BSAP ≥25%)	0.099	0.055	0.069	-0.008	0.207

Company response 20 January 2023: Additional utility estimates, derived from the 24-month EASE data cut, are provided below. These have been incorporated as an option in the updated model (v1.2), to provide internal consistency with transition scenarios derived from 12-month data.

Patient utility scores were estimated from patient-level data collected in the EASE DBP using the EQ-5D-5L (adults) or EQ-5D-Y (children and adolescents). Utility scores for adult patients were mapped from the EQ-5D-5L using the Hernandez Alava *et al.* algorithm as recommended in the NICE Methods Guide. Adult EQ-5D-3L tariffs were applied directly to EQ-5D-Y responses, in line with the analysis conducted using 12-month EASE data.

The 24-month data included n=144 EQ-5D observations that corresponded to patient visits in which BSAP was recorded (an increase of 38 observations relative to the 12-month data cut). In line with the 12-month data analysis, a generalised linear model (GLM) with a log-link function (Figure 8) provided superior fit to a nonlinear approach in terms of R-squared (0.106 *versus* 0.065), with similar AIC (0.725 *versus* 0.766) and BIC (-688.78 *versus* -688.07) statistics.

Mean utility scores at health state midpoints, and corresponding measures of variability, are provided in Table 13.

Figure 4: EASE observed EQ-5D utility scores with GLM predictions for health state midpoints (24-month data)

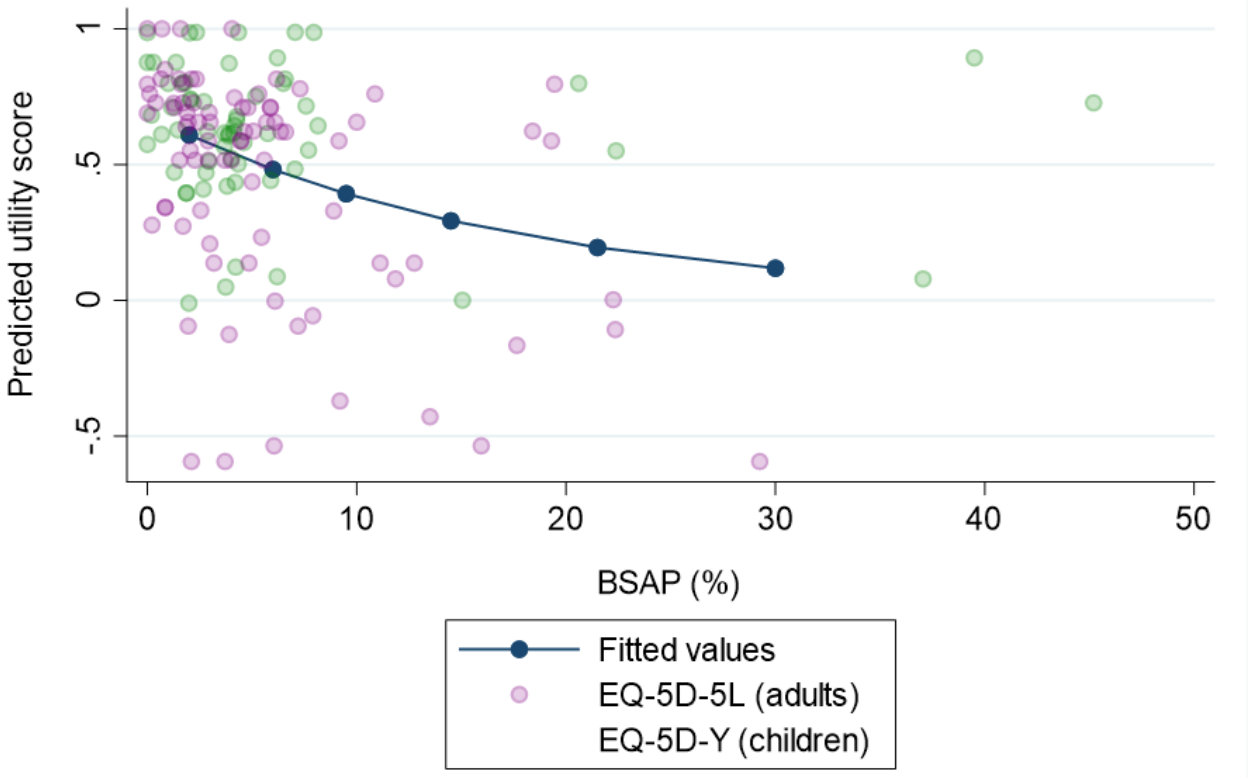


Table 13: Estimated utility scores and standard errors by model health state (GLM approach, 24-month data)

B5. Priority: Please clarify why 24-month data from the OLP was not used in the modelling (12-month data were used instead in the extrapolation). If possible, provide analyses using the 24-month data.

Company response 12 January 2023: As discussed on the clarification call of 19th December 2022, 24-month data were available shortly before submission to NICE in November 2022. Given limited time before submission it was only possible to provide aggregate figures in the submission and to use these to validate extrapolations modelled using 12-month data, but there was insufficient time to perform the data cleaning and analysis required to include the 24-month data directly in the economic model.

Company response 20 January 2023: The updated economic model (v1.2) includes functionality to apply patient transition and utility estimates using data from the 24-month EASE OLP data cut, as an alternative to the 12-month OLP based estimates described in the CS.

As described in section B.2.4 of the CS, numbers of observations within visit windows were lower than expected in the OLP, with this attributed to being due largely to the impact of COVID-19 on patients and carer's ability to adhere to visit schedules as originally planned. To minimise censoring, analyses of 24-month patient data applied the approach to visit windowing described in section B.2.6.2 of the CS, whereby

	Margin	Standard error	P>t	Lower 95% CI	Upper 95% CI
HS1 (BASP 0-≤4%)	0.609	0.037	0.000	0.537	0.680
HS2 (BSAP 5-7%)	0.482	0.037	0.000	0.410	0.553
HS3 (BSAP 8-10%)	0.392	0.053	0.000	0.288	0.496
HS4 (BSAP 11-18%)	0.293	0.068	0.000	0.160	0.425
HS5 (BSAP 19-24%)	0.194	0.072	0.007	0.054	0.335
HS6 (BSAP ≥25%)	0.118	0.064	0.063	-0.007	0.243

observations were not restricted to those falling within visit windows. Figure 5 below (Figure 10 of the CS), illustrates mean BSAP trajectories across EASE DBP and OLP visits, using this approach.

Figure 5: [redacted]

A data challenge presented by the relatively small number of observations at DBP visits is that transition probability estimates corresponding to later time points are particularly sensitive to the influence of outliers. This is a particular challenge in the context of the natural history of EB where cyclical fluctuation in disease severity occurs at the patient level due to the chronic cycle of partial-thickness wounds formation, healing and opening of new wounds.

As can be seen in Figure 6, there are few data points to inform estimates of transition rates to or from health states above 10% BSAP (Health states 4, 5 and 6), between the 12-month (Day 450) and 24-month (Day 810) visits. Of the small number of observations in this interval, several demonstrate substantial changes in BSAP. While the magnitude of such change is comparable to outliers observed at earlier time points,

the influence of outlying patients on mean estimates of absolute and relative change in BSAP (and transitions estimated from these measures), is substantially more pronounced in the OLP in the absence of sufficient numbers of patients to balance out natural fluctuations in severity.

Figure 6: [redacted]

Filsuvez gel is not expected to (directly) influence the rate at which new wounds develop. Instead, its clinical impact is on increasing the rate of wound healing, with the expectation that patients with faster-healing wounds will have fewer partial-thickness wounds at any given time and therefore resolve to a less severe steady state than those whose wounds heal more slowly. While the outliers discussed above present a data challenge as a driver of mean values, the distribution of the majority of patient results correspond well to the steady state assumptions applied in the model as a means of extrapolation. The scatterplots above both demonstrate that in the majority of patients that do not experience extreme changes, improvements achieved during the DBP are sustained at both 12- and 24-month visits with no overall trend away from a steady (x=y) state. This is supported further by the trajectory of OLP patients originally randomised to control gel (see Figure 5), who show a similar trend (with marginal improvement) between 12 and 24 months, having been using Filsuvez gel for a similar duration to those randomised to the active arm.

Choice of EASE data cut (12- or 24-month) is selectable from the model dashboard: a scenario analysis applying transition probabilities and utility estimates derived from 24-month data and assuming a steady state (no further transitions between severity states) beyond 24 months has been stored in column G of the model dashboard.

Figure 7 provides a comparison of the estimated change from baseline in mean BSAP using 24-month data with these assumptions, relative to the 12-month base case summarised in the CS.

Figure 7: [redacted]

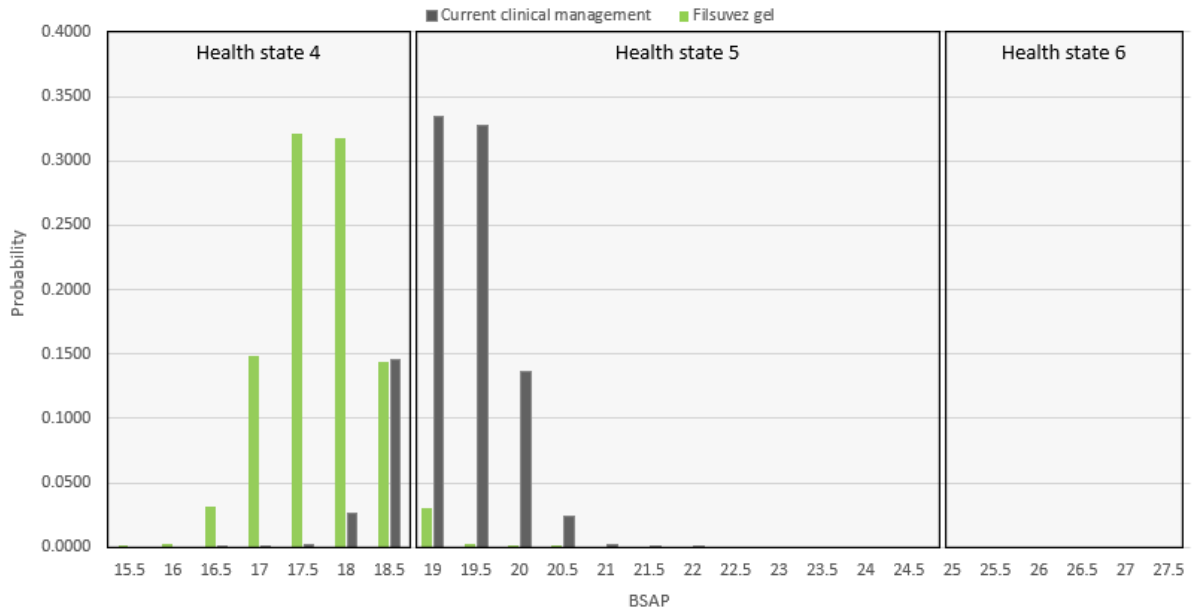
B6. Priority: Please provide the methodology used to calculate the probability of transition between the chosen health states. Would these transition probabilities be affected if it wasn't assumed that all patients were in the middle of the health state? Please clarify whether any tests were performed to validate that the BSAP data were normally distributed within health states.

Company response 12 January 2023: BSAP values at 30-day intervals was derived at the patient level from EASE data (corresponding to scheduled monthly visits in the DBP, and interpolated between visits, assuming a linear rate of change, in the OLP). ANCOVA models were specified in STATA v17.0 to predict 30-day change in BSAP

according to study arm and follow-up visit (specified as a factor variable, interacted with arm), controlling for absolute BSAP score at the previous visit. From these models, estimates of marginal mean change and standard errors were calculated according to treatment arm and time point for patients transitioning from the midpoint BSAP of each of the six model health states.

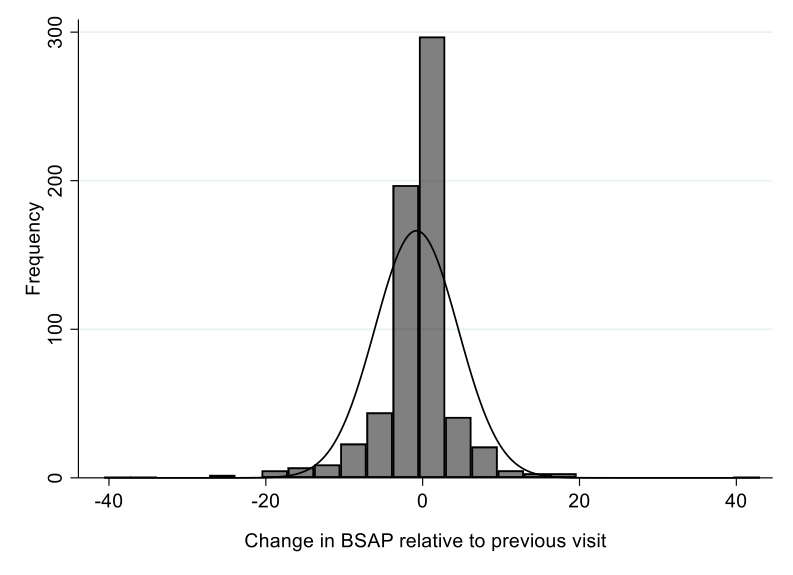
Using an approach similar to that outlined in NICE guidance NG82 (visual acuity), the mean change and variance were used to estimate proportions of patients moving to and from each health state at each time point.(12) As an illustrative example, Figure 8 shows the estimated distribution of BSAP among patients transitioning from health state 5 at day 60, based on a mean (SE) change in BSAP of -2.5 (0.52) among current clinical management patients and -4.0 (0.55) among Filsuvez gel patients.

Figure 8: Illustrative example of predicted BSAP scores among patients transitioning from health state 5 at day 30



As highlighted, this approach imposes an assumption that the *change* in patients' BSAP is normally distributed. To assess the plausibility of this assumption, Figure 9 presents a histogram of change in BSAP (relative to 30 days prior), with a normal distribution curve overlaid.

Figure 9: Histogram showing the distribution of change in BSAP relative to 30 days prior: EASE observations pooled across DBP and OLP visits (normal distribution curve overlaid)



B7. Priority: Please provide an alternative analysis where a continuity correction is applied to the EASE transitions. An analysis that may be worth considering is adding one additional hypothetical observation and dividing equally amongst possible transitions, that could be restricted to only moving one health state (better or worse) or remaining in the same health state.

Company response 12 January 2023: The model has been updated to include an optional continuity correction in the deterministic analysis. Functionality has been added to choose between no correction, division of a hypothetical observation across all health state transitions, and division across transitions to adjacent/ same health states. In keeping with the original submission version, a continuity correction is applied to all cells when running the PSA, to avoid errors when sampling from a Dirichlet distribution.

B8. Priority: Clinical advice provided to the EAG suggested that the efficacy of treatment in patients with JEB might not be the same as in patients with RDEB and DDEB. This is possibly shown in Figure 12 of the CS, although the EAG acknowledges the small number of patients with JEB. Please provide exploratory analyses assuming that only patients with RDEB and DDEB receive treatment. Note this would mean that

new transition probabilities would need to be calculated. If appropriate, please continuity correct these data too.

Company response 12 January 2023: As outlined in the CS (B.2.7), small numbers of subjects in subgroups other than RDEB (which accounted for 78% of the EASE DBP baseline sample), severely constrained the capacity for meaningful subgroup analyses of primary and secondary endpoints. The base approach adopted by the company reflects the opinion of clinical experts in the multi-stakeholder panel discussions that there is no clinical expectation for a difference in clinical efficacy between subgroups, and therefore whole population treatment effects can be appropriately generalised across EB types in the absence of sufficiently granular data.

To support the exploratory analysis of alternative assumptions, the model has been updated with a scenario reflecting transition probabilities derived from DEB patients only.

Company response 20 January 2023: The updated model version (v1.1) provided by the company on 12th January included transition probabilities derived from DEB patients only, using the 12-month EASE data cut. An equivalent analysis has been explored in the model version (v1.2) accompanying this form.

As discussed in section B5 above, patient transitions between 12 and 24-month OLP visits are particularly sensitive to outliers, with limited numbers of observations relative to earlier study visits. Restricting the sample further by EB type increases the influence of outliers, yielding transition probability estimates that result in clinically implausible extrapolations. To reflect the opinion that observations between 12 and 24-month visits do not support further disaggregation, the 24-month DEB subgroup analysis applies day 90 to 450 transition rates for extrapolations beyond day 450 by default. To explore this further, the above assumption can be controlled via a toggle on TRANSITIONS sheet cell K327.

B9. Priority: Please clarify whether there is a discrepancy between the number of carers assumed in the modelling and in the estimation of the utility impact on carers where it is stated that *'you are the main caregiver*'. Please comment on how the utility values for caregivers would change if there were fewer caregivers in the less severe

health states and more caregivers in the more severe health states as assumed in the model's base case.

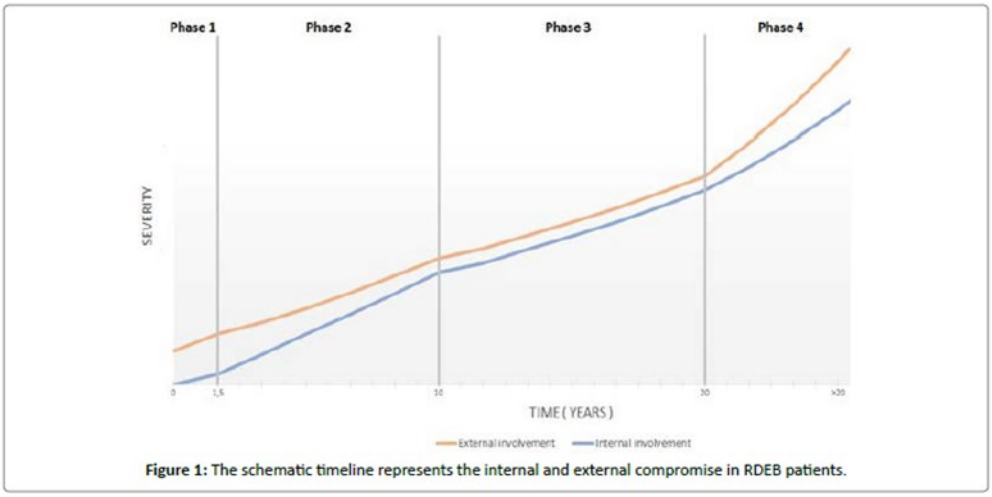
Company response 12 January 2023: As discussed on the clarification call (19th December 2022), to avoid participant fatigue and simplify the time trade off (TTO) study, participants were only asked to assume they are the main caregiver of the patient, therefore no additional questions were posed surrounding being an additional/ secondary caregiver. Hence, the utility value is assumed to be the same for all caregivers, regardless of the number of caregivers. Scenarios are explored in the model applying different numbers of caregivers per health state, including a scenario where one caregiver is applied regardless of health state (therefore directly in line with the vignette specification), the ICER in this scenario (with PAS) is £112,973/ QALY. No data could be identified to quantify the utility of additional caregivers. Hypothetically, it could be expected that the inclusion of more than one carer being involved in the caring role for patients in the relatively more severe states would result in a slightly better utility per carer than the vignette specification of the respondent being the main caregiver as the burden can be shared. It is also likely that the assumption of less than one full time carer in the least severe state would also lead to slightly higher utilities compared to the vignette specification of one main caregiver, given the total time spent caring would be less. Therefore, adjustments for both scenarios would be expected to shift utility impact in the same direction, and therefore not be expected to have a significant impact on cost effectiveness results.

B10. Priority: Please clarify whether there is likely to be confounding of the utility values generated by the vignettes due to the presence of aspects that differ even though they are not impacted on by the treatment. For example, difficulty in bowel movements change by health state, but this may not be impacted on by treatment which could improve health state. Please clarify whether treatment is likely to impact on difficulty in bowel movements, throat stretches, osteoporosis, fused digits, whether people can eat or drink normally and outpatient visits.

Company response 12 January 2023: Treatment with Filsuvez gel is not likely to directly impact on the extra-cutaneous aspects mentioned in the clarification question, above. However, while we are unaware of any published data sources directly linking improvements in wound burden and disease severity to these specific extra-cutaneous outcomes, there is evidence supporting that a reduction in wound burden can reduce

systemic inflammation and have an impact on a number of other extra-cutaneous outcomes (for example, anaemia, iron depletion, growth retardation), and overall correlation between external involvement and internal involvement in disease trajectory, is well-known (Figure 10).(2, 13)

Figure 10: Internal and external compromise in RDEB patients



Source: The Natural History of Severe Recessive Dystrophic Epidermolysis Bullosa – 4 Phases Which May Help Determine Different Therapeutic Approaches. Bageta et al. 2021.(2)

There is no data, or evidence collected in EASE to show an association between wound burden and the specific extra-cutaneous aspects of DEB and JEB, of difficulty in bowel movements, throat stretches, osteoporosis, fused digits, whether people can eat or drink normally (although based on the expert feedback we have received input that a reduction in outpatient visits may be expected with decreased wound burden). However, in the development of the vignettes in the TTO study, clinical experts were fully consulted to validate the states and so the aspects included reflect the opinions of clinical experts as to the expected impact that reducing BSAP and hence reducing wound burden (as a proxy for disease severity), would have. Whilst there is always a risk of some bias dependent on what is included or not included in vignettes (i.e., to make the vignettes sufficiently descriptive but manageable for a member of public to comprehend for the purposes of the TTO exercise), we do not feel this has overly confounded the relative utility values.

The health state vignettes were developed as part of the TTO exercise employed to elicit health state utility values to validate the EQ-5D data collected as part of the EASE

OLP, and to provide carer utilities that were not available from EASE using EQ 5D (CS Section B.4.5.3.2). There was alignment between EASE-derived EQ-5D patient utilities and those generated from the TTO, in terms of utility decreasing as disease severity increases (CS Table 23 and Table 27). For the patient utility estimates there are higher absolute values across health states compared to the EASE EQ-5D derived values. Therefore, the absolute values for the health states from the EASE-derived EQ-5D data were thought to be most reflective of the HRQoL of patients with DEB or JEB (at 0.56 for best health state and 0.08 for worst health state) and coupled with the EQ-5D representing the NICE reference case, these values were used in the base case, and TTO values in scenario analysis.

B11. ***Priority:*** *Please clarify why the discontinuation rate observed in the OLP was not used (█% over the 2 period), but clinical opinion was used instead which had a much lower rate of (1% per annum).*

Company response 12 January 2023: Feedback from clinicians and a patient representative at the multi stakeholder panel meeting suggested that in clinical practice only a small proportion of patients would be expected to discontinue treatment with Filsuvez gel due to the favourable safety profile and lack of other available existing alternatives.(14)

Also, several of the reasons for discontinuation in the EASE trial were linked to trial protocol criteria and would not correspond to treatment cessation in real-world usage: for example, the incidence of SCC or other localised complications led to trial discontinuation, but would not be expected to lead to discontinuation (other than to the area of the body immediately affected, for the duration of the event) in clinical practice. Patient listings also identified discontinuations due to the practicalities of meeting trial criteria in terms of travel to follow-up visits, particularly during the Covid-19 pandemic, that would not apply in a real-world setting. It is also useful to note that discontinuation rates tended to decrease over time in the EASE OLP, so thus maybe more reflective of what would be seen in clinical practice.

Base discontinuation rates are intended to reflect a conservative approach in terms of impact on cost-effectiveness results, but can be modified in the model dashboard.

B12. Priority (Original wording 12th Jan Response): Please clarify whether patients who discontinue treatment after 90 days are always assumed to remain in the health

state **before** discontinuation. Please comment on the plausibility of this assumption which means that patients discontinuing treatment in HS1 would remain in this health state until death on standard care. Please also explore the impact on the results if people who discontinue are instead move to a health state based on the distribution of people across health states who have had 90 days of standard of care.

Company response 12 January 2023: Patients treated with Filsuvez gel transition between health states for up to 1 year in the base case of the model. After 1 year, the cohort of patients remain in current EB health states until discontinuation or death. The assumption in the model is that the cohort of patients will reach an equilibrium where the proportion of patients in each health state does not change over time, but individual patients will still be able to transition to and from health states, i.e., the individual patient movements counteract each other, keeping the cohort distribution between health states steady. This assumption is made to reflect patients in UK clinical practice, where over time with the implementation of Filsuvez gel, it is expected that the cohort of patients will maintain a "steady state" where patient distribution across health states remains constant, but individual patients will fluctuate over time. The model imposes this assumption as a simplification, in lieu of data to follow individual patient fluctuations and transitions through the model.

B12. Priority (updated wording 20th Jan response): Please clarify whether patients who discontinue treatment after 90 days are always assumed to remain in the health state **after** discontinuation. Please comment on the plausibility of this assumption which means that patients discontinuing treatment in HS1 would remain in this health state until death on standard care. Please also explore the impact on the results if people who discontinue are instead move to a health state based on the distribution of people across health states who have had 90 days of standard of care.

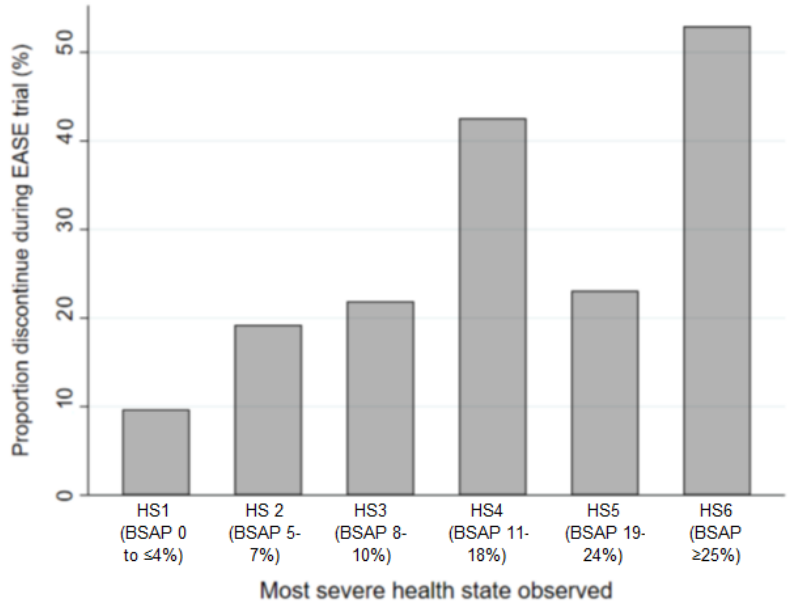
Company response 20 January 2023: Thank you for providing clarification on this question. To expand on this in the context of responses to B5 above, the imposition of steady state assumptions is intended to reflect the assumption that while severity may be expected to fluctuate at the individual level due to the dynamic nature of EB, no change in the overall distribution of patients at the cohort level is expected beyond the time point specified. The model imposes this assumption as a simplification in the absence of robust data to inform longer-term transitions.

Under base settings, patients that discontinue after 90 days remain in the state in which they resided immediately prior to discontinuation (consistent with the rule applied to current clinical management patients beyond 90 days). As requested above, functionality has been added to the model (selectable from DASHBOARD cell E74) to distribute patients that discontinue at any time point according to the distribution of (surviving) patients receiving standard of care at 90 days. Please note that this scenario may lead to counterintuitive scenarios whereby discontinuation triggers a decrease in severity, particularly if used alongside scenarios in which discontinuation rates are varied by severity.

B13. Priority: Please clarify whether there was any observed correlation between the health state of the patient and discontinuation. It may be plausible that those in worse health states would discontinue more rapidly than those in less severe health states. If there is a noticeable correlation then incorporate this into the model.

Company response 12 January 2023: Patient-level data suggest that rates of discontinuation were higher among patients that had spent time in more severe health states (Figure 11).

Figure 11: Proportion of patients discontinuing during EASE trial according to most severe health state observed



In keeping with the response to clarification question B11, several of the reasons for discontinuation may not be generalisable to a real-world setting, and there is

uncertainty as to whether higher severity patients are disproportionately likely to have broken EASE trial protocol (e.g. due to the presence of complications), and therefore whether this correlation can be generalised beyond the trial.

The model has been updated to allow for separate discontinuation rates by health state to explore sensitivity to this assumption. Assuming a five-fold difference in the probability of discontinuation across health states, from 1% per annum in health state 1 to 5% per annum in health state 6, the ICER (with PAS applied) decreases by £1,358 to £94,292 compared to the base case in which an annual rate of 1% is applied across all health states.

B14. The reason for the selection of the bounds for the health states considered (0-4%, 5-7%, 8-10%, 11-18%, 19-24% and 25%+) is not compelling as it appears to be based on forming equal groups at baseline. Were clinicians asked to recommend their own groupings? Please clarify why the EASE baseline (pooled) was not preferred to an arbitrary estimate of ⅙ of the population in each group.

Company response 12 January 2023: No existing categories exist to define EB disease severity by BSAP cut-offs, therefore, to allow for the largest patient numbers for each health state in terms of generating robust transitions and health state utility estimates, health states were defined using equal distributions at EASE baseline. Interviews were then held with a clinical expert (Professor Jemima Mellerio) to validate these health state categories. She had no disagreements with the health states proposed and agreed that these were a good fit for capturing different levels of EB severity for patients seen in clinical practice. These health states were also discussed and supported as appropriate by the clinicians participating at the multi-stakeholder panel meeting.(14)

A uniform baseline distribution across health states was chosen to reflect potential under-representation of more severe patients in the EASE trial, but the model allows for EASE baseline characteristics to be applied.

B15. Please clarify why the EB subtype distribution was taken from Petrof *et al* rather than the EASE study.

Company response 12 January 2023: Petrof *et al. 2022* was used to model EB subtype distribution as this was considered to be most representative of the patient

distribution in UK clinical practice, given the longitudinal observation of patients in the UK over a number of years in the study.(15) It is likely that due to the study inclusion/ exclusion criteria, the EASE trial distribution overestimates the number of RDEB-S patients than would be expected in clinical practice.

B16. Please clarify why the starting age in the base case was set to 0.5 years. This appears to be calculating the cost-effectiveness of incident cases rather than prevalent cases. Is the intention that only incident cases would be treated?

Company response 12 January 2023: The licensed indication for Filsuvez gel is to treat patients from the age of 6 months, while DEB and JEB can be diagnosed from birth, 0.5 years was used as the starting age in the model, hence in principle this is akin to modelling the treatment of future incident cases. Setting the start age to 0.5 allows for following the cohort over a full lifetime horizon to assess all relevant costs and health benefits while also enabling differences in adults and children to be captured. However, it is recognised that in practice and at least initially Filsuvez gel might not only be used to treat incident cases. Therefore, a scenario analysis is explored using the average age at EASE baseline (16.6 years), this scenario has only a very small impact on the cost-effectiveness results (ICER of £96,023/ QALY with PAS).

B17. Please clarify why the time horizon is set to 50 years in the base case. This would not represent a lifetime horizon. When setting the starting age to 18 years and assuming a 100-year time horizon 3% of patients in the RDEB-S group remain alive at the end of the model. The EAG suspects that this is not intentional. Please clarify if this is the case and amend the model if needed.

Company response 12 January 2023: Thank you for this observation. A shorter 50-year time horizon can be said to be pragmatic to avoid very long-term extrapolations (100 years) based on short term trial data (90-day RCT plus up to 24-month OLP), and captures almost all relevant costs and health effects. However, to reflect the point made by the EAG, the model base case has been amended to include a 100-year time horizon, to reflect a lifetime horizon. This has only a very small impact on the ICER.

B18. Please clarify whether marked changes in results in Table 13 of the CS when n=53 rather than n=50 indicates heterogeneity in outcomes between patients and

different patients providing results. For example, the change in EBDASI is a reduction of 0.3 (n=50) but is a reduction of 0.9 (n=53).

Company response 12 January 2023: The change from n=50 to n=53 patients reflects the net addition of n=3 patients between an interim analysis and the final efficacy analysis. Specifically, due to the update in the SAP (Version 6.0, 9th September 2022), n=5 patients were removed from the previous interim Month-12 analysis and n=8 patients added to the final Month-12 analysis, therefore the marked change in results is attributable to the movement of n=13 patients, in total.(16)

As described in CS B.2.4.1.1, the changes in Version 6.0 of the SAP related to the analysis performed for efficacy at Month 12 and Month 24, updated to use a new visit windows. Previously a year was considered to have 360 days (that is 30 days per month), however it was noted that when capturing the data at the investigator sites, the conventional year length of 365 days was generally used. Thus, the window was updated to 365 days ±14 days for Month 12 and to 730 days ±14 days for Month 24. Therefore, as the windows changed from 360 days to 365 days for Month 12 and from 720 to 730 days for Month 24, some visits were shifted and changed from scheduled to unscheduled visits and vice versa, resulting in both the gain and loss of patients, as in this particular example.(16)

B19. Please provide analyses using the most favourable elicited values for treatment and the least favourable elicited values for treatment to allow the committee to gauge the uncertainty associated with the elicitation.

Company response 12 January 2023: As discussed at the NICE clarification call on 19th December 2022, the EAG have now seen the SEE report (see section B.3 response) and provided specific queries relating to the SEE valuations which will be responded to by 20th January.

B20. Please clarify why the Van Hout *et al*. mapping was used rather than Hernandez Alava *et al.* as described in 4.3.16 of the NICE Methods Guide.

Company response 12 January 2023: The Van Hout *et al*. mapping algorithm was used rather than Hernandez Alava *et al.,* given that the utility analyses for the model were prior to the new NICE methods guidance being published, following guidance in

the previous NICE methods guide from 2013, where Van Hout *et al.* was listed as the recommended method to obtain EQ-5D utility values.

B21. In the PSA, utility values are constrained to not be higher than less severe states, which can introduce bias. Other approaches (such as Ren S, Minton J, Whyte S, Latimer NR, Stevenson M. A new approach for sampling ordered parameters in probabilistic sensitivity analysis. Pharmacoeconomics 2018; 36 (3), 341-347) exist. Please quantify how often the minimum constraint is employed for all sets of ordered parameters.

Company response 12 January 2023: A macro has been incorporated into the model to quantify how often the minimum constraint is employed for patient and carer utility values. For the base case patient utilities over 1000 iterations, the constraint is applied 527 times.

The base case carer utility values sourced from the TTO study have relatively high standard deviations (0.21-0.27), meaning that the minimum constraint is present in a total of 895 out of 1000 (88%) iterations.

B22. Please provide evidence based on data from EASE that the BSAP value is likely to be in the midpoint of the chosen health state. That is, justify that the aggregated values of people in HS4 (BSAP 11-18%) could be accurately approximated by all patients having a BSAP of 14.5%. If BSAP were lognormally distributed then the true midpoint of the data between more severe bands is likely to be lower than that currently assumed.

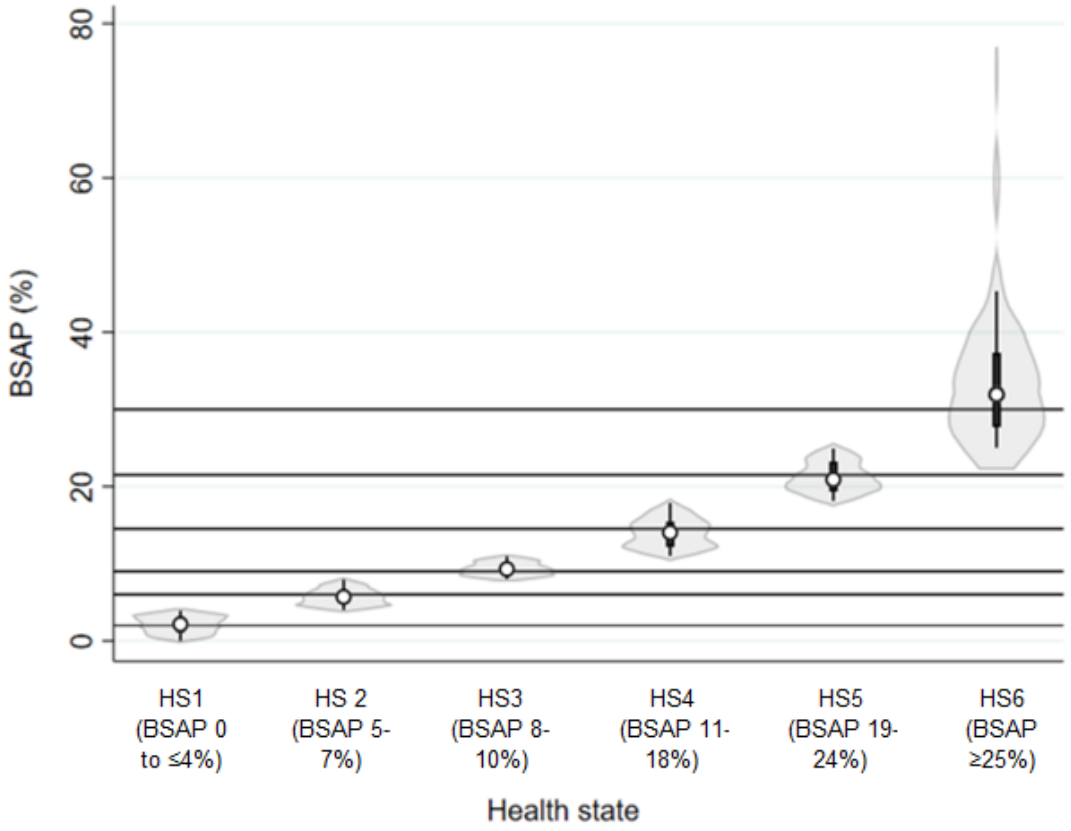
Company response 12 January 2023: Table 14 and Figure 12 compare median BSAP by health state (reflecting EASE observations pooled across all patient visits) against the midpoints assumed in the CEM, showing that it is likely that the BSAP value is likely to be in the middle of each health state, and close to a BSAP of 30 for the most severe health state.

Table 14: Comparison of EASE Observed and Health State Midpoints

Health state	Median BSAP (EASE observations)	Health state midpoint assumed
HS1 (BSAP 0 to ≤4%)	2.2	2.0
HS 2 (BSAP 5-7%)	5.7	6.0
HS3 (BSAP 8-10%)	9.3	9.5

Health state	Median BSAP (EASE observations)	Health state midpoint assumed
HS4 (BSAP 11-18%)	14.0	14.5
HS5 (BSAP 19-24%)	20.9	21.5
HS6 (BSAP ≥25%)	31.9	30.0

Figure 12: Violin Plot of BSAP Midpoints



B23. Please clarify why HST8 (in Table 30) was deemed relevant to this decision problem.

Company response 12 January 2023: Thank you for your observation. The utility values in Table 30 of the submission are from the cross-sectional study (CSS).(17) The heading label, 'HST8', is incorrect, and should be 'CSS'.

B24. Please clarify why the bandage frequency data (Figure 9 of the CS) was not used in the population of the model, but the results from the SEE were preferred. Please

provide a comparison of the expected costs associated with dressings predicted by the model in 90 days and that estimated from the observed EASE data.

Company response 12 January 2023: Figure 9 in the company submission shows the change in weekly frequency of dressing changes. To calculate cost per BSAP health state for dressing changes in the model, the number of dressings applied per visit was elicited from clinical experts in the SEE, and this data was used to estimate the cost of dressing changes per BSAP health state. A mean annual cost of dressing changes was elicited from PEBLES (Pillay *et al.*),(18) and then weighted per BSAP health state in the Filsuvez gel cost-effectiveness analysis using the SEE results. The number of dressings applied at each visit was not collected in EASE, therefore the costs could not be calculated. In addition, we feel the data on dressing and bandage frequency from the SEE conducted with UK clinicians is likely to be most representative of clinical practice in the UK compared to resource use data from EASE.

B25. Please clarify whether using a standardised mortality ratio for RDEB-S patients would give a discernibly different ICER than assuming a mortality rate of 0.0028 per cycle. Is the assumption of a constant hazard of death plausible?

Company response 12 January 2023: The economic model has been updated to allow for overall survival among RDEB-S patients to be approximated using a standardised mortality ratio (SMR) relative to the general population. An SMR of 74.1 has been applied, based on the difference between age-specific mortality rates from a digitisation of the Petrof *et al.(15)* Kaplan-Meier overall survival curve for RDEB-S and general population rates. Workings for this calculation are included in the KM sheet of the updated model.

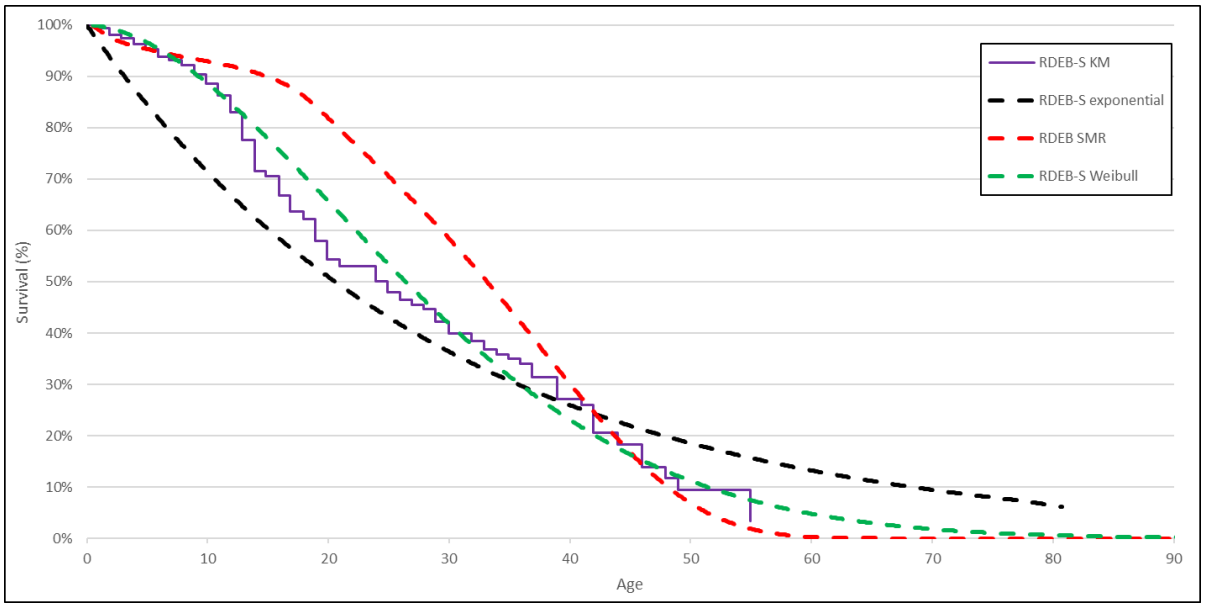
A potential challenge presented by the SMR approach is whether the age profile of the general population curve is applicable to RDEB-S cases. A particular issue is that increased mortality at very young ages (<1 year) in the general population may be inflated to unreasonably high rates when applying the SMR. To adjust for this, age-specific rates below 1 year are capped at the rate observed among 1-2 year olds.

In the absence of conclusive clinical evidence as to the plausibility of a constant hazard of death, survival in the RDEB-S group has been explored further by adding a Weibull distribution as a scenario. This provides a marginal improvement relative to the

exponential curve in terms of statistical fit (AIC 7709.5 relative to AIC 8087.8 for the exponential). A comparison of the three choices of curve against the Petrof Kaplan-Meier curve are shown in Figure 13, below. For all options, the model imposes an adjustment whereby age-specific mortality rates cannot fall below those in the general population.

RDEB-S survival approach can be selected from a new input cell in the model dashboard. Since the model applies does not assume a difference between treatment arms in mortality rates, the sensitivity of cost-effectiveness results to the choice of distribution is very low.

Figure 13: Comparison of RDEB-S survival curves applied in the updated CEM against Petrof Kaplan-Meier curve



B26. Please clarify why it was thought that '*at any one time up to 150-175 patients will be using Filsuvez gel*'. Please clarify why patients would not want this treatment were it to be recommended.

Company response 12 January 2023: These figures were first discussed and agreed at the scoping meeting. They were agreed in consultation with senior clinical experts from two of the specialist centres treating EB patients. They have been verified with both clinicians and by the NICE Topic Selection Oversight Panel (TSOP), as part of their deliberations around Filsuvez gel meeting the HST criteria.

There are two factors underpinning these figures. The first is the number of patients presenting with severe forms of EB in each of the four specialist centres in England and, secondly, because of entrenched behaviour regarding the current treatment regime of patients, there is reluctance from patients and carers to adopt new treatment approaches, even if the new treatment is supported by evidence for improved outcomes.

B27. In the cost sheet 'E16:F17' there is a '#REF!'. Please clarify whether this affects the intended functionality of the submitted mode.

Company response 12 January 2023: Formulae for COSTS sheet cells E16:J17 have been amended to remove unused options from the CHOOSE statement. The corresponding named range "list_costsource" has also been restricted to two options to reflect this change. Intended functionality and model results are not affected.

B28. In the cost sheet 'F37:F42' the if statement refers to 'Vary by health state' which is not an option for 'LV_oleogeltubes_month'. Please clarify whether this affects the intended functionality of the submitted model and if not clarify how to run the analysis where the number of tubes varies by health state.

Company response 12 January 2023: This was a legacy option and is not functional within the model. The IF statement has been removed.

B29. Please provide details on the linear regression of the number of Oleogel tubes used in EASE that provides evidence for cells F128:F133 of the Costs worksheet. Please clarify whether a linear regression model is appropriate.

Company response 12 January 2023: This was a legacy option using placeholder assumptions and is not functional within the model. The unused values in COSTS cells F126:G133 have been removed.

B30. Please clarify why a Bank of England inflation rate was used rather than a health-related one as provided in the PSSRU document

Company response 12 January 2023: Thank you for your observation. We agree the PSSRU rate would be appropriate to use. This has now been updated to the health-related inflation rate reported in the PSSRU document. (NHSCII Pay and Prices 2020/2021). This update does not change the base ICER.

B31. Please confirm that whilst the utility of carers does not decline over time that this is not a problem when there is no mortality difference between arms and utility decrements associated with each health state are assumed. In investigating this, the ERG believes that the formulae in cells P14:P19 should use variable names such as LV_CarerUtility_HS1 rather than referencing J14:J19. Please comment on the EAG's belief that if utilities were assumed multiplicative and carer utility declined over time that this would be marginally favourable to the treatment.

Company response 12 January 2023: As the economic model does not assume treatment effects on mortality, incremental carer QALYs are driven solely by patient distributions across severity states.

While age-related decrements could feasibly be applied to carer utilities, doing so would require several assumptions around the dynamic characteristics of carers over a patient lifetime. Most importantly, informal caregiving responsibilities are likely to transfer from parents of children and adolescents to partners or siblings as patients age, such that decreases in carer QALYs attributable to ageing are likely to be offset by adjustments to the assumed age profile of carers over time. Given the reliance upon assumptions to apply this correction, and the likelihood that net impact would be limited for the reasons stated, it was considered more transparent to treat the elicited carer utilities as generalisable across carer profiles. The company is not aware of a precedence for age adjustments in previous NICE appraisals or specific guidance on this matter.

B32. Please clarify that the base case in the model assumes no worsening in BSAP over time in the RDEB-S group. This appears to contrast with text on p142 of the CS. Please provide documentation relating to the calculation of distribution amongst health states when an increase of 1.3% in BSAP is assumed for the R-DEB-S group as this is not clear from the spreadsheet.

Company response 12 January 2023: No worsening of BSAP over time is assumed in the RDEB-S group in the base case. A scenario exploring an increase of 1.3% per annum for RDEB-S patients is applied, where there is minimal impact on incremental cost-effectiveness results.

The distribution of patients over time when applying a 1.3% increase in BSAP per annum in the RDEB-S subgroup is shown in Figure 14 and Figure 15.

Figure 14: Filsuvez gel arm (RDEB-S) distribution

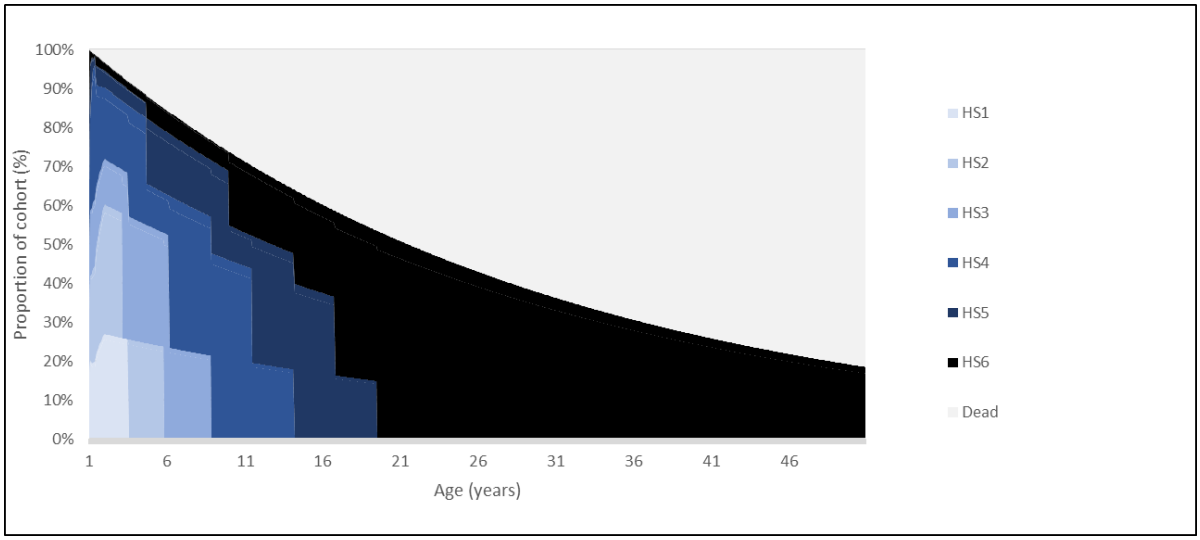
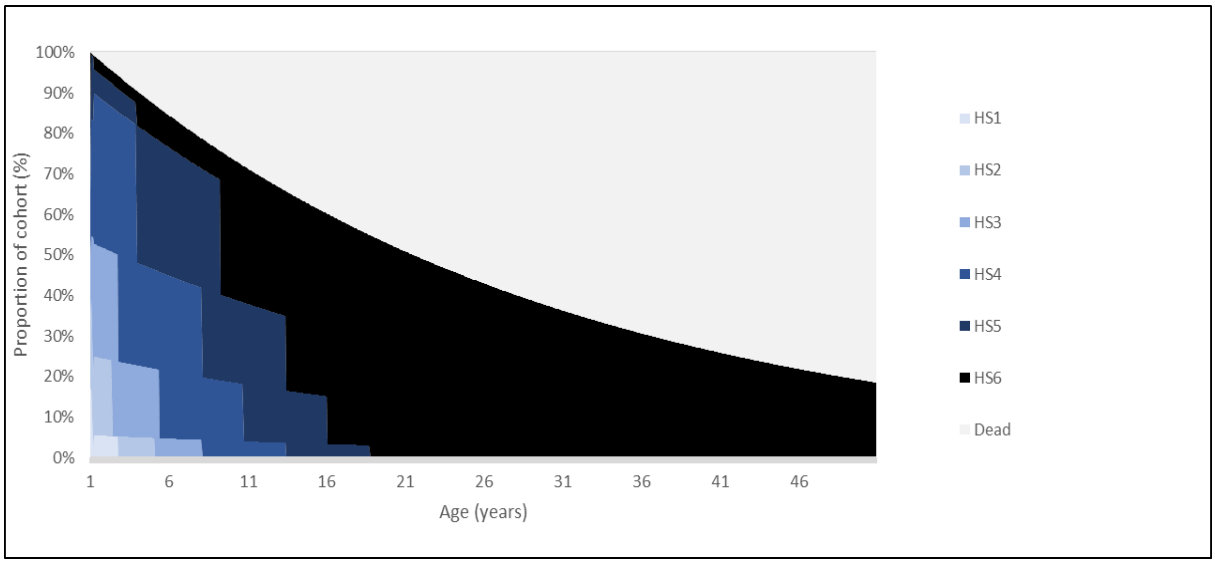


Figure 15: CCM arm (RDEB-S) distribution



B33. In the calculation of the Markov traces for treatment it is noted that the transitions for Day450 plus are used from day 150. This does not influence the results as the transition probabilities between day 90 and day 450 are the same as those 450+ but has been highlighted in case different probabilities are used for these two periods in adaptations (as may be needed if two-year data are used for transition probabilities). Please amend the model if appropriate.

Company response 12 January 2023: The model has been amended to apply the appropriate transition probability matrices. This does not impact base case results.

B34. Please clarify whether the exchange rate used in J82 of the Costs sheet is correct. The supplied link appears to relate to exchange rates in 2012, not 2020.

Company response 12 January 2023: The exchange rate in the cost sheet of the model was incorrect; this has now been updated to reflect a EUR-GBP 2020 conversion rate. This does not impact base case results.

B35. Please clarify whether costs calculation in CCM worksheets CA to CF should use row 16 in the first bracket as these are people linked to the treatment arm. For example, cell CA17 should use E16 rather than E17 in this bracket. The EAG notes that this will not currently affect the results as the costs are assumed independent of treatment.

Company response 12 January 2023: Thank you for noting this. Formulae in the CCM sheets have been updated to correspond to the CCM arm costs. This does not impact base case results.

B36. The EAG has noticed a very slight discrepancy in the mortality rates of JEB compared to the rates in RDEB (other) and DDEB. For example, in cell Z100 of JEB CCM, the assumed probability of death is 0.0029119, whereas in DDEB CCM and RDEB-O CCM this value is 0.0029502. Please clarify why this is happening and attempt to amend the model so that the same probabilities of death are used in all three types of EB.

Company response 12 January 2023: The CEM has been corrected to align mortality assumptions for JEB with RDEB-other and DDEB. This change has minimal impact on aggregate results (ICER of £95,980.06/ QALY).

Additional updates following 24/01/2023 call:

1. **Revision of paid care unit cost source**

As discussed on 24th January 2023, the hourly carer cost of £12.50 reported in Pillay *et al*. (2020) and applied in the submission model (18) likely underestimates the true cost of paid care. During this discussion, the PSSRU unit cost handbook (hospital nursing costs) was identified as a more appropriate source of cost estimates. (19)

The model base case has been updated to include an hourly care cost of £51.00, reflecting the hourly cost of a band 6 hospital-based nurse. This revision reduces the

model base case ICER from £95,650/ QALY to £86,052/ QALY. The Pillay estimate applied in the original model version may be reinstated using DASHBOARD cell E75.

2. **Addition of EASE observed transitions**

As requested on 24th January 2023, transition probabilities calculated directly from observed patient transitions have been reinstated as a model option. An additional sheet (EASE OBSERVED) has been added to model version 1.3, detailing numbers of patients observed transitioning between health states from 12- and 24-month data cuts. Transition matrices using this approach have been recalculated for consistency with the mean change approaches (12 and 24-month data cut analyses) in terms of visit windowing and health state definitions.

12-month data cut transition probabilities may be applied via the model DASHBOARD (cell E37). This applies observed transition probabilities up to day 90 in both arms, and the base case approach (whereby Filsuvez transitions beyond 90 days are derived on the basis of mean change between annual follow-up visits) thereafter. Setting the steady state time to 90 days in DASHBOARD cells E34 and E35 will assume no further change in health state beyond 90 days in either arm, consistent with the observed transition approach applied in model version 1.0.

Section C: Textual clarification and additional points – All responses provided 12 January 2023

C1. There appears to be a typo in the following sentence, please amend. '*The analysis of the impact of wounds on sleep showed a slight increase (better sleep) from OLP baseline to Month 3 in patients who received Filsuvez gel in the DBP, and a slight increase (worse sleep) in those who previously received the control gel.*'

Company response: Thank you for your observation. The sentence should read: 'The analysis of the impact of wounds on sleep showed a slight decrease (better sleep) from OLP baseline to Month 3 in patients who received Filsuvez gel in the DBP, and a slight increase (worse sleep) in those who previously received the control gel.'

C2. There may be a typo in the following sentence. Please amend if so, if not, please clarify how the mean time is greater than the mean range in the most severe group. '*The mean time to perform dressing changes for self-reported patients was 4.54 hours (SD: 2.16) with a mean range of 1 hour for patients with BSAP Health State 1 (category of ≤4%), to 3.75 hours for patients with a BSAP Health State 6 (category of ≥25%)*'.

Company response: Thank you for your observation. The sentence should read: '*The mean time to perform dressing changes for self-reported patients was 2.13 hours (SD: 3.41) with a mean range of 1 hour for patients with BSAP Health State 1 (category of ≤4%), to 3.75 hours for patients with a BSAP Health State 6 (category of ≥25%)*', in CS Section 4.6.1.3.

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	DEBRA UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	DEBRA is a national charity and patient support group for people living with epidermolysis bullosa. We provide: 1. care and support to improve the quality of life of families living with EB 2. information and training to those working and living with EB 3. we fund pioneering research into EB to find effective treatments and ultimately cures DEBRA is funded through our network of 100+ shops, individual donations, corporate supporters, trust donations, and money raised by the public through events, runs and challenges. We currently support over 3,000 members (people affected by EB, their families and carers, and some healthcare professionals and researchers who work with EB). Our vision is for a world where no one suffers with EB.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in	Amryt Pharmaceuticals are part-funding an Insight Study we will conduct to better understand what it means to live with EB. Quantifiable data of this kind about EB is poor in the UK, and this study is therefore essential for us to better advocate for our members. Amryt are contributing £56,000 towards the study. Amryt Pharmaceuticals also funded £15,000 towards us delivering a "Members' Weekend" in May 2022. This annual event allows individuals and families living with EB to travel across the UK to meet each other, as well as other EB experts and staff from DEBRA, for information, support, and peer-connection.

the evaluation stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	The member services directorate at DEBRA works with people living with EB every day. Our role in advocating on their behalf with healthcare services, government benefit schemes, and educational services means that we have an in-depth knowledge of the everyday impact that EB has on the lives of our members. We are with families from our first visit to their homes when a new-born has been diagnosed, through their journey often becoming unpaid carers for their family members. We help them navigate the complicated systems of benefit schemes, and the lack of awareness of their condition amongst their schools, GPs, and places of work. We provide advice, support, and funding to cope with all stages of life for example during heatwaves that exacerbate the condition we would provide cooling equipment which directly improves health outcomes. And we are there are the end of life to support the families who've lost loved ones to the condition. We involve our members voice in all elements of our charitable activity as much as possible, so that all our plans and practices have members at their heart. Specific to this consultation, we have also asked members from our "involvement network" who have lived experience of dystrophic or junctional EB to send us their testimony about what it is like to live with, or care for someone with, the condition, and what they think about the current care available on the NHS. We have collated their experiences to inform our response to this consultation.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	People living with EB live in constant and debilitating pain, and in severe cases it can be fatal. Our member [redacted] has submitted her testimony to explain what it is like for her to live with EB. "I have suffered with Dystrophic Epidermolysis Bullosa (Recessive) for 56 years now. Born with RDEB, my whole body is affected, more so on my feet, legs, hands, and elbows. My skin is prone to rubbing off with friction, and I often wound myself doing everyday activities. I also find that seams in my clothes rub holes in my skin, hence why I say I 'suffer'. I have tried an endless amount of medication and creams in a bid to ease my suffering, but to no avail. Walking, eating, and sleeping can all result in damage to my skin." **Physical condition** The reality of living with EB is not just simply trauma or friction causing the skin to blister and tear easily, but large areas of skin may simply be missing, raw and bleeding requiring 2-4 hours of specialised dressing changes daily. This invariably worsens with age as the inflammation and scarring associated with this condition take hold. Chronic pain is a key factor with most people experiencing pain every day – specifically at dressing changes at a level often requiring morphine-based pain relief. They experience intractable itch with the continued healing, wounding, and scarring process. Patients invariably have mitten hands and feet rendering them useless as the digits are fused together reducing hand function and ability to walk. EB is chronically disabling. Our member [redacted] describes that "It's painful. I have sores on my hands and legs most days. It stings when I have a bath. Its itchy, my skin blister if I itch". [redacted], one of our members, is [redacted] and describes the itch she experiences "My feet were really swollen and really sore. It was also very itchy. Everyone was telling me to stop itching because you're going to make it worse, but it was really hard to ignore the itch." Internal blistering of all mucus membranes may be experienced with oesophageal dilatation a commonly required surgical procedure. Our member, [redacted], goes on to describe her difficulties eating. "It affects my swallowing, I choke on the smallest particles of food, I have to regurgitate the food back up or press on my throat to force it down. I have to sit up straight when I eat. I can't have a conversation when I'm eating as I have to concentrate on chewing every mouthful as small as possible before I swallow." [redacted] is [redacted] and has Recessive Dystrophic Epidermolysis Bullosa (RDEB). EB affects every part of [redacted]'s life – the continual blistering causes constant pain and itching as well as severe problems eating and drinking. She

	has lost a lot of weight and cannot run around like other children. She says "EB stops me from having a normal life, and that is what I want. " This is a rare, complex, multi organ condition. Optimal management requires a multidisciplinary approach and revolves around the protection of the skin against slightest injury, use of careful wound care dressings, aggressive nutritional support, and early medical or surgical interventions if needed to manage any complications. The multidisciplinary team consists of a dermatologist, paediatrician, anaesthetist, surgeon pathologist, medical geneticist, pain specialist, specialised nurses, psychiatrist or psychologist, social worker, hand therapist, physiotherapist, occupational therapist, ophthalmologist, gastroenterologist, dentist, otolaryngologist, and endocrinologist. [redacted] says "My fingers closed, and I had an operation on my hands. Four months later they were closed again. I had another operation on my throat because I couldn't swallow food or water. It was very helpful, but it started closing again. I have a gastronomy button now, a tube that goes in your stomach and you give food or drinks with a syringe. I also use it to drink my medicines because they taste disgusting!" People living with DEB and JEB are susceptible and can succumb to skin cancers and have to undergo further painful and exhausting treatments. **Implications for mental health** The constant pain, and need for often daily painful and invasive care to wounds, can take its toll on the mental health of the person with EB and their family. Our member talks about how her son's "mental health is very poor and this impacts on mine and that of my daughter who has curtailed her life and career to support him." Another member [redacted] describes how despite having to make significant adjustments to her life to live with EB "I hide it. People don't understand what it is. I don't want anyone to feel sorry for me." There is such low awareness of EB and how it affects people, and this can often lead to feelings of loneliness and isolation, and it can be hard to access the care and support needed. Our member, [redacted], whose daughter lives with Dystrophic EB says "It is heartbreaking to see her in pain, bottling up her worries so she doesn't impact others and doing her best to live her life just as her peers do. Yet often missing out." **Implications for school/work/equality of experience**

	As well as the extreme pain, many people with EB face huge barriers to other elements of their life where their disability means they are not welcome or treated equally. There are financial and educational issues specifically in EB because of the specialist nature of the condition. Schooling can be patchy due to the time it takes for children to have their bandages changed daily, and having to miss school due to ill-health, lack of specialist equipment available for them, travel to medical appointments and fatigue. Finding appropriate employment can be difficult with many adjustments needed and challenges of travel and time required in managing the condition often not making this viable. Our member laments the fact that her "son is in constant pain and has been unable to pursue his career as a mathematician due to his seven-hour medical treatments each day and the medication needed to cope with this". **Costs to the family and society** The costs of EB are far-reaching. The cost of drugs, medical tests and interventions, hospitalisations, dressings, and practical aspects of daily life are only part of the whole which also includes carers, social support, and productivity loss. Parents often need to give up work to become full-time carers meaning they have fewer resources to support their family or adults with EB cannot work so rely on state benefits. The impact on the family as a whole is devastating, especially the impact on siblings who are side-lined and possibly drawn into caring roles as well. [redacted] worries for her younger daughter who doesn't have EB "Our younger daughter often has to take second place because of the time and support her sister needs. And that is not fair." Families and people living with EB need more equipment to enable them to live as comfortably as possible, whether that's fans in hot weather or constant heating during winter, the cost of which are growing exponentially. They may need wheelchairs, specialist furniture, footwear, clothing, bedding and eating aids, as [redacted] describes "EB impacts our home life; our furniture, our bathroom, clothes we buy, holidays we go on, places we visit – it's endless". Household goods are often used more than in an average household. For example, at DEBRA we provide hardship grants and often need to replace washing machines to manage the additional burden of washing dressing retention garments and of multiple bedding changes as those living with EB are frequently injured at night, simply from moving normally in their sleep. It's a stark reality that EB patients with end stage EB-related cancer need dark coloured bedding and towels to help manage the psychological issues of seeing extensive blood and fluid loss due to extreme wounds and fungating cancer at the end of life.

	The study, "Understanding the socioeconomic costs of dystrophic epidermolysis bullosa in Europe: a costing and health-related quality of life study," was published in the *Orphanet Journal of Rare Diseases,* and shows that on average, the direct nonmedical costs, which include caregiver services, were roughly five times as high as the direct medical costs of healthcare. There were also indirect costs related to low productivity in the workplace and early retirement and they represent 6.8% of the total costs. **Parent/carer perspective** Our member demonstrates the impact of EB on some parents "My son…was born with no skin on his feet, knees, and hands and even where there was intact skin, it blistered. It was so hard to bond - I did not hold my baby for the first six months. He is the first person in my family to have EB, so it came as an enormous shock. (He) has a full skin check every day, which involves me lancing all blisters that have occurred overnight. I dress all the wounds and put protective bandages on before dressing him as well as giving him pain killers. The daily routine is quite structured to ensure he feels safe and secure at all times. He has his large dose of morphine before the evening meal so he is ready for his bath and can cope with more dressing changes… The most difficult thing about EB is seeing your child in pain, knowing that the care you are giving is causing so much distress. I have to draw disability living allowance to help soften the blow of not being able to return to work as I am now a full-time carer."

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	As there are no approved treatments for EB, we find people living with EB are grateful for any suggested care, whether it is a type of bandage, or method of bandaging that protects them, or a barrier cream or topical medicine. But there are no treatments designed specifically for EB that significantly reduce their pain, wound care, or scarring. [redacted] simply says, "I don't have any treatment." And another member describes how the treatment available is only wound care. "The daily removal of whole-body dressings, wound cleaning and debriding, application of creams and medications and replacement of dressings is the only means of preventing infection and potential sepsis, but this can take up to 8 hours a day". What is more, the care of severe wounds inflicts further pain and distress, as our member describes "The treatment is only an alleviation of symptoms and a preventative measure, but it causes immense pain, alleviated only by a mix of heavy duty pain relief. This leads to long periods of unconsciousness". Our member fears that this care is likely to become more difficult as pressures on the NHS are exacerbated "The daily treatments are only possible because of the availability of nurses and carers, one each day. The current recruitment crisis means that my son's team can be depleted at a moment's notice. He has a wonderful team, but they are human beings who also get ill and his life feels like a knife edge some weeks". People living with EB sometimes struggle to access care in their local area, due to the complexity of their condition, and a lack of awareness of the condition amongst most GPs.

8. Is there an unmet need for patients with this condition?	There is a significant unmet need - there are no treatments on the NHS specific to EB. There are no NICE guidance or advice or quality standards products for EB. [redacted] says "We don't have treatments. We do have awesome caring medical professionals who help with management of the condition. But that is all." She goes on to say that the most disappointing element of what is currently available to them is "that nothing helps makes it better. It's about minimising the damage not improving things." As there are no approved treatments for EB, patients are managed using polypharmacy (oral and topical medicines), washes, emollients, dressings to manage the complexity of EB and its manifestations. Wound healing is managed on a case-by-case basis with a range of options, which change if the skin becomes sorer or infected accordingly. New strategies are desperately required, and new topical agents would be a replacement for, or in addition to, these existing strategies that are used in lieu of any EB-specific treatments. Our member worries that her "son has wounds which have not healed in over three years, and we fear the development of squamous cell carcinoma".

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Improving wound healing leads to reduced pain, itch and dressing changes, and perhaps longer-term benefits such as less inflammation and improved function in day-to-day life. With reduced pain comes less anxiety and potentially other tangible benefits. Our members hope it will lead to "quicker healing wounds" and "reduction in healing times for wounds, and potential reduction in pain levels" due to "reducing the pain of dressing changes". They hope that there may be "fewer areas with wounds". In a 2015 clinical trial using mesenchymal stromal cell therapy conducted in children with RDEB, wound healing was improved, and the following qualitative benefits were observed; "The general improvement to skin condition, together with increase in skin resilience in trauma, enabled the children to participate more fully in play and family life. One parent reported a one-fifth reduction in the child's oral morphine analgesia requirement." "Some parents reported a reduction in the amount of the time required to provide skin care for their children. The amount of dressings required has also reduced. A parent reported about 50% reduction in dressings. One parent described he often needed to return home to assist with his child's skin care - he saw a reduction in unscheduled absence from work as his child's skin condition improved. One parent reported that the improvement to her child's skin condition was one of the key factors that enabled her to take up part-time employment." "The improvement to the children's RDEB has led to improved quality of family life" REF: Petrof et al, J Investigative Derm 2015 The impact of a positive change in treatment is not limited to the individual, and the impact on the family, parents, and siblings, is of critical importance. We would urge the committee to consider the impact of a small incremental change this treatment can provide. This can have a large meaningful change to an individual and their carers. This is well documented in a number of disease areas but very relevant here particularly considering the severity of impact on daily life.

	Our member [redacted] says "whenever we hear there is a medicine to reduce the pain and the itch we get very excited. I wish other people who don't have EB knew what it feels like. The doctors are trying to make things better, but EB is really hard for everyone."

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	We're not aware of any disadvantages. We would query whether putting on the gel could be painful with open wounds or could cause further wounds through friction.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	DEBRA UK has a community support team that help families gain access to appropriate healthcare, the correct financial state benefits and supporting with school applications, housing, and access to work. Equality for patients with EB impacts hardest on those that have least and who may be culturally disadvantaged. Those with fewer resources always struggle the most to access the care they need, due to costs associated with organising travel to treatment centres or accessing the appropriate specialist healthcare likely to be aware of this product.

Other issues

13. Are there any other issues that you would like the committee to consider?	For the final word, we turn again to our members "Anything that can reduce pain and accelerate healing will reduce the cost of pain medication and may reduce the cost of care if wounds heal more rapidly." And [redacted] believes "it's been a long time coming".

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• There are no treatments for EB, and even small incremental or numerical change in treatment options can have a large meaningful change both physically and financially to individuals and their families. • Dystrophic and junctional EB are characterised by a life of extreme pain and functional challenges, which impacts on every element of their life. • People living with EB are subjected to hours of daily bandage changes due to poor wound-healing in the condition, so any treatment that promotes faster wound-healing could help them live a little better each day. • The costs to the NHS of bandages and trying out treatments not designed for EB are considerable. A technology that could reduce the amount of bandages for people with EB could also represent a cost-saving to the NHS as well as each of those families. • Better wound-healing represents less pain, less anxiety, better quality of life, more independence, and more time for whole families to live a better life together.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted] on behalf of the British Association of Dermatologists (BAD) Therapy & Guidelines sub-committee
2. Name of organisation	British Association of Dermatologists (the BAD)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes ~~or No~~ A specialist in the treatment of people with this condition? Yes ~~or No~~ A specialist in the clinical evidence base for this condition or technology? Yes ~~or No~~ Other (please specify):
5a. Brief description of the organisation (including who funds it).	The BAD is a not-for-profit organisation whose charitable objectives are the practice, teaching, training, and research of dermatology. It works with the Department of Health, patient bodies and commissioners across the UK, advising on best practice and the provision of dermatology services across all service settings. It is funded by the activities of its members.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of the treatment is to aid wound healing and reduce wound size.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	For patients over 10 years old a wound to heal and remain healed for at least 3 months. For patients under 10 years old wounds heal faster so difficult to give estimate. An improvement by 50% would likely be clinically significant for the patients. Size reduction also depends on wound size, location and duration.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There are no approved treatments for patients with epidermolysis bullosa. There is an unmet need and urgent need for treatments to prevent recurrent wounds, aid wound healing and as a result reduce pain, itch and wound infections.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Currently the condition is managed by a multidisciplinary team of hospital doctors and allied healthcare professionals. The condition is managed by supportive care, screening for complications, nutritional support, advice on wound dressings.

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are a number of clinical guidelines for managing most aspects of EB published by Debra International. EB health care - Clinical Practice Guidelines | DEBRA International (debra-international.org)
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is a clear pathway of care. The paediatric and adult EB services have been commissioned by NHSE for the past 20 years. There are two paediatric and two adult centres in England. Care may vary depending on resources between centres. No major differences of opinion between professionals across the two paediatric and two adult centres and clear transition pathways between them.
9c. What impact would the technology have on the current pathway of care?	It may provide an additional tool in care provision. It will sit alongside dressings and other topical treatments available and hopefully will aid wound healing. If it improves wound healing and patient itch, then it would have a significant impact on hospital visits/contacts and may even lead to global reduction in wound burden and reduce long-term risk of developing squamous cell carcinoma. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6560757/
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It will be used alongside available resources and in the same way as current care is delivered.
10a. How does healthcare resource use differ between the technology and current care?	It will be an additional resource. Currently using topical creams and dressings to aid wound healing.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care and once approved *hopefully* it would be available for prescription by primary care practitioners. Patients and parents/carers currently undertake dressing changes at home and would be able to apply the product themselves as part of routine care.
10c. What investment is needed to introduce the technology? (For example, for	No investment is required.

facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Based on the clinical trials we are hopeful the technology will be helpful to improve wound healing in some patients. The EASE study showed improvement in wound closure and if this seen in real-world practice and wounds stay healed potentially in children over 10 years old then this will be very beneficial. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6560757/
11a. Do you expect the technology to increase length of life more than current care?	If wounds heal and stay healed and therefore the wound burden over the entire body is reduced, in theory the risk of developing squamous cell carcinoma in adulthood will be reduced.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Hopefully yes, if patients' wounds heal faster. Faster healing of wounds would likely reduce pain, itching and wound infections over time. This, in turn, would be expected to improve quality of life for patients. A reduction in time spent undertaking dressing changes due to a smaller wound burden would also improve quality of life. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6560757/ and https://pubmed.ncbi.nlm.nih.gov/28611842/.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Technology will be as easy to use for patients and healthcare professionals as current care.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Initiation and stopping the treatment will depend on wound assessment and response to treatment as well as patient preference.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	If approved, it will be the first EB-specific treatment available. If wound healing improves and the wound reduce or heal, this is likely to lead to improvement in quality of life for patients. We hope the technology is better in wound healing than current care options. If this technology allows the wounds to heal quicker and they stay healed for longer and lead to pain and itch reduction, then it could potentially lead to long-term health benefits such as reduction in chronic inflammation leading to a reduced risk of developing squamous cell carcinoma.
16a. Is the technology a 'step-change' in the management of the condition?	It may lead to improvement in wound care but to what extent we will have to review in the real-world practice.

16b. Does the use of the technology address any particular unmet need of the patient population?	There is a massive unmet need for a cure in EB. This technology may help wound healing but will not address the multi-systemic nature of recessive dystrophic and junctional EB. It will not have an impact on eye and gastrointestinal complications.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No significant side effects to our knowledge.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Reduction in wound size, wound healing, reduction in pain and itch. Yes, they were measured.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
18d. Are there any adverse effects that were not apparent in clinical	Not to our knowledge.

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	A very small number of individuals have used the technology in real-world experience so unable to compare.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not to our knowledge.
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• First ever EB-specific treatment • Unmet need for EB patients • Hope to aid wound healing and reduce wound size • •

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NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	NHS England

3. Job title or position	Commissioning Manager Highly Specialised Team
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? x commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Various clinical guidelines are in place to manage aspects of EB care.
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The service is provided by 4 highly specialised teams across England according to an agreed service specification, so the pathway of care is well defined with good collaboration across centres.
8. What impact would the technology have on the current pathway of care?	No impact expected
The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	A small number of patients are receiving compassionate supply of product.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, in line with usual patient management and changes of dressing at home.
• How does healthcare resource use differ between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Gel applied at home which we would expect to be delivered through homecare
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No investment would be required
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this	A process for management and remote advice for patients and families in application and wound management would be needed but this is usual practice in the service.

include any additional testing?	
11. What is the outcome of any evaluations or audits of the use of the technology?	No comment
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	No, equity of access to the service is monitored
12b. Consider whether these issues are different from issues with current care and why.	Similar issues to current care.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa. A Single Technology Appraisal

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Date completed	06/03/2023

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Declared competing interests of the authors

None of the authors has any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Mark Clowes critiqued the company's search strategy. Chris Carroll summarised and critiqued the clinical effectiveness data reported within the company's submission. Shijie Ren and Sa Ren critiqued the statistical aspects of the submission. Matt Stevenson and Andrew Rawdin critiqued the health economic analysis submitted by the company. Matt Stevenson led the team. All authors were involved in drafting and commenting on the final report.

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Abbreviations

AE	Adverse Event
BBE	Birch Bark Extract
BSAP	Body Surface Area Percentage
CCM	Current Clinical Management
CFB	Change From Baseline
CI	Confidence Interval
CS	Company Submission
CSR	Clinical Study Report
CSS	Cross Sectional Survey
DBP	Double Blind Period
DEB	Dystrophic Epidermolysis Bullosa
DDEB	Dominant Dystrophic Epidermolysis Bullosa
EA	Exploratory Analysis
EAG	External Assessment Group
EB	Epidermolysis Bullosa
EBDASI	Epidermolysis Bullosa Disease Activity and Scarring Index
EQ-5D-3L	EuroQol 5 Dimensions 3 level
EQ-5D-5L	EuroQol 5 Dimensions 5 level
EQ-5D-Y	EuroQol 5 Dimensions Youth
FLACC	Face, Legs, Activity, Cry, Consolability Scale
GLM	Generalised Linear Model
HRQoL	Health-Related Quality of Life
HST	Highly Specialised Technology
ICER	Incremental Cost Effectiveness Ratio
IDMC	Independent Data Monitoring Committee
iscorEB	instrument for scoring clinical outcome of research for Epidermolysis Bullosa
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect Treatment Comparison
JEB	Junctional Epidermolysis Bullosa
JEB-S	Severe Junctional Epidermolysis Bullosa
MHRA	Medicines and Health care products Regulatory Agency
MRU	Medical Resource Use
NA	Not Appropriate
NHS	National Health Service

NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NR	Not Reported
OLP	Open Label Phase
OLS	Ordinary Least Squares
ONS	Office for National Statistics
OS	Overall Survival
PAS	Patient Access Scheme
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic Sensitivity Analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
RDEB	Recessive Dystrophic Epidermolysis Bullosa
RoB	Risk of Bias
RR	Risk Ratio
SAE	Serious Adverse Event
SAP	Scientific Analysis Plan
SD	Standard Deviation
SEE	Structured Elicitation Exercise
SLR	Systematic Literature Review
TBSA	Total Body Surface Area
TSD	Technical Support Document
TSQM	Treatment Satisfaction Questionnaire for Medication
TTD	Time To Treatment Discontinuation
TTO	Time Trade-Off

1. EXECUTIVE SUMMARY

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 provides the EAG's base case ICER. All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 provides a list of the EAG's key issues. These are issues that could make a large difference to the incremental cost-effectiveness ratio (ICER); limitations that only make a small difference to the ICER are not included here but are discussed in Section 5.3.4.

Table 1: The EAG's key issues

Issue Number†	Summary of issue	Report section
1	The company has used an approximation method to estimate transition probabilities between the modelled health states and assumes that assumes that transitions between health states apply for the first 12 months before reaching a steady state for birch bark extract (BBE) but assumes that patients receiving current clinical management (CCM) reach steady state after 90 days. The EAG prefers to use the data observed from the EASE study and to assume steady state for BBE is reached after 90 days.	5.3.4.1
2	The company assumes that patients receiving BBE who discontinued after 90 days of treatment would subsequently use the transition probabilities associated with CCM. However, the modelling assumed that after 90 days, the cohort of patients receiving CCM were in steady state, with no transitions between health states. As such, patients who discontinued BBE after 90 days of treatment could receive a long-term benefit despite discontinuation of treatment. The EAG preferred that patients discontinuing after 90 days be distributed in accordance with the steady state distribution associated with CCM after 90 days.	5.3.4.2
3	The company assumes that more carers are needed as the severity of a patient's condition worsens. Whilst this is plausible, the health-related quality of life (HRQoL) assumed for carers conditional on health state was estimated from vignettes stating that "*you are the main carer*". To align with the HRQoL data, the EAG has explored the assumption of one carer in all health states.	5.3.4.3
4	The company has used the results of an ordinary least squares (OLS) regression model to estimate the utility of patients with EB. The ERG prefers a non-linear approach which uses a generalised linear model (GLM)	5.3.4.4
7	The company has assumed, based on clinical advice, that after 90 days, 1% of patients would discontinue BBE each year. The EAG has explored using the discontinuation rate observed in the pivotal EASE study ([redacted]% per year)	5.3.4.7
10	The company's base case assumes no continuity correction. Where there are a small number of observations it can appear that the transition probabilities are more certain than they truly are, and it is common for continuity corrections to be performed to reduce this limitation. The company's model has the functionality to explore the use of continuity correction when using data from the EASE study, which should be considered.	5.3.4.10

† Ordered non-consecutively to tie in with the numbering in Section 5.3.4

The EAG's preferred assumptions are:

- The use of transition probabilities directly from EASE for the first 90 days with both BBE and CCM having steady state distributions after this time point.
- Assuming that patients discontinuing BBE treatment after 90 days are distributed in accordance with the steady state distribution associated with CCM

- The assumption of a single carer per patient in each health state
- The use of a GLM to estimate the utility of patients rather than a OLS regression model
- The number of outpatient appoints being calculated without data from severe junctional epidermolysis bullosa patients
- Increasing the average age to 16.67 years.

In scenario analyses based on the EAG's base case, the company's assumption relating to the number of carers per health state has been reinstated and the use of continuity corrections has been undertaken.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). The presented ICER is the ratio of the extra cost for every QALY gained.

The company's model assumes that BBE affects QALYs by:

- Increasing the HRQoL for patients by reducing their average body surface area percentage (BSAP) effected and moving patients to less severe heath states in the company's model
- Increasing the HRQoL for carers by reducing the average BSAP effected of patients and moving patients to less severe heath states in the company's model.

The company's model assumes that BBE costs by:

- The inclusion of the acquisition costs of BBE
- Reducing the resource use (such as dressing costs, formal care costs and outpatient costs) which are less as a consequence of patients spending less time in the more severe health states.

The modelling assumptions that have the greatest effect on the company's base case ICER are:

- The use of transition probabilities estimated directly from EASE for the first 90 days with both BBE and CCM having steady state distributions after this time point
- Assuming that patients discontinuing BBE treatment after 90 days are distributed in accordance with the steady state distribution associated with CCM
- The assumption of a single carer in each health state
- The assumed discontinuation rate for patients receiving BBE
- The inclusion of continuity corrections applied to transition probabilities.

1.3 Summary of EAG's preferred assumptions and resulting ICER

Table 2 summarises the results of the EAG's exploratory analysis. The EAG's base case ICER is estimated to be £302,808 (deterministic) and £304,178 (probabilistic). The company made no claim for a QALY weighting above 1 to be applied, a position that the EAG agrees with.

Table 2: The EAG's deterministic base case

Scenario	Incremental cost (£)	Incremental QALYs	Cost per QALY (£)	Change from company base case (£)
Company's base case after the clarification process	220,306	2.56	86,052	-
EA1: Amending transition probabilities	299,400	1.83	163,241	77,199
EA2: Amending distributions between health states after discontinuation of BBE	230,302	2.47	93,341	7289
EA3: Assuming one carer per health state	220,306	2.18	101,272	15,220
EA4: Estimating patient utility using a GLM rather than an OLS model	220,306	3.03	72,651	-13,401
EA5: Amending the number of outpatient appointments	220,224	2.56	86,020	-32
EA6: Amending the average age of EB patients	208,753	2.42	86,219	167
EAG base case (EA1-EA6 combined)	297,885	0.98	302,808	216,756
EAG base case (probabilistic)	297,885	0.98	304,178	218,126

Abbreviations: BBE, birch bark extract; EAG, external evidence group; EB, epidermolysis bullosa; GLM – generalised linear model; OLS – ordinary least squares; QALY, quality-adjusted life years

Table 3 provides scenario analyses starting from the EAG's base case exploring two uncertainties: one relating to the number of carer's per health state; and one related to the use of continuity corrections. The company's assumption relating to the number of carer's in each health state (0.5 in health states 1 and 2, 1 in health states 3 and 4, and 1.78 in health states 5 and 6) reduces the ICER, whereas the adoption of continuity corrections increases the ICER.

Table 3: Deterministic ICERs from scenario analyses starting from the EAG's deterministic base case results

Scenario	1 carer per patient in each health state	Company's assumption regarding the number of carers per health state
No Continuity Correction (used in the EAG's base case)	£302,808	£210,345
Continuity correction – adjacent transitions only allowed	£359,648	£248,484
Continuity correction – all transitions allowed	£416,314	£284,725

These scenarios resulted in deterministic ICERs ranging from £210,345 to £416,314. The lower value is likely to be favourable to BBE due to the inclusion of reduced extracutaneous aspects of EB that were assumed to be improved in less severe health states but where BBE may not have a benefit.

Table 4 provides scenario analyses starting from the EAG's base case exploring two uncertainties: one relating to the method of deriving patient utilities; and one related to the use of continuity corrections. The company's assumption of using an OLS model reduces the ICER, whereas the adoption of continuity corrections increases the ICER. Allowing patients to discontinue BBE treatment in the steady state period slightly increased the ICER.

Table 4: Deterministic ICERs from scenario analyses starting from the EAG's deterministic base case results changing the method for deriving patient utilities.

	Utility derived from the GLM	Utility derived from the OLS
No continuity correction (used in the EAG's base case)	£302,808	£253,396
Continuity correction – only adjacent transitions allowed	£359,648	£302,142
Continuity correction – all transitions allowed	£416,314	£343,175

In an analysis combining the use of different numbers of carers per patient, utility derived from the OLS and no continuity correction, the ICER was £185,252. The EAG believes this represents a lower bound on the ICER

The EAG also explored the impact of allowing patients in the steady state of the BBE treatment arm to discontinue. This only had a minor impact on the deterministic ICER which increased to £303,166.

The EAG's best estimate of the ICER is at least £300,000, depending on what form of continuity correction is applied, although this is formed from subjective judgements. The EAG notes that the ICER could potentially be as low as £185,000 or as high as £420,000. This uncertainty could be reduced by: undertaking larger studies which would provide more observations on the transition probabilities for patients using BBE, which could obviate the need for continuity corrections; more research on the number of carers required per health state and the impact on the HRQoL of these carers; and research on the utility of patients with EB.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The External Assessment Group (EAG) is content with the information presented in Section B.1.3 of the company submission (CS)[1] and in the clarification response[2] regarding the overview and epidemiology of epidermolysis bullosa (EB). In brief, EB is a complex group of lifelong, inherited blistering and skin fragilities with two subtypes being relevant to this Highly Specialised Technology appraisal (HST) which are: dystrophic EB (DEB) which can be dominant (DDEB) or recessive (RDEB); and junctional EB (JEB). Severe forms of EB, including DEB and JEB usually present at birth with diagnosis in early childhood or before.[3]

Natural wound healing is disrupted in EB[4] causing an inability to restore the epidermal barrier, which along with skin mechanical fragility is the reason that many patients with DEB or JEB sustain frequent erosions or blistering of the skin. Many of these wounds are classified as partial-thickness wounds as they extend beyond the epidermis and basement membrane into the upper part of the dermis. The wounds can cover a high proportion of total body surface area (BSA).[5] Wounds can remain unhealed for long periods (often being referred to as chronic when they have persisted for more than 21 days). The presence of many wounds, which differ in age and healing status makes the management of EB patients complex.[4, 6] Patients often have pain, anaemia and pruritis (itching).[3, 7] Large wounds can reduce health-related quality of life (HRQoL) and can cause an increase in the need for pain medication and the risks of developing anaemia, osteoporosis, and squamous cell carcinoma (SCC).[8] HRQoL is often markedly reduced in patients with EB and in carers and family members compared with the general population.[9-13]

Patients with EB typically experience comorbidities such as respiratory tract scarring, inflammation, sepsis, renal amyloidosis and lack or nourishment.[8] Life expectancy is linked to severity of disease, with patients with severe JEB (JEB-S) dying within the first year, whilst patients with other forms of EB can have normal life expectancy.[5, 14]

The incidence of EB is estimated to be between 19 and 41 per million live births.[3, 15] In Table 4 of the CS, the company has estimated that there are 604 people with DEB and 56 with JEB in England based on data from the National Health Service (NHS) national EB service.[16]

2.2 Critique of company's overview of current service provision

The EAG is content with the information provided in Section B.1.3 of the CS related to current service provision. In brief, there is currently no cure for EB and prior to birch bark extract (BBE) there were no therapies approved by the regulators for EB. Current clinical management focuses on wound

management, minimising complications, improving HRQoL and reducing risks of new injuries.[17-19] Table 5 in the CS provides a summary of clinical guidelines of EB management; the company states that none are UK specific.

Due to the rarity of EB, there is a nationally commissioned EB service for the UK comprising of two specialist adult centres (Hospitals Birmingham NHS Foundation Trust and Guy's and St Thomas' Hospital NHS Foundation Trust) and two specialist paediatric centres (Birmingham Women's and Children's NHS Foundation Trust and Great Ormond Street Hospital). These centres are led by a consultant dermatologist working with clinical nurse specialists and key specialists as part of a multi-disciplinary team. The company states that "*Visits to specialist EB centres in England and contact with both EB nurse specialists and the DEBRA patient group, suggest that the current standard management of EB wounds is highly variable both between centres and between patients themselves, even between patients within the same family.*" The involvement of patients with EB and their carers in management strategies has been reported to be paramount,[17, 19, 20] which results in heterogeneous management plans which can vary based on subtype of EB, size, severity and age of wounds, season of the year and age of the patient.

Care commonly consists of the use of non-adhesive dressings and bandages, topical agents, such as antimicrobials and steroids, which are used off-label. Bathing may aid dressing changes and allow supplemental cleansing using diluted acetic acid or bleach.[19] Additional actions may include, lancing and draining of blisters, attempts to reduce severe pruritis and pain management.[18, 21] Surgical procedures are also common in patients with EB, including oesophageal dilation, insertion of gastrostomy tubes, and surgery to manage contractures of the hands.[22] Ongoing research is investigating the use of cell and gene therapies, although none are currently routinely available to patients with DEB or JEB.

3 CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlined in the final NICE scope[23] and addressed in the CS is presented in Table 5. The EAG's critique of the decision problem addressed within the CS is presented in the subsequent sections.

Table 5: Company's decision problem (adapted from Table 1 of the CS with additional comments from the EAG)

	Final scope issued by NICE	Variation from scope	Rationale for variation from scope	EAG comments
Population	People aged 6 months and older with: • Dystrophic epidermolysis bullosa (DEB); or • Junctional epidermolysis bullosa (JEB)	None	NA	NA
Intervention	Birch bark extract (BBE)	None	NA	NA
Comparator(s)	Current clinical management without birch bark extract (including, but not limited to, treatments which can help ease and control infections, pain and other aspects of EB)	None	NA	NA
Outcomes	The outcome measures to be considered include: • closures of unhealed target wounds • time to wound closure • percentage of surface area of wound healed • change in total body wound burden • incidence and severity of wound infection • pain • change in itching • mortality • adverse effects of treatment • health-related quality of life (for patients and carers)	None, although the company focus on two specific outcomes in the pivotal study the Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) and body surface area percentage (BSAP)	NA	The reporting of changes in EBDASI and BSAP is appropriate.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be	None	NA	NA

	Final scope issued by NICE	Variation from scope	Rationale for variation from scope	EAG comments
	expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.			
Subgroups to be considered	If the evidence allows the following subgroups will be considered. These include: • DEB ▪ dominant DEB ▪ recessive/ severe generalised DEB • JEB • generalised severe (Herlitz) • generalised intermediate (non-Herlitz)	Subgroup data are reported for DEB (DDEB and RDEB) and JEB for the primary and first key secondary efficacy endpoints. In the cost effectiveness analysis, transition probabilities to inform patient movements through health states were calculated using the 90-day DBP EASE data (and extrapolated using 12-month OLP data). These transitions were pooled and applied to all subtypes, assuming that Filsuvez gel efficacy does not differ per subtype. A scenario is explored to assess the impact on results when considering RDEB-S patients only	Insufficient evidence and lack of clinical rationale to model patients by individual EB subgroup.	Due to the small number of patients with DDEB and JEB the clinical and cost-effectiveness of BBE in these EB subtypes are subject to considerable uncertainty

Abbreviations: BBE, Birch Bark Extract; BSAP, Body Surface Area Percentage; DBP. Double Blind Period; DDEB, Dominant Dystrophic Epidermolysis Bullosa; EB, Epidermolysis Bullosa; EBDASI, Epidermolysis Bullosa Disease Activity and Scarring Index; JEB, Junctional Epidermolysis Bullosa; NICE, National Institute for Health and Care Excellence; NA, Not Appropriate; NHS, National Health Service; OLP, Open Label Phase; RDEB, Recessive Dystrophic Epidermolysis Bullosa; RDEB-S, Severe Recessive Dystrophic Epidermolysis Bullosa.

3.1 Population

The population considered in the CS is people with DEB or JEB aged six months or over in line with the wording of the Medicines and Health care products Regulatory Agency (MRHA) licence.[24] The wording is slightly different to that in the NICE scope, but the EAG believes that both sets of wording define the same population.

3.2 Intervention

Table 2 in the CS provides comprehensive details relating to BBE, which is branded as Filsuvez® and was referred to as Oleogel-S10 during clinical development. Filsuvez® received marketing authorisation in June 2022 for the treatment of partial thickness wounds associated with DEB and JEB in patients aged six months or older.[25] MRHA approval for the same indication was granted in August 2022.[24] The precise mechanism of action of BBE in wound healing is not known.[26]

In brief, BBE is a non-aqueous gel containing 100mg of extract (as dry extract, refined) from "*Betula pendula Roth, Betula pubescens Ehrh, as well as hybrids of both species, cortex (equivalent to 0.5-1.0g birch bark), including 84-95mg triterpenes calculated as the sum of betulin, betulinic acid, erythrodiol, lupeol, and oleanolic acid. Extraction solvent: n-Heptane.*" [27] Contraindications are hypersensitivity to the active substance with treatment interrupted in the case of wound infection, and treatment discontinued in an affected area if SCC is diagnosed. BBE should not be used concomitantly with other topical products. The company states that no additional tests or investigations are required to identify the population for whom BBE is indicated in the marketing authorisation.

BBE should be applied to the wound surface at a thickness of approximately 1mm and covered by a sterile non-adhesive wound dressing. Alternatively, BBE can be applied to the dressing and then placed such that the gel is in contact with the wound. The gel should not be rubbed in and should be reapplied at each dressing change. If symptoms persist or worsen after use, or if wound complications occur, a full clinical assessment should be undertaken before continuation of treatment, and regularly re-evaluated. BBE is intended for long-term use and there is no long-term stopping rule relating to efficacy has been defined.

3.3 Comparators

In the absence of other licensed treatment for EB the comparator within this HST is current clinical management (CCM). BBE is expected to be used to supplement CCM rather than replace it although the use of BBE may impact some aspects of CCM such as the frequency of dressing changes.

3.4 Outcomes

The outcomes reported in Table 5 are included in the CS. The company focus on two further measures not defined in the NICE scope which are changes in Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) disease severity score and body surface area percentage (BSAP).

3.5 Other relevant factors

The company has submitted a patient access scheme (PAS) application to the Patient Access Scheme Liaison Unit. This represents a simple price discount of [redacted] on the list price of BBE which is £275.33 per 23.4g tube of BBE.

The company does not expect that this HST will exclude any people protected by equality legislation, nor lead to recommendations that will have an adverse impact on people with disabilities.

4 CLINICAL EFFECTIVENESS

The clinical evidence contained in the CS[1] is comprised of:

- A systematic literature review (SLR) of clinical evidence for BBE for treating partial-thickness wounds associated with the EB subtypes DEB, which can be DDEB) or RDEB, and JEB;
- Summary and results for the EASE study.

This chapter summarises and critiques the company's review methods and clinical effectiveness data, full details of which are presented in Section B.2 of the CS and CS Appendix D.[1] In this chapter, section 4.1 critiques the methods used to conduct the clinical effectiveness review, 4.2 is a summary and critique of the design and conduct of the pivotal study (EASE), 4.3 covers the efficacy evidence from the included EASE study, and 4.4 the safety evidence. The remaining sections (4.5, 4.6, and 4.7) consider ongoing studies and critique decisions regarding meta-analysis and indirect comparisons, as well as describing any additional work conducted by the EAG. Section 4.8 summarises the overall critique of the submission and clinical effectiveness evidence.

4.1 Critique of the methods of review(s)

The clinical evidence presented in the CS was informed by an SLR of studies assessing the clinical efficacy and safety of BBE for treating partial-thickness wounds associated with the EB subtypes DEB, (DDEB or RDEB), and JEB (CS Appendix D.1.1.2, Table 1).[1] The primary clinical evidence detailed in the CS comes from the EASE study (BEB-13; NCT03068780; EudraCT2016-002066-32) – an international Phase III, multi-centre, double-blind, randomised controlled trial (RCT) with a 24-month open-label, single-arm follow-up phase. Twenty-five published and unpublished reports, protocols and conference abstracts relating to this trial were identified by the SLR and update search (CS, Appendix D.1.1.2, Table 2).[1] The principal data reported in the CS were extracted from the main trial publications[28, 29] and the Clinical Study Reports (CSRs).[30, 31] EASE compared BBE to a control gel both as adjuncts to CCM.

CCM of EB is heterogeneous and includes, but is not limited to, treatments which can help ease and control infections, pain and other aspects of EB. There is therefore no one principal comparator for BBE (CS, Section B.1.1, Table 1).[1] The EASE study used a control gel as a comparator, but the full range of more typical medications and therapies used in practice were permitted in both arms (CS, Section B.2.3.1, Table 8).[1] Clinical advice to the EAG suggests that this approach represented a reasonable comparator for BBE.

Given the availability of a head-to-head Phase III RCT comparing BBE with an acceptable comparator, and the absence of any trials of other licensed treatments for this indication, the CS argues that an

indirect treatment comparison (ITC) and network meta-analysis (NMA) was not necessary (CS, Sections B.2.8 and B.2.9).[1]

The safety evidence reported in the CS comprised a narrative summary of data from the EASE study (CS, Section B.2.10).[1]

4.1.1 Searches

Appendix D of the CS reports an SLR of clinical effectiveness of BBE for the treatment of partial thickness wounds associated with DEB and JEB.

Searches are reported in full, covering a wide range of databases including all those required by NICE, as well as international Health Technology Assessment websites, conference proceedings and registers of ongoing trials. Search strategies are well-designed including appropriate population terms and search filters based on those developed at the Canadian Agency for Drugs and Technologies in Health, with modifications that the company explained were designed to increase their sensitivity (clarification response, question A14[2]).

The EAG noted a recurring typographical error in the grey literature searches for the clinical review: "patrial thickness wounds" (as opposed to "partial thickness wounds"). The company acknowledged this error and re-ran the searches with this string corrected, screening – and ultimately excluding – the additional results retrieved (clarification response A15[2]). Given this reasonable effort to redress its mistake (and acknowledging the company's familiarity with the evidence base in this area) the EAG accepts that it is unlikely that any relevant studies would have been overlooked.

4.1.2 Inclusion criteria

The inclusion and exclusion criteria for the SLR are reported in Table 6. These criteria were consistent with the NICE scope (CS, Section B.1.1 Table 1)[1] with the exception of small differences in terms of the population age. The NICE scope reported that patients must be ≥6 months of age, whereas the SLR criteria indicated from birth and the submitted evidence, from the EASE study, had inclusion criteria limited to ≥4 years of age, which was reduced to >21 days following an Independent Data Monitoring Committee (IDMC) safety review part way through the trial (CS, Section B.1.1 Table 1).[1]

The SLR criteria included the key effectiveness outcomes from the final NICE scope. These included: closures of unhealed target wounds; time to wound closure; percentage of surface area of wound healed; change in total body wound burden; incidence and severity of wound infection; pain; change in itching; mortality; adverse effects of treatment and HRQoL (for patients and carers) (CS, Section B.1.1 Table 1).[1]

Table 6: Inclusion and exclusion criteria for the SLR (adapted from CS Appendix D.1.1, Table 1)

Clinical effectiveness	Inclusion criteria	Exclusion criteria
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)
Intervention and comparators	▪ Oleogel-S10 (as referred to by any terminology relating to the product and active ingredients) ▪ 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
Outcomes	Any wound-related clinical effectiveness, safety and tolerability, and PRO outcomes will be eligible for inclusion.	Any other outcomes not listed e.g., epidemiology, resource utilisation, pharmacokinetics.
Study design and 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 ▪ Pharmacokinetics ▪ Pharmacodynamics ▪ Non-systematic reviews ▪ Opinion pieces ▪ Editorials ▪ Letters ▪ Commentaries ▪ Press release ▪ Prospective and retrospective observational cohort studies ▪ Case studies/ reports/ series
Limits	No date or language* limits applied, with the exception of conference proceedings (2020-2022 only).	Conference abstract pre-2020

Abbreviations: DDEB, dominant dystrophic epidermolysis bullosa; DEB, dystrophic EB; EB, epidermolysis bullosa; JEB, junctional EB; NMA, network meta-analyses; PRO, patient reported outcomes; RCTs, randomised controlled trials; RDEB, recessive dystrophic epidermolysis bullosa; SLR, systematic literature review.
*Records translated to judge eligibility. Where this is not possible, records were detailed in the report.

4.1.3 Critique of study selection and data extraction

CS Appendix D.1.1.2[1] reports that, for all citations, both the title/abstract and full-text screening stages of study selection were undertaken independently by two reviewers, and any discrepancies were reconciled by a third independent reviewer. The EAG considers independent study selection by two or more reviewers, as conducted here, to be best practice in systematic reviewing. The results of the study selection process were detailed, as required, by a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (CS Section B.1.12, Figure 1).[1]

The company's data extraction methods are reported in CS Appendix D.1.1.2.[1] Data extracted from the included studies are presented in Sections B.2.3-2.7 and 2.10 of the CS.[1] Details of the data extraction process were not provided in the CS, but were clarified in response to a question from the EAG (clarification response, A7).[2] The process was undertaken independently by two reviewers, and any discrepancies were reconciled by a third independent reviewer. The EAG considers independent data extraction by two or more reviewers, as conducted here, to be best practice in systematic reviewing.

4.1.4 Quality assessment

CS Appendix D.1.1.2[1] reports that the quality assessment process was undertaken independently by two reviewers. The CS did not detail the process in the event of disagreement between the two reviewers, but this was clarified in response to a question by the EAG (clarification response, A8).[2] The process was undertaken independently by two reviewers, and any discrepancies were reconciled by a third independent reviewer, but this was not found to be necessary. The EAG considers independent risk of bias/quality assessment by two or more reviewers, with referral to a third if necessary, to be best practice in systematic reviewing.

4.2 Results of the company's SLR: the EASE study

The clinical SLR presented in the CS identified one trial of BBE that was relevant to the decision problem: EASE (BEB-13; NCT03068780; EudraCT2016-002066-32) – an international Phase III, multi-centre, double-blind, RCT with a 24-month open-label, single-arm follow-up phase. This study forms the key evidence for the clinical effectiveness and safety of BBE within the CS. Twenty-five published and unpublished reports, protocols and conference abstracts relating to this trial were identified by the SLR and update search (CS, Appendix D.1.1.2, Table 2).[1] The principal data reported in the CS were extracted from the main trial publications[28, 29] and the Clinical Study Reports (CSRs).[30, 31] The EAG believes that no additional relevant published Phase III trials of BBE in EB patients have been omitted from the CS that could have provided data on safety and efficacy.

4.2.1 Study design of the EASE study

EASE is a Phase III, randomised, international, multi-centre, double-blinded, RCT initiated in March 2017 and conducted in 51 centres across 26 countries, including two centres in the UK (NCT03068780). EASE is a two-phase efficacy and safety trial with a 90-day double-blind, randomised phase (DBP), followed by a 24-month, single arm, open-label phase (OLP). Details of study location, treatments, trial inclusion and exclusion criteria, permitted and prohibited concomitant medications and relevant outcomes are reported in Table 7. In the DBP, patients were randomised (stratified by EB subtype) to receive either the BBE gel or a control gel; in the OLP, all patients received the BBE gel (Table 7). The primary completion date was June 2020, but the final completion date is listed as May 2022 (NCT03068780). Overall, 252 paediatric and adult patients with EB were enrolled, and 223 patients who satisfied all eligibility criteria were randomised.

Table 7: Summary of the trial design of EASE (adapted from CS, Section B.2.3.1, Table 7)

Study name	EASE (previously BEB-13; NCT03068780, EudraCT2016-002066-32)
Objectives	To compare the efficacy, safety and tolerability of BBE (Oleogel-S10, Filsuvez® gel) with a control gel in patients with inherited EB (DEB, JEB and KEB) (DBP)
Location	Global, multi-centre study. 51* study sites across: Argentina, Australia, Austria, Brazil, Chile, Colombia, Czech Republic, Denmark, France, Georgia, Germany, Greece, Hong Kong, Hungary, Ireland, Israel, Italy, Romania, Russia, Serbia, Singapore, Spain, Switzerland, Ukraine, United Kingdom, and the United States.
Design	Double-blind, randomised, controlled, Phase III, 90-day efficacy and safety study with a 24-month open-label, single-arm follow-up phase
Key dates	First subject in DBP: 19 April 2017 First subject in OLP: 24 July 2017 [redacted] Interim 6-month OLP safety database lock: 21st December 2020 Interim 9-month OLP safety database lock: 21st April 2021 Interim OLP 12-month efficacy database lock: 15 July 2021 [redacted]

Abbreviations: DBP, double-blind phase; DEB, dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; FDA, U.S. Food and Drug Administration; JEB, junctional epidermolysis bullosa; KEB, Kindler epidermolysis bullosa; OLP, open-label phase; RCT, randomised controlled trial.
*51 listed in protocol, but 49 reported in CS, Section B.2.3.1, Table 7

The patient cohorts assessed in the clinical effectiveness review are presented in Table 34, Appendix 1 and a summary of the EASE study methodology is provided in Figure 1.

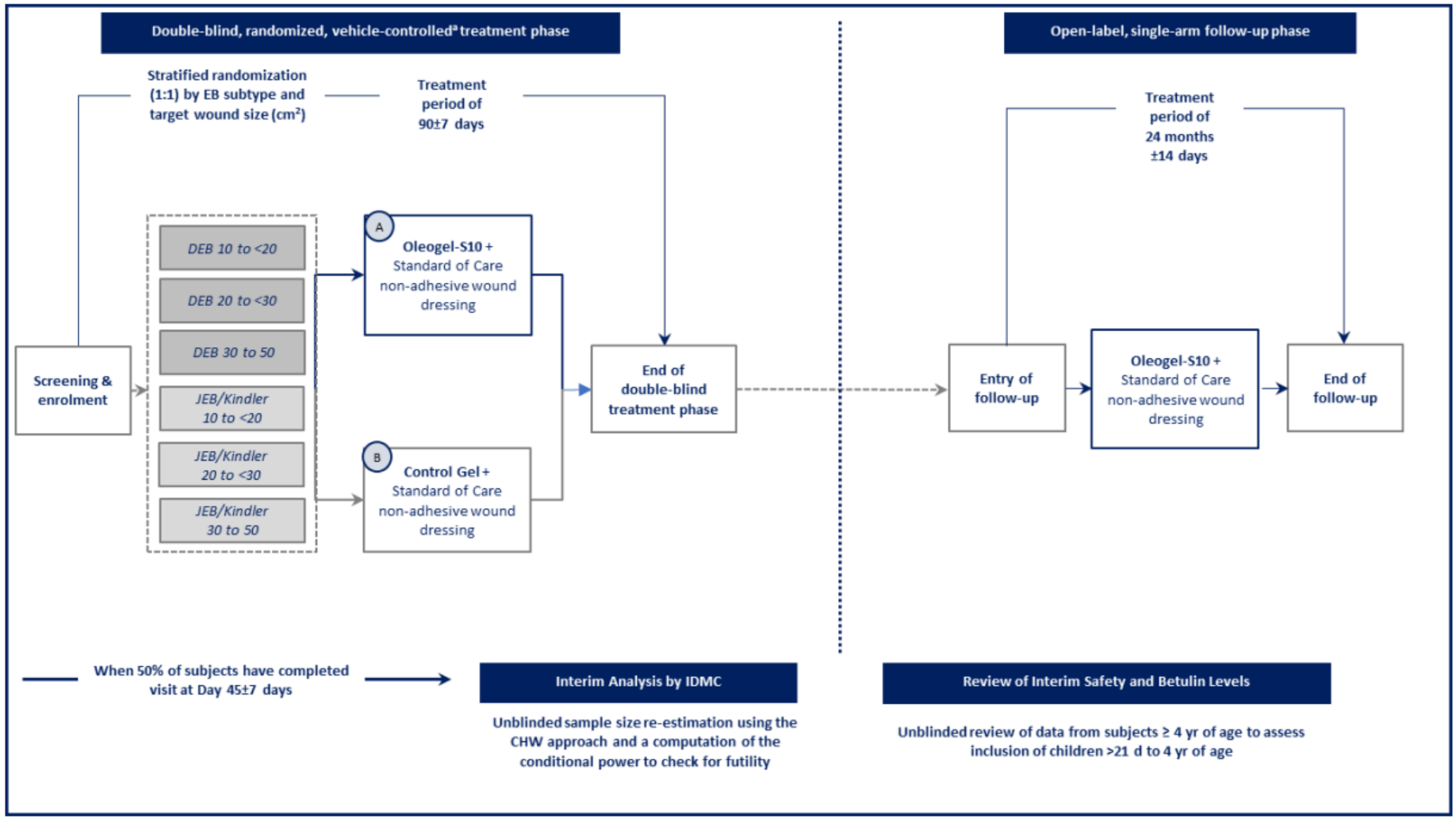


Figure 1: Overview of trial design of EASE (reproduced from CS, Section B.2.3.1, Figure 5)

Table 8: Summary of trial methodology of EASE (reproduced from CS, section B.2.3.1, Table 8)

Study phase	**Double blind phase (DBP)[28, 32]**	**Open-label phase (OLP)[28, 31, 32]**
Duration of phase	**90 days**	**24 months**
Sample size	A total of 223 subjects (109, Filsuvez gel; 114, control gel) were randomised and received at least one dose of study medication.	A total of 205 (91.9%) subjects continued into the OLP
Key inclusion criteria	Male and female patients with DEB, JEB, or KEB[a] ≥ 4 years of age (reduced to > 21 days following an IDMC safety review in 2019) EB target wound 10–50 cm^2 in size aged ≥ 21 days and < 9 months outside of the anogenital region	Completion of EASE DBP (or early transfer to OLP at INV discretion)
Key exclusion criteria	EBS[b] EB target wound with clinical signs of local infection Use of systemic antibiotics for wound-related infections within 7 days Administration of systemic or topical steroids within 30 days immunosuppressive or cytotoxic chemotherapy within 60 days Previous stem cell transplant or gene therapy for EB Current and/ or former malignancy including BCC/ SCC	NA
Method of randomisation	Subjects were randomised 1:1 to receive either Filsuvez gel or control gel. Randomisation was conducted according to blinded patient number, and the randomisation key was held solely by an independent statistician. Subjects were stratified according to their EB subtype and target wound size (cm^2) into the following groups: • DEB 10 to < 20; • DEB 20 to < 30; • DEB 30 to 50; • JEB/ KEB[a] 10 to < 20; • JEB/ KEB[a] 20 to < 30; • JEB/ Kindler[a] 30 to 50.	The OLP was single-arm, all subjects were to be treated with Filsuvez gel however OLP data were analysed by prior Filsuvez gel and prior control gel use

Study phase	Double blind phase (DBP)[28, 32]	Open-label phase (OLP)[28, 31, 32]
Duration of phase	**90 days**	**24 months**
Method of blinding	Patients, caregivers, and investigators were blinded to their assigned intervention during the 90-day DBP, through use of a matched control gel as the control arm. An independent unblinded biostatistics team maintained the randomisation scheme key. All randomisation materials, remained restricted until after DBP completion, and subsequent locking of the study database for the DBP.	In the OLP, all subjects were to be treated with Filsuvez gel and there was no blinding applied during that period. Both the investigator and the subject were aware of the treatment to be received.
Intervention	Filsuvez gel (n=109 randomised and received treatment) 100g of Filsuvez gel consists of 10g active pharmaceutical ingredient birch bark extract and 90g sunflower oil. To be administered topically at approximately 1mm (0.04 inch) thickness to the EB target wound and to all areas on the subject's body that were affected by EB partial-thickness wounds. Wound areas were then to be covered with a standard of care non-adhesive wound dressing. The randomised treatment was to be applied during all dressing changes (at least every 4 days) until the EDBP.	Filsuvez gel (n=205 entered the OLP) Topical Filsuvez gel was to be administered to all areas on the subject's body that were affected by EB partial-thickness wounds on day 0 of the OLP. Wound areas were to be covered with standard of care non-adhesive wound dressings. This procedure was to be repeated during all dressing changes (at least every 4 days) until the end of treatment at Month 24.
Comparator	Control gel (n=114 randomised and received treatment) 100 g of the sterile control gel consists of 85g sunflower oil, 5g Cera flava/ yellow wax, and 10g Carnauba wax. To be administered topically at approximately 1mm (0.04 inch) thickness to the EB target wound and to all areas on the subject's body that were affected by EB partial-thickness wounds. Wound areas were then to be covered with a standard of care non-adhesive wound dressing. The randomised treatment was to be applied during all dressing changes (at least every 4 days) until the EDBP.	The OLP was single-arm, all subjects were to be treated with the intervention, Filsuvez gel
Concomitant medications	The following medications/ therapies were permitted during both the DBP and OLP of the trial: • Liquid antiseptics at each dressing change to clean and/or reduce microbial colonisation of target wounds and additional wounds matching target wound criteria prior to study treatment; • Bathing (e.g., with chlorhexidine, diluted bleach, or salt) prior to study treatment at each wound dressing change;	

Study phase	**Double blind phase (DBP)[28, 32]**	**Open-label phase (OLP)[28, 31, 32]**
Duration of phase	**90 days**	**24 months**
	• Systemic antibiotics, except for the treatment of infections of the EB target wound or additional wounds matching target wound criteria; • Inhaled/ ophthalmic/ topical steroids for oesophageal strictures; • Supportive therapy upon the investigator's discretion. During both the DBP and OLP, the following were permitted for treatment of any EB wound, except the EB target wound or additional wounds matching target wound criteria: • Silver sulfadiazine; • Topical antibiotics; • Topical steroids. The following were not permitted on areas of the participants body affected by EB wounds during the DBP: • Skin products such as creams, ointments, gels, or emollients. During the DBP and the OLP, the following were not permitted on target wounds or additional wounds matching target wound criteria unless there was complete wound closure and confirmed epithelialisation before use: • Silver dressings; • Silver sulfadiazine; • Topical antibiotics; • Topical steroids. The following were not permitted until month three of the OLP: Systemic steroids (except for inhaled, ophthalmic, or topical applications); Immunosuppressive therapy or cytotoxic chemotherapy; Systemic antibiotics for treatment of infections of the EB target wound or additional wounds matching the target wound criteria.	
Duration of follow-up, lost to follow-up information	Of the 223 randomised subjects, 199 (89.2%) completed the DBP (91.7%, Filsuvez gel *vs*. 86.8%, control gel), and 24 (10.8%) discontinued (8.3%, Filsuvez gel *vs*. 13.2%, control gel). A total of 205 (91.9%) subjects continued into the OLP. This included 199 subjects who completed the DBP and 6 subjects (all in the control gel group) who discontinued the DBP prematurely due to worsening of the EB target wound status or due to EB target wound infection and continued into the OLP prematurely (at the investigator's discretion).	Of the 205 subjects who entered the OLP, a total of [redacted] completed the OLP, and [redacted] discontinued the OLP. The primary reason for discontinuation was withdrawal of consent [redacted], followed by AE [redacted], and other reasons [redacted].
Primary outcome	Proportion of patients with first complete target wound closure within 45 days based on INV assessment	NA

Study phase	Double blind phase (DBP)[28, 32]	Open-label phase (OLP)[28, 31, 32]
Duration of phase	**90 days**	**24 months**
Secondary outcomes	<u>Key secondary (confirmatory) efficacy endpoints:</u> • Time to first wound closure up to 90±7 days of treatment • Incidence of first complete wound closure of EB target wound • Incidence of wound infection • Maximum severity of wound infection • CFB in total body wound burden (EBDASI, Section I: Skin, Activity (not Damage), only) • CFB in itching (Itch Man Scale/ Leuven Itch Scale) <u>Other secondary endpoints:</u> • CFB in EB target wound size • CFB in % of TBSA affected by EB PTW • CFB in background and procedural pain (FLACC, Wong-Baker FACES) • Response to treatment/ treatment satisfaction (TSQM) • CFB in sleep quality (Likert scale) • Number of days missed from school or work • Incidence, severity, and relatedness of AEs • Local tolerability <u>Post-hoc analyses</u> • Dressing change frequency	• Incidence of Target Wound Infection in the OLP • Maximum Severity of Wound Infection in the OLP (between baseline and Month-24) • CFB in Total Body Wound Burden in the OLP (EBDASI, Section I: Skin, Activity (not Damage), only; Months 3, 12, 24) • CFB in BSAP affected by PTW by Visit (Months 3, 12, 24) • CFB in itching (Itch Man Scale/ Leuven Itch Scale; Month 3 only) • CFB in background and procedural pain (FLACC, Wong-Baker FACES; Month-3 only) • CFB in sleep quality (Likert scale) (Month-3 only) • Number of days missed from school or work (Month-3 only) • Status of target wounds by visit (Month-3 only) • CFB in disease severity by the iscorEB (Months 12, 24) • CFB in patients' quality of life as assessed by the EQ-5D (Months 12, 24) • Response to treatment/ treatment satisfaction (TSQM)

Abbreviations: AE, adverse event; BCC, basal cell carcinoma; BSAP, body surface area percentage; CFB, change from baseline; cm^2, square centimetre; DBP, double blind phase; DEB, dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; EBDASI, epidermolysis bullosa disease activity and scarring index; EBS, epidermolysis bullosa simplex; EDBP, end of double blind phase; EQ-5D, EuroQol 5-dimension; FLACC, Face, Legs, Activity, Cry, Consolability scale; g, gram; IDMC, Independent Data Monitoring Committees; INV, investigator-assessed; JEB, junctional epidermolysis bullosa; KEB, Kindler EBV; OLP, open label phase; mm, millimetre; n, number; NA, not applicable; PTW, partial-thickness wound; RCT, randomised controlled trial; SCC, squamous cell carcinoma; TBSA, total body surface area; TSQM, treatment satisfaction questionnaire for medication.

[a] Previously known as Kindler syndrome. KEB patients were eligible for inclusion in the EASE trial however no patients with KEB were recruited.

[b] One participant with EBS was included in each intervention arm of the EASE trial (recruited before the V4.0 protocol amendment excluded EBS participants).

4.2.2 Quality assessment of EASE study

The company's quality assessment of EASE was undertaken using the Cochrane Risk of Bias (RoB) tool (version 2),[33] which is the international standard for the quality assessment of RCTs. The findings of this quality assessment are reported in CS, Section B.2.5 and CS, Appendix D.1.3, Table 4.[1] These are provided in Table 34, Appendix 1. The assessments are based on information in the CSRs, protocols and full publications. It should be noted that the Cochrane RoB 2 tool is only suitable for assessing the randomised, 90-day, DBP of the EASE study, and is not appropriate for assessing the single-arm OLP of the trial. For this reason, the EAG considers the assessment reported in the CS only to apply to the DBP of EASE.

The EAG agrees with the assessments reported in the CS for the 90-day DBP of the EASE study: the low risk of bias concerning the randomisation process, outcome measurement, missing outcome data and selective reporting, and the judgement of "*some concerns*" regarding deviations from the intervention (based on dressing changes and investigational product remaining). Regarding outcome measurement, the EAG notes that the primary outcome measure (proportion of patients with first complete closure of the target wound within 45 days [+/-7 days]) is not a validated measure in EB but an assessment developed for the EASE study, which attempted to take into account wound chronicity and likelihood of healing.[28, 29] The EAG accepts that no validated measure for this outcome currently exists, and that the majority of the other outcome measures are accepted measures. The EAG agrees with the company's overall conclusion of "*some concerns*" relating to risk of bias in this trial for the initial 90-day DBP.

However, a separate quality assessment was required for the OLP, which is a single arm follow-up study. As a result, the EAG requested that the company clarify whether the risk of bias assessment concerned both the DBP and the OLP of the EASE study and, if so, why a separate risk of bias assessment was not conducted for the OLP. The company responded by confirming that the initial assessment was for both the DBP and OLP of the EASE study, and therefore conducted a separate quality assessment of the OLP using the Cochrane ROBINS-I tool[34] (clarification response, A10).[2] This assessment is presented in Table 35, Appendix 1. The EAG agrees with the company's assessment of the OLP of EASE as being at moderate risk of bias due to drop-outs due to discontinuations ([redacted][30]) and the open-label nature of the study.

The EAG also raise moderate concerns relating to the domains of baseline confounding and compliance. Regarding baseline confounding, participants had previously either received BBE gel or the control gel, before all participants received the BBE gel in the OLP, so the potential for baseline confounding was

present. However, separate results were provided for participants depending on the initial DBP treatment arms, and there was no substantial evidence of confounding. Regarding compliance, the figure of 99% for compliance during the OLP reported in Q.4.5 (Table 35, Appendix 1) is based on actual and intended treatment duration (calculated by: Actual treatment duration overall / Treatment duration * 100) (clarification response, A.3 and A.5[2]). The CS also refers to "*compliance*" in terms of major protocol deviations regarding dressing changes and return of the investigational product (CS, Section B.2.5[1], and clarification response A.3 and A.4[2]). This latter figure is unlikely to be as high as 99% for the OLP, given that the CS reported that the proportion of patients with a major protocol deviation during the 90 days of the DBP was 35% (CS, section B.2.5 and Appendix D.1.3, Table 4).[1]

4.2.3 Participant flow and analysis populations

In EASE, 223 paediatric and adult patients with EB were randomised either to BBE gel (n=109) or the control gel (n=114) at the start of the DBP of the trial. Overall, 199 (89.2%) participants completed the DBP of the study, and 24 (10.8%) discontinued (BBE gel: 8.3%; control gel: 13.2%). The most common reasons for discontinuation were "*other*" or "*withdrawal of consent*". Six subjects, all in the control gel group, discontinued the DBP prematurely due to worsening of the EB target wound status or due to EB target wound infection, and continued into the OLP prematurely at the investigator's decision.

Two hundred and five subjects entered the EASE 24-month OLP following the DBP. All subjects received BBE gel. The 205 included 199 subjects who had completed the 90-day DBP and six subjects from the control gel group who discontinued prematurely, as described above. A total of [redacted] completed the OLP, while [redacted] discontinued the OLP. [redacted] subjects completed the study but did not have an OLP visit. The primary reason for discontinuation was [redacted], followed by [redacted] and [redacted] Figure 2 presents a CONSORT diagram of participant flow in the EASE study.

Source: CS, Appendix D.1.2, Figure 2[1]

Figure 2: Participant flow in EASE study (reproduced from CS, Appendix D.1.2, Figure 2)

4.2.4 Baseline characteristics in EASE

Participant characteristics in EASE for both DBP and OLP are presented in Table 36, Appendix 1 (and CS, Section B.2.3.2.1[1]). The median age in the DBP was 12 years (range: 6 months to 81 years) and 70% of participants were aged 18 years or less. While the EASE study had inclusion criteria limited to ≥4 years of age, which was reduced to >21 days following an IDMC safety review part way through the trial (CS, Section B.1.1 Table 1), this age range is consistent with the NICE scope of ≥6 months of age. The EASE study had the following proportions of patients with relevant subtypes: 195/223 (87.4%) participants had DEB and 26/223 (11.7%) had JEB participants; there were two (0.9%) participants with Epidermolysis Bullosa Simplex (EBS patients were excluded according to criteria, see Table 8 above).

The reported characteristics were generally well balanced between groups for the DBP and also between the patients that went forward from each group to the OLP. The EASE study randomisation process was stratified by subtype (DEB and JEB) and wound size (see Table 8), as these are potential prognostic factors in terms of wound healing.[30] It was noted in the CS that the treatment arms were less well balanced in terms of DEB subtypes (DDEB and RDEB), CS, Section B.2.3.2.1.[1] The BBE gel group had a higher proportion of subjects with RDEB compared with the control gel group (83.5% versus 73.7%) and accordingly, a lower proportion of subjects with DDEB (5.5% versus 12.3%). It should also be noted that the CS also reported estimated numbers of UK patients with EB subtypes, based on Office for National Statistics (ONS) data (CS, Section B.1.3.2, Table 4).[1] This analysis found the following: 65% of patients had the DDEB subtype and 31% had the RDEB subtype, which compared with 9% and 78.5% in the EASE study. These subtypes might represent a prognostic factor for clinical outcomes, which in turn might affect how far the findings of the EASE study are generalisable to the UK clinical population.

In terms of the second stratification factor, wound size, this was generally well balanced between groups for the DBP and also between the patients that went forward from each group to the OLP. In the overall EASE population, the mean size of the target wound at baseline was 19.20cm^2 (standard deviation [SD]: 9.40cm^2). The majority of the participant population (64.6%) had a target wound sized between 10 to <20 cm^2; 21.1% had a target wound sized between 20 to <30 cm^2; and 14.3% had a target wound sized between 30 to 50 cm^2. Wound age is also a potential prognostic factor[35]: the older the wound, the less likely the wound will achieve the primary outcome and completely heal. The median age of the target wound was 35.5 days, for all participants, but the CS reported that this included data from 14 participants (n=8, BBE gel, n=6, control gel), who had wounds >9 months of age (range: 11.5-156 months).[1] These participants were included because they were enrolled prior to an early protocol

amendment that capped target wound age at a maximum of 9 months. The CS reported that, in the subset of subjects with a target wound age of no more than 9 months (n=208), as per the final protocol, median wound age was 32.0 days. In the overall EASE study population (n=223), there was a difference between arms in the median wound age: 39 days in the BBE gel group versus 32 days in the control gel group.[1]

In the trial protocol, treatment with the BBE gel or control gel was administered to the designated target wound, and "*additional*" wounds that satisfied the target wound criteria, and all "*other*" partial thickness wounds that did not satisfy these criteria (clarification response, A2).[2] In response to a request by the EAG, the company provided details of the number of "*additional"* but not "*other*" partial thickness wounds per patient in each arm at DBP baseline (clarification response, A2).[2] The majority of participants had only a single wound that satisfied the target wound criteria (n=76 (70%) in the BBE gel arm and n=84 (74%) in the control gel arm. Only 63 participants had one or more "*additional*" wounds (usually only one), and the proportions were generally balanced between arms (see Table 9).

Table 9: Number of additional wounds per subject (adapted from clarification response, A2, Table 1)

	BBE gel n=33	**Control gel n=30**	**All subjects n=63**
Number of additional wounds per subject matching the target criteria, n (%)			
One	25 (75.8)	17 (56.7)	42 (66.7)
Two	6 (18.2)	12 (40.0)	18 (28.6)
Three	1 (3.0)	0	1 (1.6)
Four	1 (3.0)	1 (3.3)	2 (3.2)

In summary, the BBE gel and control gel groups were generally well balanced at baseline in both the DBP and the OLP, with the exception of the potential prognostic factors of wound age and DEB subtype. The proportion of DEB patients with the DDEB and RDEB subtypes in the EASE study differed substantially from the estimated proportions of these subtypes in the UK EB population, based on the data provided in the CS: 65% of patients had the DDEB subtype and 31% had the RDEB subtype, which compared with 9% and 78.5% in the EASE study (Section B.1.3.2, Table 4).[1]

4.2.5 Study endpoints in EASE

The study endpoints are presented in Table 10.

Table 10: Study endpoints for the DBP and OLP (adapted from CS, Section B.2.3.1, Table 8)

Study phase	Double blind phase (DBP)[28, 32]	Open-label phase (OLP)[28, 31, 32]
Duration of phase	**90 days**	**24 months**
Primary outcome	Proportion of patients with first complete target wound closure within 45 days based on INV assessment	NA
Secondary outcomes	<u>Key secondary (confirmatory) efficacy endpoints:</u> ▪ Time to first wound closure up to 90±7 days of treatment ▪ Incidence of first complete wound closure of EB target wound ▪ Incidence of wound infection ▪ Maximum severity of wound infection ▪ CFB in total body wound burden (EBDASI, Section I: Skin, Activity (not Damage), only) ▪ CFB in itching (Itch Man Scale/ Leuven Itch Scale) <u>Other secondary endpoints:</u> ▪ CFB in EB target wound size ▪ CFB in % of TBSA affected by EB PTW ▪ CFB in background and procedural pain (FLACC, Wong-Baker FACES) ▪ Response to treatment/ treatment satisfaction (TSQM) ▪ CFB in sleep quality (Likert scale) ▪ Number of days missed from school or work ▪ Incidence, severity, and relatedness of AEs ▪ Local tolerability <u>Post-hoc analyses</u> ▪ Dressing change frequency	▪ Incidence of Target Wound Infection in the OLP ▪ Maximum Severity of Wound Infection in the OLP (between baseline and Month-24) ▪ CFB in Total Body Wound Burden in the OLP (EBDASI, Section I: Skin, Activity (not Damage), only; Months 3, 12, 24) ▪ CFB in BSAP affected by PTW by Visit (Months 3, 12, 24) ▪ CFB in itching (Itch Man Scale/ Leuven Itch Scale; Month 3 only) ▪ CFB in background and procedural pain (FLACC, Wong-Baker FACES; Month-3 only) ▪ CFB in sleep quality (Likert scale) (Month-3 only) ▪ Number of days missed from school or work (Month-3 only) ▪ Status of target wounds by visit (Month-3 only) ▪ CFB in disease severity by the iscorEB (Months 12, 24) ▪ CFB in patients' quality of life as assessed by the EQ-5D (Months 12, 24) ▪ Response to treatment/ treatment satisfaction (TSQM)

Abbreviations: AE, adverse event; BCC, basal cell carcinoma; BSAP, body surface area percentage; CFB, change from baseline; cm^2, square centimetre; DBP, double blind phase; DEB, dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; EBDASI, epidermolysis bullosa disease activity and scarring index; EBS, epidermolysis bullosa simplex; EDBP, end of double blind phase; EQ-5D, EuroQol 5-dimension; FLACC, Face, Legs, Activity, Cry, Consolability scale; g, gram; IDMC, Independent Data Monitoring Committees; INV, investigator-assessed; JEB, junctional epidermolysis bullosa; KEB, Kindler EBV; OLP, open label phase; mm, millimetre; n, number; NA, not applicable; PTW, partial-thickness wound; RCT, randomised controlled trial; SCC, squamous cell carcinoma; TBSA, total body surface area; TSQM, treatment satisfaction questionnaire for medication.
[a] Previously known as Kindler syndrome. KEB patients were eligible for inclusion in the EASE study however no patients with KEB were recruited.
[b] One participant with EBS was included in each intervention arm of the EASE study (recruited before the V4.0 protocol amendment excluded EBS participants).

The primary outcome in the DBP was the proportion of patients with first complete target wound closure within 45 days (+/-7 days) based on blinded investigator assessment. Full details of the target wound criteria, their selection and assessment, are presented in Table 11.

In response to a request by the EAG, the company also clarified the details of the wound burden assessments using the EBDASI disease severity score and BSAP measures (clarification response, A2).[2] These assessments included not only the target wound, but "*additional"* wounds that satisfied the target wound criteria, and all "*other*" partial thickness wounds that did not satisfy these criteria (clarification response, A2).[2] The EASE study required the treatment of all target, "*additional*" and "*other*" partial thickness wounds. The potential efficacy of this treatment of all such wounds was measured using the EBDASI disease severity score and by the total body surface area (TBSA) affected by EB partial-thickness wounds, which was measured as BSAP. The EBDASI assessment utilised in EASE was limited to the Activity part of Section I (assessment of the skin except for the anogenital region) only, not the full EBDASI instrument, and was applied at day 30, day 60, and day 90. BSAP was measured using the Lund and Browder method at baseline, day 30, day 60, and day 90, and the total BSAP was the overall sum of BSAP values recorded for nine anatomical regions. In response to a clarification request by the EAG, the company confirmed that these nine anatomical regions were the same for all patients in the EASE study (clarification response, A1).[2]

Table 11: Summary of the EASE study wound selection and assessment methods (reproduced from CS, Section B.2.3.1, Table 9)

Study phase	Double blind phase (DBP)[28, 32]	Open-label phase (OLP)[28, 31, 32]
Target wound criteria	EB partial-thickness wound identified by investigator 10–50cm^2 in surface area > 21 days and < 9 months old Outside the anogenital region Target wound identified with two appropriate anatomical landmarks on either side of it. The baseline reference image was taken with these landmarks. Future visits will refer to the baseline reference image to ensure that the correct wound is assessed. All other wounds that matched target wound criteria were to be photo-documented similarly. Target wound must involve loss of the epidermis, with extension into the dermis allowable.	Target Wound criteria as per the DBP
Target wound assessment method	For the assessment of wound closure and re-epithelialization, the investigator will photograph the EB target wound and all other wounds that match target wound criteria with the ARANZ Silhouette® system. This system measures accurately, precisely, and reliably, provides high quality imaging, and a standardised documentation. A 3D model of the wound based on photographic data, derives measurements of the model, and records standardised notes. Automatic flash ensures consistent lighting across images.	Target wound assessment method is as per the DBP The target wound closure categories included closed, not closed, not assessed, and missing. The category of not closed was further divided into 3 subcategories: unchanged from baseline; improved from baseline; and worsened from baseline.
Target wound assessment schedule	Visits: Days 0, 7 (+/- 2), 14 (+/- 5), 30 (+/- 7), 45 (+/- 7), 60 (+/- 7), 90 (+/- 7; end of DBP). Plus, a confirmation of complete closure (CCC) of the EB target wound visit, up to 1 week+2 days after first complete closure. Post-treatment assessments will be made within one week of wound closure to determine durability of healing.	The status of target wounds was not included as an OLP efficacy endpoint in the SAP; however, an assessment was performed at OLP baseline and Month 3.

Abbreviations: CCC, confirmation of complete closure; cm^2, square centimetre; DBP, double-blind phase; EB, epidermolysis bullosa; OLP, open-label phase, SAP, statistical analysis plan.

The statistical analysis is based on the study populations described below. Patients who were randomised but not treated were not assigned to any of the analysis sets.

Table 12: Summary of statistical analysis sets from EASE (adapted from CS, Section B.2.4.1.1, Table 11)

	Population
Full analysis set (FAS)	Includes all randomised patients treated at least once with study treatment. Participants are analysed according to the randomised treatment regimen (if different from the received treatment).
Safety analysis set (SAS)	Includes all patients treated at least once with study medication. Participants are analysed according to the treatment regimen received.
Completer analysis set (CAS)	Includes all patients from the FAS who did not discontinue the double-blind phase of the study early, irrespective of the reason for discontinuation. Participants are analysed according to the randomised treatment regimen.
Per protocol set (PPS)	Includes all patients who have met the eligibility criteria, received the planned study medication, and have reasonably adhered to all relevant protocol conditions.[a] Participants are analysed according to randomised treatment regimen.

Source: Adapted from EASE SAP (v5.0 Final)
Abbreviations: CAS, completer analysis set; FAS, full analysis set; PPS, per protocol set; SAS, safety analysis set

Efficacy endpoints were similar between the DBP and OLP with the exception that the primary efficacy outcome from the DBP - the proportion of patients with complete closure of the target wound within 45 days – was not assessed in the OLP. The secondary efficacy endpoints were very similar between the DBP and OLP and some endpoints evaluated a similar time frame (e.g., approximately 90 days or 3 months from DBP or OLP baseline). OLP baseline was defined as the first day of the OLP (OLP day 0) which occurred at day 90 of the DBP; however, OLP baseline only included subjects that entered the OLP.

Two additional efficacy endpoints were assessed in the OLP: the assessment of disease severity by Instrument for Scoring Clinical Outcome of Research for Epidermolysis Bullosa (iscorEB) and quality of life by EQ-5D-5L and the EQ-5D-Y.[30, 36] However, the addition of these endpoints was not implemented consistently, with the result that few participants had baseline assessments, which in turn resulted in limited data and prevented meaningful interpretation of change from baseline (CFB) assessments.

4.3 Clinical effectiveness of BBE gel (Oleogel-S10)

Efficacy endpoints were presented and described for the EASE DBP (database lock: 26th of August 2020) in CS Section B.2.6.1 and for the EASE OLP (database lock: 1st of July 2022) in CS Section B.2.6.2.[1]

4.3.1 Clinical effectiveness in the DBP (90 days)

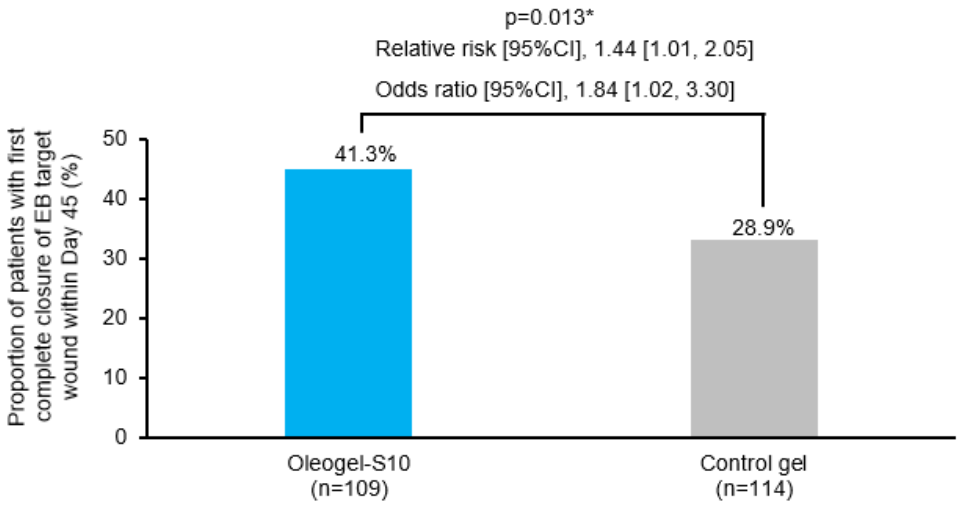
The clinical efficacy results of the EASE DBP (database lock: 26th pf August 2020) are summarised in Table 13, Table 14, Table 15, and Table 16.

In terms of the primary outcome, BBE gel treatment significantly increased the probability of target wound closure by day 45 (+/- 7) compared with the control gel: 41.3% vs 28.9%; risk ratio (RR) 1.44 (95% confidence interval (CI): 1.01-2.05, *p*=0.013) (Table 13).

Table 13: Clinical efficacy results for primary outcome from the EASE DBP (adapted from CS, Section 2.6.2, Table 12)

Study name		**EASE DBP (90 days)[32]**	
Analysis type		**Full analysis set**	
Intervention		**BBE gel**	**Control gel**
Size of study group		109	114
Primary endpoint	**Name**	**Proportion of patients with first complete target wound closure within 45 days based on INV assessment**	
	n (%)	Closure: 45 (41.3) Non-closure: 64 (58.7)	Closure: 33 (28.9) Non-closure: 81 (71.1)
	Relative risk (95% CI)	1.44 (1.01, 2.05)	
	Odds ratio (95% CI)	1.84 (1.02, 3.30)	
	***P*-value**	0.013[a]	

Abbreviations: BBE, Birch Bark Extract; DBP, Double blind phase; INV, investigator



Source: Murrell DF, et al. Presented at, EADV Virtual Congress, 29-31 October 2020. D3T03.3B.[37]
Abbreviations: CI, confidence interval; DBP, double-blind phase; EB, epidermolysis bullosa; n, number of subjects.; IDMC, Independent Data Monitoring Committee.
*Pre-specified adjustment to account for IDMC interim sample size re-estimation

Figure 3: The proportion of patients with first complete target wound closure within 45 (+/- 7) days in the EASE study DBP (reproduced from CS, Section 2.6.2, Figure 6)

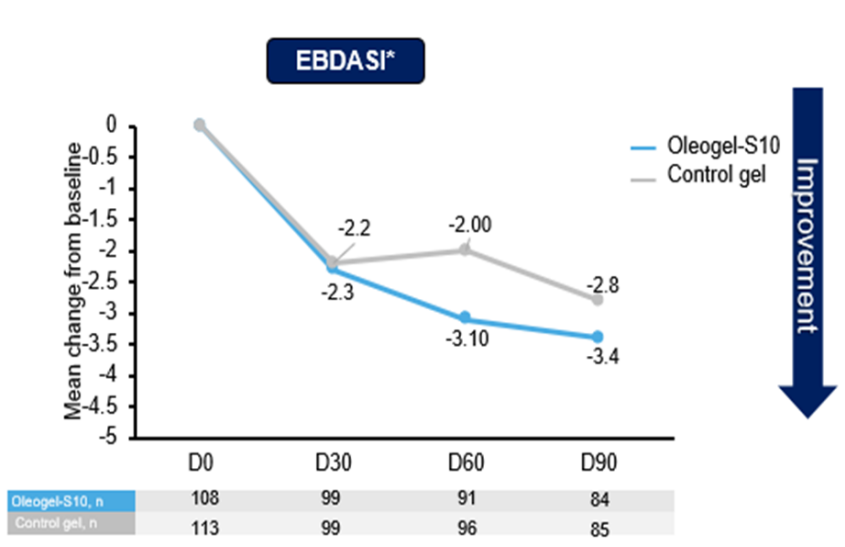
A summary of the key secondary outcomes for wounds is presented in Table 14. There was no significant difference between patients using BBE or control gel in median time to first complete closure of target wound by day 90 based on clinical assessment (p=0.302) or in the proportion of participants with first complete closure of target wound by day 90 based on investigator assessment (p=0.296). There was no significant difference between patients using the BBE or the control gel in incidence of target wound infection up to day 90, based on AE reporting or use of antibiotics (p=0.326). In terms of the maximum severity of target wound infections: one mild infection was reported in one patient using BBE gel, and three moderate and one severe infection in patients using the control gel.

Table 14: Clinical efficacy results for key secondary wound closure outcomes by day 90 from the EASE DBP (adapted from CS, Section 2.6.2, Table 12)

Study name		**EASE DBP (90 days)[32]**	
Analysis type		**Full analysis set**	
Intervention		**BBE gel**	**Control gel**
Size of study group		109	114
Key secondary endpoint	**Name**	**Time to first complete closure of target wound by day 90 based on clinical assessment**	
	Median [days] (95% CI)[b]	92.0 (50.0, NE)	94.0 (89.0, NE)
	***P*-value**	0.302	
Key secondary endpoint	**Name**	**Proportion of patients with first complete closure of target wound by day 90 based on INV assessment**	
	n (%)	Closure: 55 (50.5) Non-closure: 54 (49.5)	Closure: 50 (43.9) Non-closure: 64 (56.1)
	Relative risk (95% CI)	1.16 (0.88, 1.52)	
	Odds ratio (95% CI)	1.34 (0.78, 2.32)	
	***P*-value**	0.296[c]	
Key secondary endpoint	**Name**	**Incidence of target wound infection up to day 90 based on AE reported and/ or use of topical/ systemic antibiotics**	
	n (%)	Infection: 2 (1.8) No infection: 107 (98.2)	Infection: 5 (4.4) No infection: 109 (95.6)
	Relative risk (95% CI)	0.44 (0.08, 2.34)	
	Odds ratio (95% CI)	0.43 (0.08, 2.33)	
	***P*-value**	0.326[d]	
Key secondary endpoint	**Name**	**Maximum severity of target wound infection up to day 90 based on AE reporting of PTs only**	
	n (%)	Mild: 1 (0.9) Moderate: 0 Severe: 0 Life-threatening: 0 Death: 0	Mild: 0 Moderate: 3 (2.6) Severe: 1 (0.9) Life-threatening: 0 Death: 0

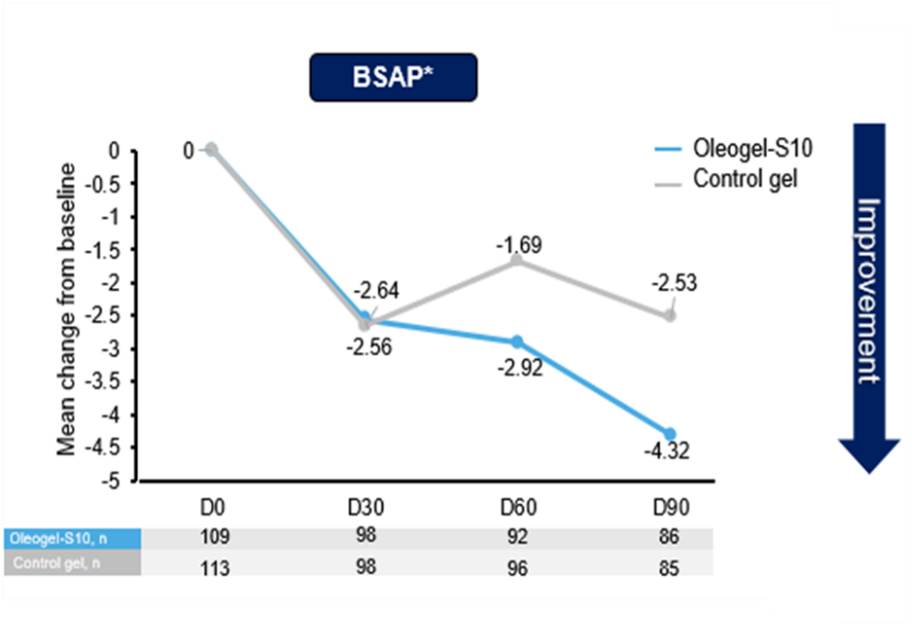
Abbreviations: BBE, Birch Bark Extract; CI, Confidence Interval; DBP, Double blind phase; INV, investigator; n, number; NE, not estimable; OR, Odds ratio; RR, risk ratio

There was a trend in favour of BBE gel compared with the control gel for improvements in wound burden at day 90 according to both the EBDASI and the BASP (Figure 4 and Figure 5), but any differences between the two treatments were non-statistically significant (p=0.887 and p=0.111, respectively) (Table 15). There was also a trend in favour of BBE gel compared with the control gel in terms of reduction in target wound size at day 90 based on the blinded evaluation of photographs (p=0.615), but again there was no statistically significant difference between the two treatments (Table 15).



Source: Murrell DF, et al. Presented at, EADV Virtual Congress, 29-31 October 2020. D3T03.3B[37]
Abbreviations: EBDASI, Epidermolysis Bullosa Disease Activity and Scarring Index.
*At all timepoints, comparison between BBE gel vs. control gel was not significant

Figure 4: Change in EBDASI by day 90 (reproduced from CS, Section 2.6.2, Figure 8)



Source: Murrell DF, et al. Presented at, EADV Virtual Congress, 29-31 October 2020. D3T03.3B.[37]
Abbreviations: BSAP, body surface area percentage.
*At all timepoints, comparison between BBE gel vs. control gel was not significant

Figure 5: Change in BSAP by day 90 (reproduced from CS, Section 2.6.2, Figure 7)

Table 15: Clinical efficacy results for secondary wound burden outcomes by day 90 from the EASE DBP (adapted from CS, Section 2.6.2, Table 12)

Study name		**EASE DBP (90 days)[32]**	
Analysis type		**Full analysis set**	
Intervention		**BBE gel**	**Control gel**
Size of study group		109	114
Key secondary endpoint	**Name**	**Change from baseline to day 90 in total body wound burden (assessed using EBDASI)**	
	Mean (SD)	n=84 -3.4 (7.22)	n=85 -2.8 (7.53)
	LS Mean (SE)	n=84 -0.44 (0.90)	n=85 -0.56 (0.85)
	95% CI of LS mean	-2.22, 1.35	-2.25, 1.12
	Difference in LS means (SE)	0.12 (0.86)	

	95% CI of difference in LS means	-1.58, 1.83	
	***P*-value**	0.887[e]	
Other secondary endpoint	**Name**	**Change from baseline to day 90 in BSAP (TBSA affected by EB PTW) assessed on the Lund and Browder chart**	
	Mean (SD)	n=86 -4.32 (7.027)	n=85 -2.53 (8.852)
	LS Mean (SE)	n=86 -3.41 (0.82)	n=85 -2.13 (0.79)
	95% CI of LS mean	-5.03, -1.80	-3.68, -0.58
	Difference in LS means (SE)	-1.28 (0.80)	
	95% CI of difference in LS means	-2.87, 0.30	
	***P*-value**	0.111[j]	
Other secondary endpoint	**Name**	**Percentage change from baseline in EB target wound size at day 90**	
	Mean (SD)	n=75 -54.35 (82.792)	n=81 -48.73 (71.492
	LS Mean (SE)	n=75 -58.83 (12.42)	n=81 -52.55 (11.57)
	95% CI of LS mean	-83.37, -34.29	-75.40, -29.69
	Difference in LS means (SE)	-6.28 (12.46)	
	95% CI of difference in LS means	-30.90, 18.33	
	***P*-value**	0.615[h]	

Abbreviations: BASP, Body surface area percentage; BBE, Birch Bark Extract; CI, Confidence Interval; DBP, Double blind phase; EB, Epidermolysis bullosa; EBDASI, Epidermolysis Bullosa Disease Activity and Scarring Index; INV, investigator; LS, Least squares; n, number; NE, not estimable; OR, Odds ratio; PTW, Partial-thickness wounds; RR, risk ratio; SD, Standard deviation; SE, Standard error; TBSA, Total body surface area.

At day 90, there was also no significant difference between patients using the BBE gel or the control gel in terms of outcomes such as: itching (using Itch Man Scale for patients aged 4-13 years and Leuven

Itch Scale for patients aged >14 years and over); procedural pain (measured using Wong-Baker FACES for participants aged ≥4 years and the Face, Legs, Activity, Cry, Consolability scale (FLACC) for those aged <4 years (Wong-Baker FACES: -1.32 with BBE gel vs -0.18 with the control gel, *p*=0.051; FLACC: -2.57 with BBE gel vs -1.17 with control gel, *p*=not estimable); or background pain (Wong-Baker FACES: -0.94 with BBE gel vs -1.11 with the control gel, *p*=0.771; FLACC: -0.71 with BBE gel vs 0 with control gel, *p*=not estimable); (Table 16). There were also no reported differences at day 90 between the two treatment arms in terms of sleep quality, days missed from school or work, or treatment satisfaction using the Treatment Satisfaction Questionnaire for Medication (TSQM) (Table 16).

Table 16: Clinical efficacy results for patient-reported secondary outcomes by day 90 from the EASE DBP (adapted from CS, section 2.6.2, Table 12)

Study name		**EASE DBP (90 days)[32]**	
Analysis type		**Full analysis set**	
Intervention		**BBE gel**	**Control gel**
Size of study group		109	114
Key secondary endpoint	**Name**	**Change from baseline in itching (assessed using Itch Man Scale for patients aged 4-13 years and Leuven Itch Scale for patients aged 14 years and over)**	
	Mean change in Itch Man Scale	n=39 -0.44	n=43 -1.0
	***P*-value**	0.182[f]	
	Leuven Itch Scale	Frequency: -8.13 Severity: -4.95 Duration: -0.93 Consequence: -4.39 Distress: -0.44 Surface area: -1.54	Frequency: -10.14 Severity: -10.76 Duration: 0.98[g] Consequence: -3.54[g] Distress: -0.26 Surface area: 0.68
	***P*-value[f]**	Frequency: 0.344 Severity: 0.528 Duration: 0.779 Consequence: 0.940 Distress: 0.797 Surface area: 0.598	
Other secondary endpoint	**Name**	**Change from baseline in <u>procedural pain</u> to day 90 (assessed using FLACC for patients <4 years of age, and Wong-Baker Faces for those ≥4 years of age)**	

	Mean change in Wong-Baker FACES score	n=76 -1.32	n=78 -0.18
	***P*-value**	0.051[f]	
	Mean change in FLACC score	n=7 -2.57	n=6 -1.17
	***P*-value**	NE	
Other secondary endpoint	**Name**	**Change from baseline in <u>background pain</u> to day 90 (assessed using FLACC for patients <4 years of age, and Wong-Baker Faces for those ≥4 years of age)**	
	Mean change in Wong-Baker FACES score	n=79 -0.94	n=79 -1.11
	***P*-value**	0.771[f]	
	Mean change in FLACC score	n=7 -0.71	n=6 0.0
	***P*-value**	NE	
Other secondary endpoint	**Name**	**Change from baseline in impact of wounds on sleep quality (Likert Scale) to day 90**	
	Mean (SD)	n=40 -0.8 (2.17)	n=37 -1.0 (3.22)
	LS Mean (SE)	n=40 -0.75 (0.50)	n=37 -1.12 (0.46)
	95% CI of LS mean	-1.75, 0.25	-2.05, -0.20
	Difference in LS means (SE)	0.37 (0.57)	
	95% CI of difference in LS means	-0.77, 1.51	
	***P*-value**	0.519[k]	
Other secondary endpoint	**Name**	**Number of days missed from school or work until day 90**	
	Mean [days] (SD)	n=54 4.7 (7.50)	n=57 5.0 (7.57)

	Proportion who had missed days, n (%)	33 (61.1)	37 (64.9)
Other secondary endpoint	**Name**	**Response to treatment (TSQM) before wound dressing changes at day 90 in patients aged ≥4 years of age**	
	LS mean (SE)	n=22 4.77 (0.38)	n=22 4.47 (0.32)
	95% CI of LS mean	4.00, 5.54	3.82, 5.11
	Difference in LS means (SE)	0.30 (0.44)	
	95% CI of difference in LS means	-0.60, 1.20	
	***P*-value**	0.501[1]	

Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; BBE, Birch Bark Extract; BSAP, body surface area percentage; CI, confidence interval; DBP, double-blind phase; EB, epidermolysis bullosa; EBDASI, epidermolysis bullosa disease activity and scarring index; FLACC, face, legs, activity, cry, consolability scale; INV, investigator-assessed; LS, least squares; n, number; NE, not estimable; PTs, preferred terms; SD, standard deviation; SE, standard error; TBSA, total body surface area; TSQM, Treatment Satisfaction Questionnaire for Medication.

[a] CMH statistical test with CHW adjustment applied; CMH test stratified by EB subtype and target wound size class. Odds ratio >1 represents a favourable outcome for BBE gel treatment.

[b] Parameter and model estimates based on a Log-rank test performed without consideration of any stratification.

[c] CMH statistical test stratified by EB subtype and target wound size class. Odds ratio >1 represents a favourable outcome for BBE gel treatment.

[d] CMH statistical test stratified by EB subtype and target wound size class. Odds ratio <1 represents a favourable outcome for BBE gel treatment.

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

[f] Parameter and model estimates based on a 2-sided Wilcoxon Rank Sum test using the van Elteren extension stratified by EB subtype and target wound size class.

[g] Scaled-up values used for these domains (values recorded with an incorrectly sized scale were converted to a common scale and multiplied by 10 as: Scaled-up subscore = [(recorded answer*10)/actual VAS length]*10. Actual VAS length used as provided by the study clinical team).

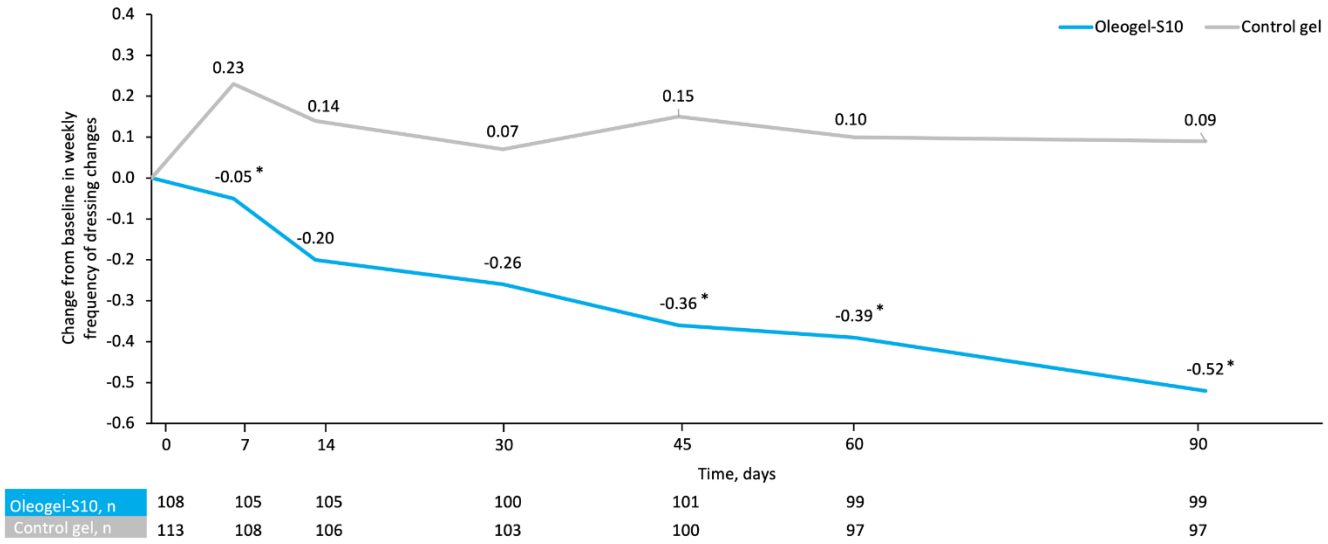
[h] Parameter and model estimates based on an ANCOVA on the percentage change from baseline with Treatment group and EB Subtype as fixed effects and size of target wound at baseline as a covariate.

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

[j] Parameter and model estimates based on an ANCOVA on the change from baseline with treatment group and EB subtype as fixed effects and baseline W-QoL Scale score baseline as a covariate.

[k] Parameter and model estimates based on an ANCOVA on the TSQM overall score with treatment group and EB subtype as fixed effects and TSQM overall score at day 7 as a covariate.

The company notes that the non-significant reduction in procedural pain for BBE gel compared with the control gel might be associated with an observed reduction in the required frequency of dressing changes for BBE gel compared with the control gel at days 45, 60, and 90 (day 45: -0.38 vs 0.18, p=0.003; day 60: -0.42 vs 0.13, p=0.005; day 90: -0.55 vs 0.11, p=0.001 [post-hoc analysis]) (Figure 6). However, this relationship is uncertain.[32]



Source: Kern et al. (2022).[29]
Frequencies are calculated based on the response at each visit. Daily dressing changes are assigned a frequency of 1.000, dressing changes every 2 days are assigned a value of 0.5000 etc. Where a combination of frequencies is reported the frequency is calculated for each and then the mean value is taken e.g., dressings every 1–2 days; (1.000 + 0.500)/2 = 0.750. Frequencies per day are multiplied by 7 to obtain the weekly frequency.
* Analysis of covariance (ANCOVA) was conducted and a statistically significant difference between BBE 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).

Figure 6: Change from baseline in weekly frequency of dressing changes during the EASE study DBP (reproduced from CS, Section 2.6.1, Figure 9)

4.3.2 *Clinical effectiveness in the OLP (24 months)*

The clinical efficacy results of the EASE OLP (database lock: 1st of July 2022) are summarised in Table 17 and Table 37, Appendix 1. All participants received the BBE gel. The primary outcome from the DBP was not assessed in the OLP. All other secondary outcomes were measured, as well as EQ-5D-5L. EQ-5D-Y and iscorEB, which were not measured in the DBP. The CS reported that none of the efficacy analyses in the OLP were powered for statistical significance (CS, Section B.2.6.2).[1]

Wound burden assessments were made at 3, 12 and 24 months; assessments of wound infection, EQ-5D-5L, EQ-5D-Y, and iscorEB at 12 and 24 months; and the other patient reported outcomes (e.g., itching, pain, sleep quality and treatment satisfaction) at 3 months only. Loss to follow-up was >10% at month 3, >25% at month 12 and >30% at month 24, with very small numbers of respondents for some outcome measures (e.g., HRQoL assessed by EQ-5D-5L, EQ-5D-Y, and iscorEB).

The CS presented two sets of data for EBDASI and BSAP: data from within visit windows (365±14 days for Month 12 and 730±14 days for Month 24) and data from without visit windows, but reported for the nearest time point to when a patient was actually assessed (CS, Sections B.2.4.1.1 and B.2.6.2).[1]

The CS reports that the former had smaller numbers of patients assessed because visits within these windows were affected by Covid-19, where-as the latter assessment permitted the inclusion of more patients (CS, Sections B.2.4.1.1 and B.2.6.2).[1]

The findings of the wound burden assessed by EBDASI and BSAP in the OLP present a complex picture (Figure **7** and Figure 8). The trend for those participants who received BBE gel during the DBP was for a continued improvement in wound burden by the EBDASI measure to month 3, but a slight worsening at month 12 and at month 24. By contrast, the trend for participants who received the control gel during the DBP was for a worsening in wound burden by the EBDASI measure to month 3, followed by a substantial improvement by month 12, and a worsening again (similar to scores at baseline at OLP day 0: [redacted] versus [redacted]) at month 24 (Figure 7, A). The trends were the same for the data excluding the visit windows, but less marked (Figure 7, B).

A similar picture was presented for the findings of the BSAP wound burden assessments: improvements to 3 and 12 months, and a slight worsening to 24 months, for patients who received BBE gel in the DBP, but with the exception that participants who received the control gel during the DBP, while experiencing a worsening to month 3, enjoyed a slight improvement to months 12 and to month 24, rather than a worsening (Figure 8, A). Again, the trends were the same for the data excluding the visit windows, but these were less marked (Figure 8, B).

The CS (Section B.2.6.2) did not provide any explanation for the variation in trends over time, only commenting on the change from baselines to the 2-year endpoint, or why the different patient groups from the DBP of the EASE study might have difference responses in the OLP.

A

B

Source: Amryt Pharmaceuticals. Clinical Study Report Addendum Version 2.0. [30]
Abbreviations: D, day; DBP, double-blind phase; EBDASI, Epidermolysis Bullosa Disease Activity and Scarring Index; M, month; n, number; OLP, open-label phase; TBWB, total body wound burden.
*Former treatments refer to the treatments that patients were randomised to during the DBP
A. Change from Baseline in TBWB Based on the Mean EBDASI Skin Activity Score by Visit in the OLP Including OLP Visit Windows (FAS).
B. Change from Baseline in TBWB Based on the Mean EBDASI Skin Activity Score by Visit in the OLP Excluding OLP Visit Windows (FAS).

Figure 7: EBDASI improvements throughout the EASE OLP for patients receiving BBE gel (reproduced from CS, Section B.2.6.2, Figure 11)

A

B

Source: Amryt Pharmaceuticals. Clinical Study Report Addendum Version 2.0.[30]
Abbreviations: BSAP, body surface area percentage; D, day; DBP, double-blind phase; M, month; n, number; OLP, open-label phase.
*Former treatments refer to the treatments that patients were randomised to during the DBP
A. Change from Baseline in Total Body Surface Area Percentage by Visit in the OLP Including OLP Visit Windows (FAS).
B. Change from Baseline in Total Body Surface Area Percentage by Visit in the OLP Excluding OLP Visit Windows (FAS).

Figure 8: BSAP improvements throughout the EASE OLP for patients receiving BBE gel (reproduced from CS, Section B.2.6.2, Figure 10)

Table 17: Summary of clinical efficacy results for wound burden from EASE OLP (adapted from CS, Section B.2.6.2, Table 13)

Study name	**EASE OLP (24 months)[30]**								
Timepoint	**Month-3**			**Month-12**			**Month-24**		
Analysis type	**Full analysis set**								
Intervention	**Former BBE gel**	**Former control gel**	**All patients**	**Former BBE gel**	**Former control gel**	**All patients**	**Former BBE gel**	**Former control gel**	**All patients**
Size of study group	100	105	205	100	105	205	[redacted]	[redacted]	[redacted]
Name	**Change from OLP day 0 in total body wound burden (assessed by EBDASI)**								
Mean (SD)	n=73 -1.0 (5.79)	n=70 0.4 (5.85)	n=143 -0.3 (5.84)	n=55 -0.4 (6.26)[b] n=58 -0.5 (6.20)	n=50 -0.3 (6.62)[b] n=53 -0.9 (7.17)	n=111 -0.7 (6.65)	[redacted]	[redacted]	[redacted]
LS mean (SE)	n=73 -0.45 (0.92)	n=70 1.05 (0.90)	NR	n=55 -0.81 (1.28)[b] n=58 -0.61 (1.23)	n=50 -1.41 (1.20)[b] n=53 -2.01 (1.20)	NR	[redacted]	[redacted]	[redacted]
95% CI of the LS mean	-2.28, 1.37	-0.74, 2.83	NR	-3.36, 1.74[b] -3.04, 1.82	-3.80, 0.98[b] -4.39, 0.37	NR	[redacted]	[redacted]	[redacted]
Difference in LS means (SE)	-1.50 (0.95)		NA	0.60 (1.22)[b] 1.40 (1.22)		NA	[redacted]		[redacted]

Study name	**EASE OLP (24 months)[30]**								
Timepoint	**Month-3**			**Month-12**			**Month-24**		
Analysis type	**Full analysis set**								
Intervention	**Former BBE gel**	**Former control gel**	**All patients**	**Former BBE gel**	**Former control gel**	**All patients**	**Former BBE gel**	**Former control gel**	**All patients**
Size of study group	100	105	205	100	105	205	[redacted]	[redacted]	[redacted]
95% CI of difference in LS means	-3.37, 0.37		NA	-1.83, 3.03[b] -1.02, 3.82		NA	[redacted]		[redacted]
***P*-value[c]**	0.116		NA	0.625[b] 0.253		NA	[redacted]		[redacted]
Name	**Change from OLP day 0 in total body wound burden (assessed by EBDASI) without visit windowing (*post hoc* analysis)**								
Mean (SD)	n=86 -0.7 (5.63)	n=89 0.9 (6.12)	n=175 0.1 (5.92)	n=67 -1.0 (6.39)	n=73 -0.9 (6.27)	n=140 -0.9 (6.31)	[redacted]	[redacted]	[redacted]
Name	**Change from OLP day 0 in BSAP of TBSA affected by EB PTW (using Lund and Browder chart)**								
Mean (SD)	n=72 -0.22 (4.127)	n=69 -0.06 (5.422)	n=141 -0.14 (4.788)	n=56 -1.63 4.462)[b] n=58 -1.91 (4.461)	n=50 -1.11 7.635)[b] n=53 -1.29 (7.469)	n=106 -1.39 (6.140) n=111 -1.61 (6.065)	[redacted]	[redacted]	[redacted]
LS mean (SE)	n=72 0.49 (0.75)	n=69 1.00 (0.74)	NR	n=56	n=50	NR	[redacted]	[redacted]	[redacted]

Study name	**EASE OLP (24 months)[30]**								
Timepoint	**Month-3**			**Month-12**			**Month-24**		
Analysis type	**Full analysis set**								
Intervention	**Former BBE gel**	**Former control gel**	**All patients**	**Former BBE gel**	**Former control gel**	**All patients**	**Former BBE gel**	**Former control gel**	**All patients**
Size of study group	100	105	205	100	105	205			
				-1.95 (1.10)[b] n=58 -2.06 (1.00)	-1.30 (1.04)[b] n=53 -1.79 (0.99)				
95% CI of the LS mean	-0.99, 1.98	-0.47, 2.47	NR	-4.12, 0.23[b] -4.05, -0.07	-3.36, 0.76[b] -3.76, 0.18	NR			
Difference in LS means (SE)	-0.51 (0.79)		NA	-0.65 (1.05)[b] -0.27 (1.00)		NA			
95% CI of difference in LS means	-2.07, 1.06		NA	-2.73, 1.42[b] -2.25, 1.72		NA			
***P*-value[d]**	0.523		NA	0.535[b] 0.791		NA			
Name	**Change from OLP day 0 in BSAP of TBSA affected by EB PTW (using Lund and Browder chart) without visit windowing (post hoc analysis)**								

Study name	**EASE OLP (24 months)[30]**								
Timepoint	**Month-3**			**Month-12**			**Month-24**		
Analysis type	**Full analysis set**								
Intervention	**Former BBE gel**	**Former control gel**	**All patients**	**Former BBE gel**	**Former control gel**	**All patients**	**Former BBE gel**	**Former control gel**	**All patients**
Size of study group	100	105	205	100	105	205	[redacted]	[redacted]	[redacted]
Mean (SD)	n=85 -0.18 (4.087)	n=87 0.34 (6.295)	n=172 0.08 (5.310)	n=67 -1.54 (4.493)	n=73 -1.54 (6.447)	n=140 -1.54 (5.578)	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; BBE, Birch Bark Extract; BSAP, body surface area percentage; CFB, change from baseline; CI., confidence interval; EB, epidermolysis bullosa; EBDASI, epidermolysis bullosa disease activity and scarring index; EQ-5D-Y, EuroQol 5-dimension Youth; EQ-5D-5L, EuroQol 5-dimension 5-level; FLACC, face, legs, activity, cry, consolability scale; LOCF, last observation carried forward; LS, least squares; n, number; NE, not estimable; NR, not reported; OLP, open label phase; PTs, preferred terms; PTW, partial-thickness wound; SD, standard deviation; SE, standard error; TBSA, total body surface area.

[a] Percentages calculated from absolute data.

[b] This data was provided as an earlier database lock of 12-month efficacy data and therefore represents fewer patients (lower n) than the 12-month data recorded at the final OLP database lock

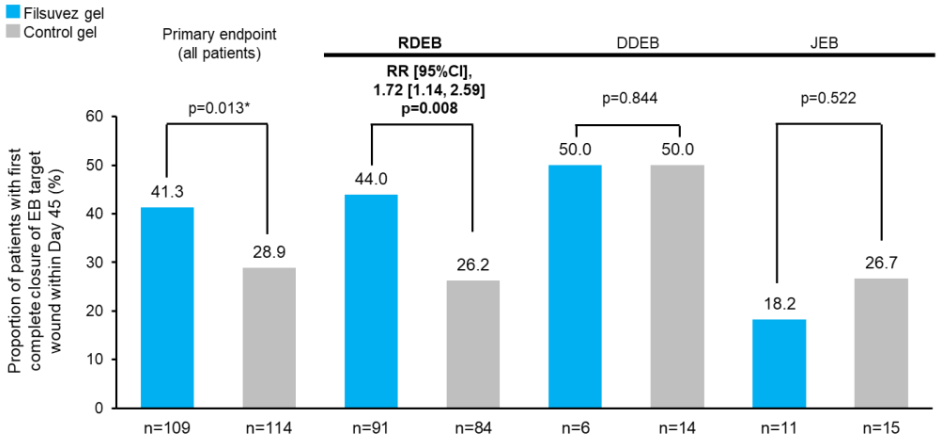
[g] Parameter and model estimates based on an ANCOVA on the change from baseline with treatment group and EB Subtype as fixed effects and baseline W-QoL Scale score as a covariate.

The CS reports that there were mostly small improvements or no improvements (and sometimes small declines) in change from baseline across all other outcomes (Table 37). The only comparison assessed for statistical significance was between participants who had received the BBE gel during the DBP, and those who had the control gel during the DBP (both groups only received the BBE gel in the OLP), e.g., the outcomes of pain, sleep and treatment satisfaction; there were no statistically significant differences reported between these groups.[1]

There were no clear trends in incidence or severity levels of target or "*additional*" wound infections at 12 and 24 months (these findings were also reported by the company for "*additional*" and "*other*" wounds at day 90 in DBP and 24 months in the OLP, clarification response, A2, Tables 2 and 3[2]). There were improvements reported in disease severity using the iscorEB at 12 and 24 months but worsening of quality of life as measured by the EQ-5D VAS at 12 and 24 months. At 3 months, there was either no improvement or a small worsening in the following outcomes: itching, procedural pain, background pain and sleep quality. There was a small improvement in treatment satisfaction. There was no reported statistically significant difference between treatment arms for any of these outcomes.

4.3.3 *Subgroup analyses*

The EASE study statistical analysis plan (SAP) prespecified subgroup analyses by EB subtype (JEB, RDEB, DDEB) for the primary efficacy endpoint (target wound closure), and the first key secondary efficacy endpoint (median time to first target wound closure) (CS, Section B.2.7).[1] Baseline demographics were not reported by subgroup in the EASE study, so it is uncertain whether there were any potentially relevant differences between arms for these subtypes. For the primary endpoint, there was only a significant difference in subtypes in target wound closure by 45 days (+/-7); this difference was in favour of the BBE gel compared with the control gel in the RDEB subgroup (n=175): 44% vs 26.2% (RR 1.72, p=0.008) (Figure 9). While the median time to first complete closure of target wound by day 90 (first key secondary endpoint) was numerically shorter for participants using BBE gel compared with the control gel in the RDEB subgroup (64.0 days vs 94.0 days), this was not statistically significant (p=0.175).[1] No relative benefits were found for the BBE gel vs the control gel for the other subgroups, but the CS stated that caution should be applied to interpreting these data as these subgroups had relatively low patient numbers (DDEB n=20; JEB n=26).[1]



Source: Bruckner et al. (2021)[38]
*Pre-specified adjustment to account for IDMC interim sample size re-estimation

Figure 9: Analysis of EASE primary endpoint by EB subtype (reproduced from the CS, Section B.2.7, Figure 12).

4.4 Critique of the safety data reported for EASE study

The frequency of any AE was high (>80% in the DBP) (

Table 18). It should be noted that the frequencies of AEs (81.7% for BBE gel vs 80.7% for the control gel), serious adverse events (SAEs) (6.4% vs 5.3%), AEs leading to drug withdrawal (2.8% vs 3.5%), and SAEs leading to study withdrawal (2.8% vs 1.8%), and AEs due to wound complications (61.5% vs 53.5%), were all similar between the BBE gel and control gel arms of the DBP (

Table 18).

In the OLP, the frequency of AEs was similar to the DBP: AEs ([redacted] for the OLP vs ≤80.7% in the DBP). The AEs for which the frequency was higher in the OLP compared with the DBP were: SAEs ([redacted] for the OLP vs ≤6.4% for the DBP); AEs leading to drug withdrawal ([redacted] vs ≤3.5%); SAEs leading to study withdrawal ([redacted] vs ≤2.8%); and SAEs leading to death ([redacted] vs 0%). There were no SAEs leading to death in any arm in the DBP and the CS reported that none of the deaths in the OLP were considered related to study treatment, and all were assessed as consistent with the course of the disease (CS, Section B.2.10).[1]

Table 18: Summary of safety and tolerability outcomes from EASE (DBP and OLP; SAS) (adapted from CS, Section B.2.10, Table 14)

	EASE DBP (90-day)[32]		EASE OLP (24-month)[30]		
	BBE gel	Control gel	Former BBE gel	Former Control gel	All subjects
	n=109	n=114	n=100	n=105	N=205
AEs, n (%)	89 (81.7)	92 (80.7)	[redacted]	[redacted]	[redacted]
Serious AEs, n (%)	7 (6.4)	6 (5.3)	[redacted]	[redacted]	[redacted]
AEs leading to drug withdrawal, n (%)	3 (2.8)	4 (3.5)	[redacted]	[redacted]	[redacted]
Serious AEs leading to study withdrawal, n (%)	3 (2.8)	2 (1.8)	[redacted]	[redacted]	[redacted]
AEs due to wound complications,[a] n (%)	67 (61.5)	61 (53.5)	[redacted]	[redacted]	[redacted]
Serious AEs leading to death, n (%)	0 (0)	0 (0)	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event, BBE, Birch Bark Extract; DBP, double-blind phase; OLP, open-label phase; SAS, safety analysis set.
[a] FDA advice led to the EASE protocol specifying "worsening of wound status, increase in wound size, reopening of wounds, and wound infections should be reported as AEs", relating to both target and non-target wounds. Most were not assessed as treatment-related by the investigator since changes in wound size from visit to visit, as well as reopening of previously closed wounds, are expected in DEB and JEB.

Specific AEs or groups of AEs are summarised in

Table 19 and Table 20. The highest reported frequencies in both the DBP and the OLP were: wound complications (53.5-61.5% in the DBP and [redacted] overall in the OLP); infections and infestations, particularly wound infections (7.3-8.8% and [redacted]); pyrexia (8.3-13.2% and [redacted]); pruritus (5.3-7.3% and [redacted] and anaemia (3.5-7.3% and [redacted]). Few other specific AEs occurred in more than 5% of patients in either phase; the only AEs to occur in >5% of patients in the OLP were [redacted]) and [redacted]) (Table 20).

Table 19: Summary of EASE DBP AEs with incidence of >5% in either arm (SAS) (adapted from CS, Section B.2.10, Table 15)

	EASE DBP[32]	
	BBE gel	**Control gel**
	n=109	**n=114**
Any AEs	89 (81.7)	92 (80.7)
Injury, poisoning, and procedural complications	69 (63.3)	66 (57.9)
Wound complication	67 (61.5)	61 (53.5)
Infections and infestations	37 (33.9)	36 (31.6)
Wound infection	8 (7.3)	10 (8.8)
Nasopharyngitis	3 (2.8)	7 (6.1)
Influenza	2 (1.8)	6 (5.3)
General disorders and administration site conditions	21 (19.3)	25 (21.9)
Pyrexia	9 (8.3)	15 (13.2)
Skin and subcutaneous tissue disorders	11 (10.1)	15 (13.2)
Pruritus	8 (7.3)	6 (5.3)
Gastrointestinal disorders	11 (10.1)	14 (12.3)
Respiratory, thoracic, and mediastinal disorders	9 (8.3)	11 (9.6)
Cough	3 (2.8)	8 (7.0)
Blood and lymphatic system disorders	8 (7.3)	6 (5.3)
Anaemia	8 (7.3)	4 (3.5)
Eye disorders	6 (5.5)	2 (1.8)
Nervous system disorders	1 (0.9)	6 (5.3)

Abbreviations: AE, adverse event, BBE, Birch Bark Extract; DBP, double-blind phase; SAS, safety analysis set.

Table 20: Summary of EASE OLP AEs with incidence of >5% of subjects overall (SAS) (modified from CS, Section B.2.10, Table 16)

	EASE OLP (24-month)[30]		
	Former BBE gel	**Former Control gel**	**All subjects**
	n=100	**n=105**	**N=205**
Any AEs	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]	[redacted]
Wound complication	[redacted]	[redacted]	[redacted]
Wound secretion	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]
Wound infection staphylococcal	[redacted]	[redacted]	[redacted]
Wound infection	[redacted]	[redacted]	[redacted]
Wound infection bacterial	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]
Oesophageal stenosis	[redacted]	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]
Skin and subcutaneous tissue disorders	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]
Eye disorder	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; BBE, Birch Bark Extract; N / n, number; OLP, open-label phase; SAS, safety analysis set.

4.5 Ongoing studies

The EAG did not identify any ongoing trials or studies of BBE gel in this population (the only current trial for BBE gel is being conducted for radiation dermatitis in breast cancer: NCT05190770). The CS states that the company plans to conduct a Category 3 (non-imposed) observational safety and effectiveness evaluation registry-based study in EB, and that no additional trials of BBE gel for use in DEB and JEB are currently planned (Section B.2.11).[1]

4.6 Evidence synthesis

The EAG agrees with the CS (section B.2.8)[1] that a meta-analysis is not appropriate given only a single relevant study was identified (EASE). The EAG agrees with the CS (Section B.2.9)[1] that an ITC is not necessary given the availability of a robust, relevant Phase III, head-to-head study (EASE) directly comparing the intervention with a reasonable comparator, and the absence of any trials of any other clearly relevant comparators.

4.7 Additional work on clinical effectiveness undertaken by the EAG

The EAG did not undertake any additional work relating to the clinical effectiveness of BBE gel.

4.8 Conclusions of the clinical effectiveness section

The pivotal study (EASE) was a Phase III, randomised, international, multi-centre, double-blinded, RCT initiated in March 2017 and conducted in 51 centres across 26 countries, including two centres in the UK (NCT03068780). EASE is a two-phase efficacy and safety trial with a 90-day DBP, followed by a 24-month, single arm, OLP. In the DBP, patients were randomised (stratified by subtype) to receive either BBE gel or control gel; in the OLP, all patients received the BBE gel. The primary completion date was June 2020, but the final completion date is listed as May 2022 (NCT03068780). Overall, 223 patients satisfied all eligibility criteria and were randomised: 109 received BBE gel and 114 received the control gel (in the DBP). Of these patients, 100 from the DBP BBE gel group and 105 from the DBP control gel group continued into the 24-month, single arm OLP. The BBE gel and control gel groups were generally well balanced at baseline in the DBP and between the patients in each arm that entered the OLP, with the exception of the potential prognostic factors of wound age and DEB subtype. The proportion of DEB patients with the DDEB and RDEB subtypes in the EASE study differed substantially from the estimated proportions of these subtypes in the UK EB population, based on the data provided in the CS (Section B.1.3.2, Table 4).[1] The EAG agreed with the CS risk of bias assessment that the DBP of the EASE study had some concerns, principally regarding deviation from the protocol, and that the OLP was at moderate risk of bias due to some baseline confounding, discontinuations ([redacted][30]), some compliance concerns, and the open-label nature of the study.

In the DBP, there was a statistically significant difference in favour of BBE gel compared with the control gel for the primary outcome, first target wound closure within 45 days (+/- 7). However, at day 90, while there were some trends in favour of the BBE gel compared with the control gel across some secondary outcomes such as wound closure at day 90, wound burden, target wound size, itching and pain, none of these differences were statistically significant; and the findings for other secondary outcomes, including sleep quality, missed days from school or work, and treatment satisfaction were reported to be similar for both the BBE and control gels.

The primary outcome was not assessed in the OLP. In this phase, the principal analyses focussed on wound burden as assessed by the EBDASI and BSAP. The trend for participants who received BBE gel during the DBP was for a continued improvement in wound burden by the EBDASI measure to month 3, but a slight worsening to month 12, and again to month 24. By contrast, the trend for those participants who received the control gel during the DBP was for a marked worsening in wound burden to month 3, followed by a substantial improvement by month 12, and a slight worsening again to month 24. A similar picture was presented for the BSAP: for the BBE gel group in the DBP, there was an improvement from OLP baseline to month 3, and again to month 12, but a slight worsening to month 24; while for the control gel group from the DBP, there was a marked worsening at month 3, but an improvement to month 12 and again to month 24. The CS did not provide any explanation for the variation in trends over time, or why the different patient groups from the DBP of the EASE study might have difference responses in the OLP.

In the OLP, there were no clear trends in incidence of severity levels of target or additional wound infections at 12 and 24 months. There were improvements reported in disease severity using the iscorEB at 12 and 24 months but worsening of quality of life as measured by the EQ-5D VAS at 12 and 24 months. At 3 months, there was either no improvement or a small worsening in the following outcomes: itching, procedural pain, background pain and sleep quality. There was a small improvement in treatment satisfaction. There was no reported significant difference between treatment arms for any of these outcomes.

The frequency of SAEs was not high and, other than wound complications and infections, which might reflect the natural history of EB, no specific type of AE was reported to occur in >10% of patients in any arm or phase of the EASE study.

The company did not conduct an NMA or ITC due to the absence of any other relevant trials of the intervention or relevant comparators.

5 COST EFFECTIVENESS

This chapter provides a summary and critique of the company's economic analysis of BBE, together with additional exploratory analyses undertaken by the EAG. Section 5.1 summarises and critiques the company's SLR of published economic analyses. Sections 5.2 and 5.3 present a detailed description and critique of the company's economic model of BBE. Section 5.4 presents the EAG's exploratory analyses, including a preferred base case. Sections 5.5 and 5.6 summarise the company's budget impact analysis and wider costs and benefits associated with the use of BBE. Section 5.7 presents overall conclusions and highlights key uncertainties.

5.1 EAG's comment on company's review of cost-effectiveness evidence

5.1.1 Objective of cost effectiveness review

Appendix G of the CS reports an SLR of economic evidence for the treatment of wounds associated with EB in adult and paediatric patients (notably, a slightly broader population than that used for the clinical effectiveness review). The search strategies are reported in full and once again appear to have been well designed and executed, using an appropriate range of sources with study type filters based on the work of reputable sources with minor modifications to increase sensitivity (clarification response A14[2]).

The EAG identified typographical errors throughout the search strategies in Appendix G1.1 – specifically in relation to the spelling of the word "syndrome" which is variously reproduced as "2yndrome", "3yndrome", "4yndrome", etc. The company gave their assurance that these errors were not present in the strategy at the time it was run, blaming a formatting error in the submission template, and providing an amended version in their clarification response (A16).[2] The numbers of results retrieved support the company's claim that terms were entered correctly at the time searches were run. Therefore, the EAG is broadly confident that the company is unlikely to have missed any relevant evidence eligible for inclusion.

5.1.2 Summary and critique of company's review of existing economic studies

The inclusion criteria for the SLR of economic studies are reported in Table 1 in Appendix G of the CS. Studies were eligible for inclusion in the review if the population related to people of any age with EB and if they were: economic evaluations; cost / resource use studies; or HRQoL studies.

The eligibility criteria for the review were not restricted by intervention or language, although case studies, animal model studies and literature reviews were excluded. For full papers there were no date restrictions; however, conference abstracts were limited to those published in 2019 or later.

The company's SLR initially identified 989 studies after duplicates were removed. After the data extraction process the company identified no economic evaluations, 4 studies reporting cost and resource use data, 4 studies reporting HRQoL data and 3 studies reporting both cost and resource use data and HRQoL data. (See Figure 1 in Appendix G of the CS for the company's PRISMA diagram). The 11 identified studies were considered by the company when populating its model and are discussed in later sections. Given the results of the company's SLR, the EAG agrees with the company that a *de novo* economic model was required.

5.2 Summary of the company's submitted economic evaluation

For ease of reading, the EAG will focus on the version of the company's model sent on the 20th of January 2023. This version of the model was submitted after the clarification process and contains amendments made to the coding of the model structure and the population of the model by the company. It is assumed that this version supersedes the previous version.

5.2.1 Population

The population considered in the CS is people with DEB or JEB.

5.2.2 Interventions and comparators

The intervention is BBE as detailed in Section 3.2; the comparator is CCM as detailed in Section 3.3.

5.2.3 Perspective, time horizon and discounting

The perspective for costs in the company's base case is that of the NHS and Personal Social Services, although the company presents a scenario analysis in which a wider societal perspective is taken with the inclusion of productivity loss and early retirement. For HRQoL, the perspective is of patients and carers, as detailed in Section 5.2.5.3. The company's base case analysis uses a time horizon of 99.63 years, although the model has the functionality to examine the impact of using shorter time periods. Cycle lengths were 30 days and half-cycle correction was employed. Both costs and benefits are discounted at 3.5% per annum.

5.2.4 Model structure

The company's economic model uses a cohort-level, state transition approach, which consists of seven mutually exclusive and exhaustive health states, six related to the severity of EB and one representing death. These severity health states are based on BSAP and are shown in Figure 10 which is reproduced from Figure 14 in the CS.

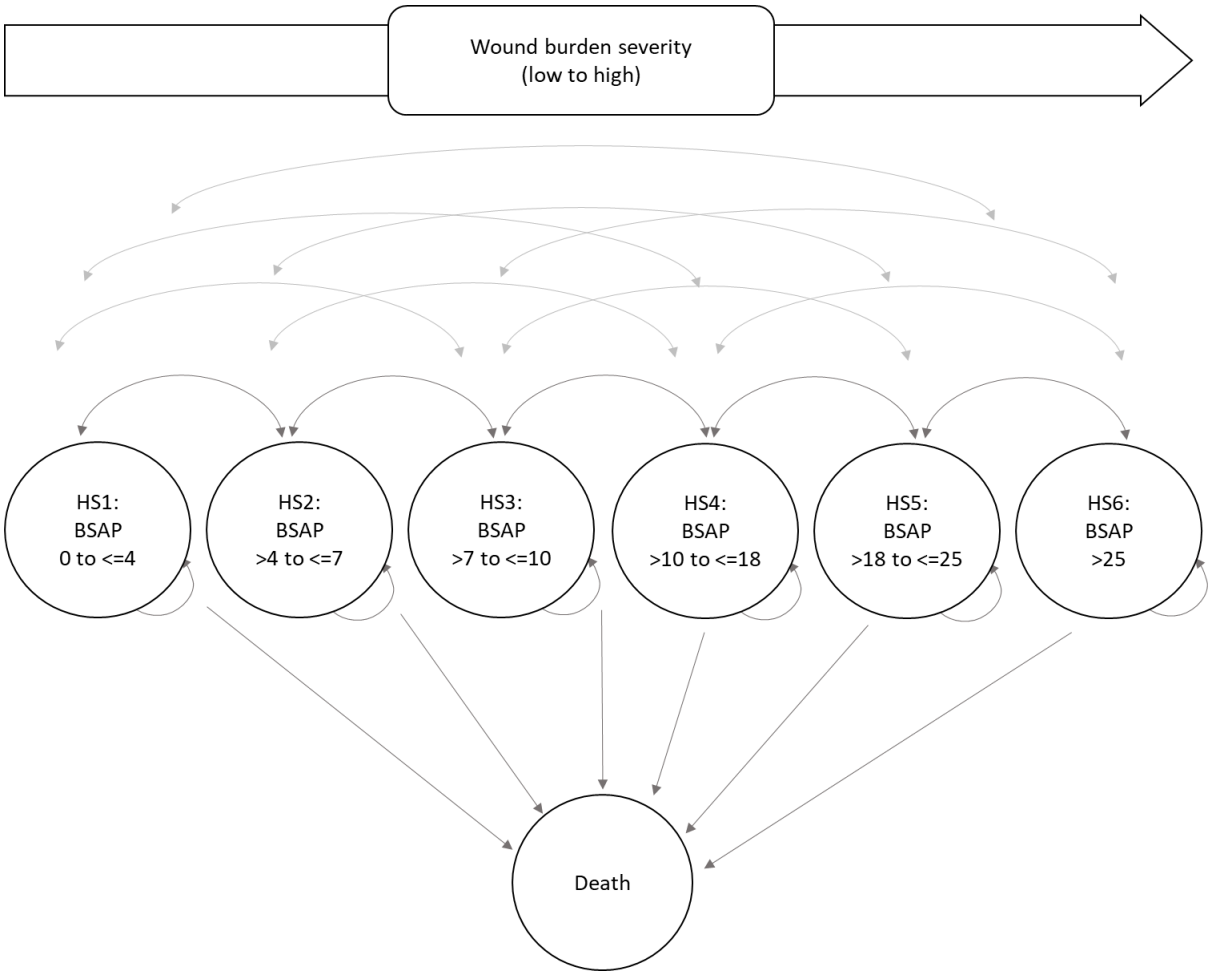


Figure 10: The company's model structure (reproduced from Figure 14 of the CS)

5.2.5 Evidence used to inform the company's model parameters

5.2.5.1 Initial patient characteristics at model entry

All patients are assumed to enter the model at 6 months old, although the company has run a sensitivity analysis assuming that the average age was that of patients in the EASE study[29] (16.67 years). The company states that this change only has a very small impact on the ICER.

The ranges of BSAP for the health states in the company's base case were selected so that the population was equally distributed between the health states. In response to clarification question B14,[2] the company stated that "*No existing categories exist to define EB disease severity by BSAP cut-offs, therefore, to allow for the largest patient numbers for each health state in terms of generating robust transitions and health state utility estimates, health states were defined using equal distributions at EASE baseline. Interviews were then held with a clinical expert (Professor Jemima Mellerio) to validate these health state categories. She had no disagreements with the health states proposed and agreed that*

these were a good fit for capturing different levels of EB severity for patients seen in clinical practice. These health states were also discussed and supported as appropriate by the clinicians participating at the multi-stakeholder panel meeting." The company also states that this could also resolve a potential under-representation on severe patients in the EASE study. The model has the functionality to use the proportions of patients, pooled across each arm, observed in each health within the EASE study rather than assume an equal distribution. These proportions were 21% in health state 1, 28% in health state 2, 14% in health state 3, 16% in health state 4, 9% in health state 5 and 13% in health state 6.

The distribution of patients between EB subtypes was taken from Petrof *et al*.[16] which estimates that 49.10% of the population would have DDEB, 26.65% would have JEB 21.83% would have RDEB and 2.43 would have RDEB-S. The company assumes that sub-type of EB did not affect transition probabilities.

5.2.5.2 Structured expert elicitation

Due to the paucity of clinical evidence in DEB and JEB, the company conducted a structured expert elicitation (SEE) using the IDEA protocol framework to elicit clinical expert opinion on: (i) disease progression, (ii) mortality and overall survival, (iii) EB complications, (iv) healthcare resource use, and (v) HRQoL. Four UK-based clinical experts with expertise in EB were recruited (one with expertise in both adult and children's care, two with expertise in children's care and one with expertise in adult care).

The company justified the use of the IDEA protocol framework based on that it is a recognised time-efficient elicitation approach which was reviewed by Bojke *et al*.[39] The company's SEE was a three-stage process which comprised two rounds of one-to-one interviews with clinical experts (Stage 1 involved experts providing their own estimates to a questionnaire and Stage 2 involved sharing anonymised Stage 1 results from all experts and providing experts an opportunity to revise their Stage 1 estimates), and a moderated group discussion to reach consensus (Stage 3).

Both disease progression and mortality estimates were discussed at Stage 3. Neither EB complications nor healthcare resource use were discussed in Stage 3, given that the estimates were generally aligned across the clinical experts at Stage 2 and were also explored in the cross-sectional study.[11, 40] HRQoL was not explored in detail in the SEE exercise due to insufficient time, but it was discussed at a multi-stakeholder panel meeting with two patient advisory group representatives, two clinical experts and two independent health economists.[41]

The SEE estimates were used to inform the model parameters on disease progress and resource use (See Section 5.2.5.3 and 5.2.5.6, respectively) in the base case and mortality in a scenario analysis (See Section 5.2.6).

5.2.5.3 Treatment effectiveness and extrapolation in the base case

Treatment effectiveness across time for both BBE and CCM have been modelled using transition probabilities. For patients who are alive, the company assumed that the change in BSAP was normally distributed using the mean value and variance observed in the EASE study over a period of 12 months - the company highlights that this methodology was used in a NICE clinical guideline for age-related macular degeneration.[42] The company also assumed that patients started in the midpoint of each health state, thus, for example, all patients in health state 3, which has a range of BSAP of >7 and ≤ 10 would have a BSAP of 8.5. In response to clarification question B22,[2] the company provided median BSAP data by health state from EASE, which were relatively similar to the assumed midpoint values.

The company's methodology resulted in transition probabilities, assuming no discontinuations or deaths, for BBE as reported in Table 21 and transition probabilities for CCM as reported in Table 22, which are adapted from Table 19 and Table 20 of the CS respectively. The company states that it is the "*opinion of clinical experts in the multi-stakeholder panel discussions that there is no clinical expectation for a difference in clinical efficacy between subgroups, and therefore whole population treatment effects can be appropriately generalised across EB types in the absence of sufficiently granular data.*"

This approach implicitly assumes that patients who improved in BSAP, but not by enough to move health state would return to the midpoint value for the next health cycle which could impact on the validity of the modelled transitions. The company's approach also explicitly assumes that the change in BSAP is normally distributed, which may be incorrect given the dynamic nature of the disease and the plausibility of large changes in BSAP. As such, the approximation method could reduce the influence of outliers in change in BSAP.

After 90 days, the company's base case assumed that the cohort of patients receiving CCM would have reached a steady state and that the distribution of patients across health states would remain unchanged. However, for the BBE arm patients continued to transition between health states using the described method for approximating transitions until 12 months before assuming steady state, where the company also assumed that patients would not discontinue treatment.

In the CS, the company stated that "*in the model, a 1.3% increase per year is applied for RDEB-S patients up until age 40, where BSAP flattens*". However, in response to clarification question B32, the company responded that "*No worsening of BSAP over time is assumed in the RDEB-S group in the base case. A scenario exploring an increase of 1.3% per annum for RDEB-S patients is applied, where there is minimal impact on incremental cost-effectiveness results.*" The EAG notes that this will be primarily due to the small proportion of patients assumed to have RDEB-S, which comprises 2.4% of the overall target population in the company's base case. The EAG has maintained the company's base case assumption of no underlying annual increase in BSAP for any EB subtype.

Table 21: Transition probabilities associated with BBE using the company's approximation method

Day 0-30						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1	1.000	0.000	0.000	0.000	0.000	0.000
HS2	0.109	0.891	0.000	0.000	0.000	0.000
HS3	0.000	0.382	0.618	0.000	0.000	0.000
HS4	0.000	0.000	0.368	0.632	0.000	0.000
HS5	0.000	0.000	0.000	1.000	0.000	0.000
HS6	0.000	0.000	0.000	0.000	1.000	0.000
Day 30-60						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1	0.934	0.066	0.000	0.000	0.000	0.000
HS2	0.000	0.993	0.007	0.000	0.000	0.000
HS3	0.000	0.002	0.998	0.000	0.000	0.000
HS4	0.000	0.000	0.003	0.997	0.000	0.000
HS5	0.000	0.000	0.000	0.822	0.178	0.000
HS6	0.000	0.000	0.000	0.000	0.976	0.024
Day 60-90						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1	0.981	0.019	0.000	0.000	0.000	0.000
HS2	0.002	0.997	0.001	0.000	0.000	0.000
HS3	0.000	0.022	0.978	0.000	0.000	0.000
HS4	0.000	0.000	0.024	0.976	0.000	0.000
HS5	0.000	0.000	0.000	0.927	0.073	0.000
HS6	0.000	0.000	0.000	0.000	0.992	0.008
Day 90 onwards						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1	0.966	0.034	0.000	0.000	0.000	0.000
HS2	0.014	0.980	0.006	0.000	0.000	0.000
HS3	0.000	0.069	0.931	0.000	0.000	0.000
HS4	0.000	0.000	0.073	0.927	0.000	0.000
HS5	0.000	0.000	0.000	0.901	0.099	0.000
HS6	0.000	0.000	0.000	0.000	0.982	0.018

Abbreviations: HS, health state.

Table 22: Transition probabilities associated with CCM using the company's approximation method

Day 0-30						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1	1.000	0.000	0.000	0.000	0.000	0.000
HS2	0.022	0.978	0.000	0.000	0.000	0.000
HS3	0.000	0.358	0.642	0.000	0.000	0.000
HS4	0.000	0.000	0.284	0.716	0.000	0.000
HS5	0.000	0.000	0.000	0.999	0.001	0.000
HS6	0.000	0.000	0.000	0.000	1.000	0.000
Day 30-60						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1	0.154	0.846	0.000	0.000	0.000	0.000
HS2	0.000	0.155	0.845	0.000	0.000	0.000
HS3	0.000	0.000	0.998	0.002	0.000	0.000
HS4	0.000	0.000	0.000	1.000	0.000	0.000
HS5	0.000	0.000	0.000	0.029	0.971	0.000
HS6	0.000	0.000	0.000	0.000	0.309	0.691
Day 60-90						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1	0.977	0.023	0.000	0.000	0.000	0.000
HS2	0.000	0.980	0.020	0.000	0.000	0.000
HS3	0.000	0.006	0.994	0.000	0.000	0.000
HS4	0.000	0.000	0.005	0.995	0.000	0.000
HS5	0.000	0.000	0.000	0.821	0.179	0.000
HS6	0.000	0.000	0.000	0.000	0.968	0.032
Day 90 onwards						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1	1.000	0.000	0.000	0.000	0.000	0.000
HS2	0.000	1.000	0.000	0.000	0.000	0.000
HS3	0.000	0.000	1.000	0.000	0.000	0.000
HS4	0.000	0.000	0.000	1.000	0.000	0.000
HS5	0.000	0.000	0.000	0.000	1.000	0.000
HS6	0.000	0.000	0.000	0.000	0.000	1.000

Abbreviations: CCM, current clinical management; HS, health state

5.2.5.4 Discontinuation of treatment

The company assumed that 8.3% discontinue BBE at 90 days in accordance with EASE data and then that 1% would discontinue per annum based on clinical opinion. During the clarification process the company added the functionality to explore the impacts of assuming differential discontinuation rates by health state. When patients discontinue treatment they are assumed to use the transition probabilities associated with CCM, which, if the patient discontinued after 90 days, would mean that the patient stayed within the same health state, as the patients in CCM were assumed to have reached steady state. During the clarification process, the company added in the functionality to explore the impact of patients discontinuing after 90 days being distributed according to the steady state distribution of patients in the CCM arm.

5.2.5.5 Health-related quality of life

The company considered several sources for HRQoL which includes data from the OLP of the EASE study, a time trade-off study (TTO) undertaken in a general UK population, a cross sectional study and data reported in the literature.

5.2.5.5.1 Health-related quality of life associated with model health states

5.2.5.5.1.1 Patients

Each health state in the model has an associated HRQoL which decreased as the severity of the condition worsened. Utility values were assigned to both patients and carers. Following a protocol amendment in the OLP, the EQ-5D-5L was introduced with the youth version (EQ-5D-Y) used for children below 15 years of age although children under the age of 4 years had responses provided by the patient's caregiver. Adult data were mapped to EQ-5D-3L values using Hernandez *et al* mapping using the '*EEPRU dataset*'.[43, 44]

The company estimated utility by using an ordinary least squares (OLS) regression approach using 12-month data from the EASE study. The fit of the OLS model to the data is shown in Figure 11, which reproduces Figure 2 in Appendix P of the CS.

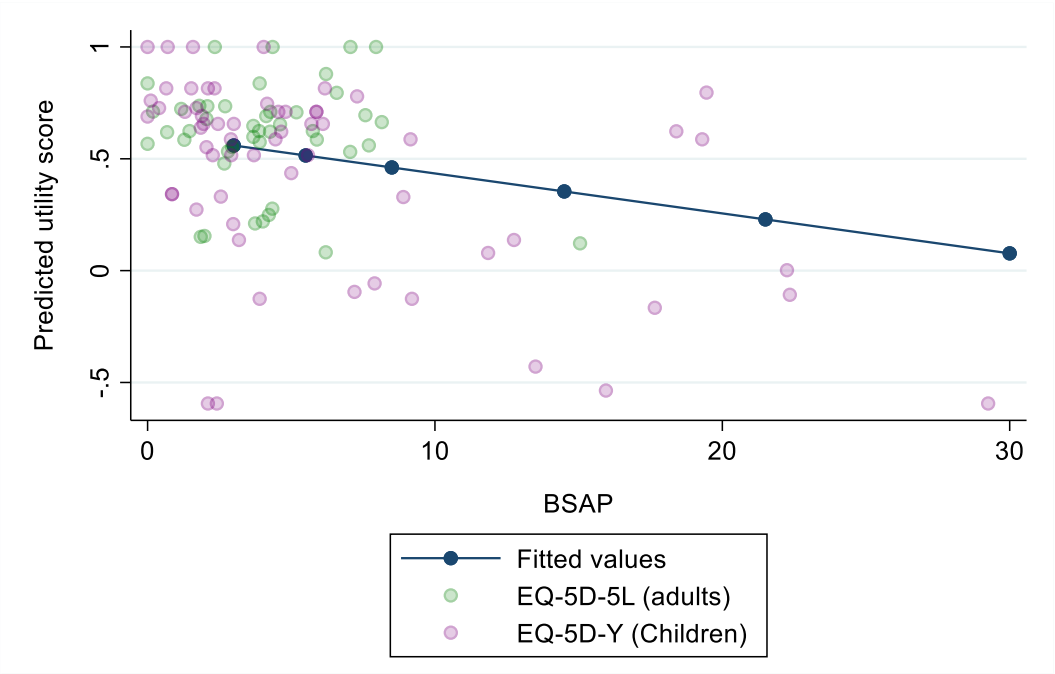


Figure 11: EASE observed EQ-5D utility scores with OLS predictions for health state midpoints (reproduced from the company's second clarification response)

During the clarification process the company explored changing the statistical fit from to explore non-linear approaches using a log-link function within a generalised linear model (GLM) which was associated with slightly improved goodness of fit, measured by the Akaike Information Criterion, the Bayesian Information Criterion, and R-squared value (see company response to clarification question B4[45]).

The EAG considers it unlikely that the utility function would be linear across the full BSAP range (in that the change in utility when moving between a BSAP of 5% to 10% is unlikely to be the same as in moving from 25% to 30%) and is content with using the GLM provided by the company. Figure 1 from the company's second clarification response[45] is replicated in Figure 12. The values assumed by the company in its base case are shown in Table 23 alongside the values produced by the GLM.

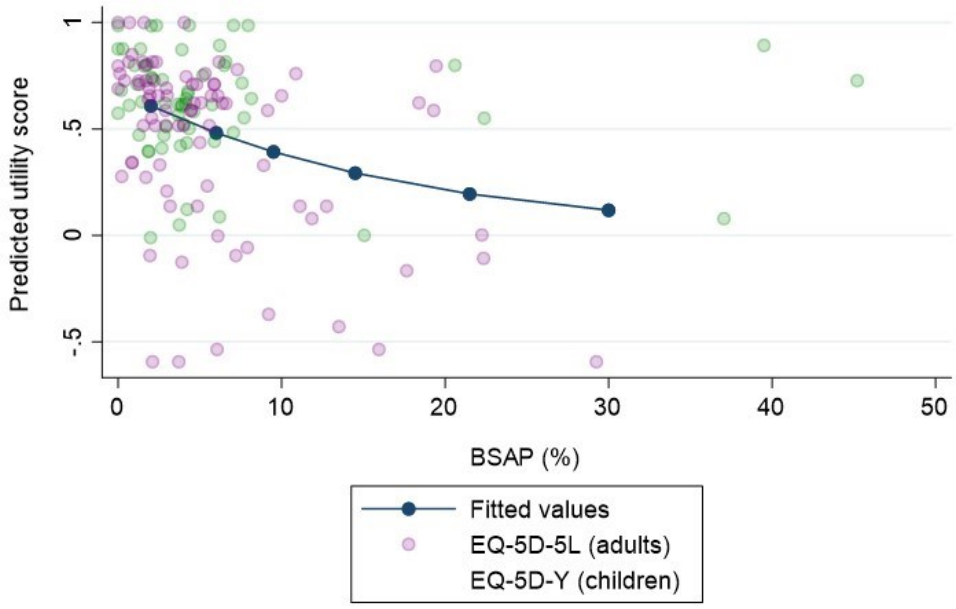


Figure 12: EASE observed EQ-5D utility scores with GLM predictions for health state midpoints (reproduced from the company's second clarification response)

Table 23: Estimated patient utility by model health state in the company's base case

	EASE 12-month data: Using an OLS Mean (95% CI) Company Base Case	**EASE 24-month data: (using a GLM) Mean (95% CI)**
HS1 (BSAP 0 to ≤4%)	0.560 (0.488 – 0.631)	0.609 (0.537 – 0.680)
HS 2 (BSAP 5-7%)	0.515 (0.448 – 0.581)	0.482 (0.410 – 0.553)
HS3 (BSAP 8-10%)	0.461 (0.389 – 0.533)	0.392 (0.288 – 0.496)
HS4 (BSAP 11-18%)	0.345 (0.234 – 0.456)	0.293 (0.160 – 0.425)
HS5 (BSAP 19-24%)	0.229 (0.056 – 0.402)	0.194 (0.054 – 0.335)
HS6 (BSAP ≥25%)	0.077 (-0.177 – 0.332)	0.118 (-0.007 – 0.243)

An online cross-sectional study (CSS) that was commissioned by the company elicited patient and carer HRQoL "*to analyse the consequences of EB that have the greatest impact on both patients and carer HRQoL; and, to better understand the impact of EB and EB management for patients and carers*". Further details are presented in the CS and in Morgan et al.[11] The mean EQ-5D value from the CSS was

0.57, with regressed values by health state shown in Table 23. The range in HRQoL values was from 0.69 in health state 1 to 0.44 in health state 6.

The company sponsored a TTO study based on vignettes to represent the six health states, which could provide more information on the impact on the lives of carers (see Section 5.2.5.3.1.1) and also for patients. The vignettes are provided in Table 25 and Table 26 of the CS for patients and carers respectively with the company stating that these were *"rigorously reviewed by experts including EB clinical experts and representatives of EB patient advocacy groups."* After a pilot conducted on 10 people, 120 people believed to be a representative cross-sectional sample of the UK population were recruited. The utility values estimated ranged from 0.82 in health state 1 to 0.53 in health state 5 – the value for health state 6 was 0.54.

The company also identified a paper by Angelis *et al*.[10] which estimated that HRQoL values amongst patients with DEB in the UK was 0.304. A previous analysis by Angelis *et al*.[9] indicated that from a cohort of patients with a mixture of EB (34.9% DEB, 62.8% EB simplex, which is not within the decision problem, and 2.3% JEB) the EQ-5D-3L value was 0.579 across 111 patients (across eight European countries) who completed the EQ-5D. Both Angelis papers used a TTO tariff approach.

The company has selected the 12-month data recorded in the EASE study modelled using OLS in its base case and conducted scenario analyses using the 24-month EASE data modelled using a GLM, and using CSS, and TTO, data.

5.2.5.5.1.2 Carers

Unfortunately, data were not collected on carer utility in EASE. The CSS commissioned by the company recorded EQ-5D-5L from 11 carers, which produced a mean value of 0.88, with recorded values greater than 0.93 for all health states apart from health state 6 which had an estimate of 0.69. Because the company believed these values were not robust due to the small sample size the company sponsored the TTO study summarised in Section 5.2.5.3.1.1. For both the TTO and the CSS the company pooled the data into three groups, which were Health States 1 and 2 combined, Health States 3 and 4 combined, and Health States 5 and 6 combined. These data are presented in

Table 24. The company uses the TTO data in its base case and the data from the CSS in a scenario analysis. The company assumed that there would be 1.78 carers per patient in the most severe health states in line with a published estimate,[46] with a lower value 0.50 assumed for health states 1 and 2 based on the advice of a multi-stakeholder panel.[41]. A scenario analysis was run assuming one carer per patient which is more aligned with the text within the vignettes which state that "*you are the main caregiver*".

Table 24: Estimated carer utility by model health state in the company's base case

	TTO (n=115*) Mean (SD)	CSS (n=11) Regressed Mean (SD)	Assumed number of caregivers per patient in each health state
HS1 and 2 (BSAP 0 to 7%)	0.85 (0.21)	0.94 (0.19)	0.50
HS 3 and 4 (BSAP 8-18%)	0.76 (0.23)	0.96 (0.19)	1.00
HS5 and 6 (BSAP ≥19%)	0.64 (0.27)	0.84 (0.17)	1.78

* After discarding results for 5 respondents who would not trade
CSS: - Cross-sectional study; TTO: - Time Trade Off

Like many models, the company's model does not consider either the implication of a carer dying with the implicit assumption that the care will be continued or that the carer's utility will decrease as the carer ages. However, as the company does not assume differential mortality between those receiving BBE and those on CCM, this simplification is unlikely to have a noticeable effect on the ICER.

5.2.5.5.1.3 Capping of utilities in the company's probabilistic sensitivity analyses

In the company's probabilistic sensitivity analyses (PSA), the company capped HRQoL so that the value for patients in a more severe state could not be higher than the value for patients in a less severe state, and similarly the values for carers of patients in a more severe state could not be higher than that of carers of patients in a less severe state. Capping changes the underlying distribution and methods are available to try and remove this bias.[47] As the company stated in its response to clarification question B21,[2] the capping had an effect in 53% of PSA iterations for patients and in more than 85% of PSA iterations for carers, and this will introduce some uncertainty in the PSA results. Analyses run by the EAG indicated that the capping method employed by the company resulted in probabilistic ICERs favourable to BBE (see Sections 5.3.4.13 and 6.2).

5.2.5.5.2 Health related quality of life associated with adverse events

The company did not include any disutility associated with AEs stating that "*It is believed that EQ-5D assessments will reflect the disease complications (treatment-emergent) experienced by patients with DEB and JEB*" and that AEs associated with BBE "*were mostly of low severity and associated with disease complications (treatment-emergent) rather than being directly associated with*" BBE or CCM.

5.2.5.6 Costs and resource use

5.2.5.6.1 BBE acquisition costs

The list price for a 23.4g tube of Filsuvez gel is £275.33; however, there is a PAS in place (which is a simple discount of [redacted]) which reduces the price to [redacted]. The mean number of tubes used per month across the DBP and 24-month OLP was [redacted].[30] This value was assumed to apply to all health states prior to treatment discontinuation. The cost for a year of BBE treatment is [redacted] at list price and [redacted] when the PAS is applied.

The costs of drugs associated with CCM have not been included in the model apart from in a scenario analysis where data from Angelis *et al*. are used; the EAG notes that these costs (for emollients and painkillers are relatively small (£59.02) per year).

5.2.5.6.2 Medical resource use and costs associated with each health state borne by the NHS

The company estimated health state specific costs borne by the NHS using a bottom-up costing approach and using data obtained from the SEE. The largest component of costs were associated with the cost of wound dressing which was reported by Pillay *et al*.[48] to be £45,884 per patient with RDEB (n=53). which the company inflated to be £47,719 in 2021 prices.[49] This value was assumed to be generalisable to patients with all forms of DEB and JEB. There was variation seen in the data presented by Pillay *et al*.[48] with four patients requiring no bandages and the company assumed that the number of dressings required would increase as the severity of EB increased. To incorporate this in the model the company used results from the SEE to estimate a ratio of dressings per visit compared with health state 1 and having assumed that patients were equally distributed across health states scaled the dressing costs such that the weighted average equalled £47,719 which is the inflated average from Pillay *et al*.[48] The resultant estimated annual dressing costs ranged from £10,122 in health state 1 to £102,669 in health state 6. Whilst there may be inconsistency between the steady state distribution for patients receiving CCM in the model and the assumption of an equal distribution across health states used to derive the costing clinical advice to the EAG suggested that the cost values used in the model were reasonable.

The costs associated with dressing changes from formal care (professional staff) was estimated using data from the SEE and assuming that the costs associated with both were £51.00 per hour from Jones *et al*.[49] assuming that the appropriate carer was a band 6 hospital-based nurse.

Details are provided in Table 34 of the CS, and it is shown that the absolute hours required and the ratio between informal and formal care differs markedly between the health states. At health state 1, an

estimated 9.66 hours of informal care and 0.21 hours of formal care per month is required; corresponding values were 42.84 hours and 30.24 hours in health state 6. The company's base case assumes the cost of formal care only and the estimated annual costs associated with the time for dressing changes range from £129 in health state 1 to £18,507 in health state 6. If informal care (from self or family) is included and also assumed to cost £51.00 per hour, which is a scenario analysis, the costs range from £6040 in health state 1 to £44,725 in health state 6.

Data from the SEE indicated that there would be an increased level of outpatient hospital visits as the severity of EB worsened ranging from 0.28 per month in health state 1 to 0.83 in health state 6. Assuming a cost of £137 per outpatient visit,[49] this resulted in an estimated annual cost associated with outpatient appointments ranging from £460 in health state 1 to £1365 in health state 6.

No other costs are considered in the modelling; therefore, these costs are identical for both BBE and CCM. The company states that this "*is expected to be a conservative assumption in the absence of data to the contrary*".

A summary of the costs by health state is presented in
Table 25. The component costs have been rounded to the nearest pound. The total costs are those reported in the CS and used in the model. The costs per health state are assumed to apply to both BBE and CCM, with the additional costs of BBE incurred where appropriate.

Table 25: Summary of health state annual costs

Health state	Dressing costs (£)	Dressing changing costs associated with nurses (£)	Outpatient costs (£)	Total costs (£)
1	10,122	129	460	10,711.10
2	17,352	165	526	18,034.76
3	31,813	2938	658	35,408.00
4	50,611	3525	822	54,958.40
5	73,748	11,897	1118	86,763.06
6	102,669	18.507	1364	122,539.99

5.2.4.6.3 Treatment administration costs

The company stated that "*as Filsuvez gel is a topical treatment, there are no additional healthcare professional costs assumed to be associated with administration or monitoring*." Clinical advice to the EAG suggested that this assumption was reasonable.

5.2.4.6.4 AE costs

The company did not incorporate costs associated with AEs in its model stating that "*there were minimal between-arm differences in safety and tolerability data collected in the 90-day DBP, and this was supported by the 24-month data collected in the OLP when all participants were treated with Filsuvez gel.*"

5.2.6 Mortality

Section B4.4.3 of the CS details the assumptions relating to mortality made in the modelling. The company states that "*Mortality data is reported for RDEB-S, DDEB, RDEB-O, and JEB-S in Petrof et al.[16] alongside general population mortality curves, calculated using UK life tables.[50] DDEB, RDEB-O, and JEB (non-severe) patients broadly follow UK general population survival rates; therefore, no excess mortality is applied to these patients in the model. Expert opinion elicited in the SEE exercise suggested that non-severe JEB patients experience mortality risks slightly worse than the general population.[51]*" The EAG notes that general population mortality was used for DDEB, RDEB-O and non-severe JEB, despite the elicited increased risk in non-severe JEB, but deems that it would have a minimal impact on the ICER. For RDEB-S the company assumed that virtually all patients would have died by 55 years of age and employed an exponential distribution with a risk of mortality of 0.0028 every 30 days. In response to clarification question B25,[2] the company explored the use of a standardised mortality ratio compared with the general population and a Weibull distribution; as the company stated that "*the sensitivity of cost-effectiveness results to the choice of distribution is very low*" the EAG is content with using the exponential distribution as in the company's base case.

5.2.7 Model validation and face validity check

The company stated that the model structure and approach was validated with six experts at a multi-stakeholder meeting and that the parameterisation of the model had been validated through the SEE and the multi-stakeholder meeting. The EAG identified a small number of minor implementation errors which were amended by the company during the clarification process.

5.2.8 Cost effectiveness results

The company's base case ICER is presented in Table 26. The ICER is estimated to be £86,052, with 53% of the incremental QALY gain being accrued by patients and 47% being accrued by carers. There is no increase in life expectancy modelled due to the use of BBE.

Table 26: The company's deterministic base case results

Treatment	Total costs (£)	Total QALYs (patient; carers)	Incremental Costs (£)	Incremental QALYs	Cost per QALY gained (£)
CCM	1,123,868	53.93 (11.31;42.63)			
BBE	1,344,174	56.49 (12.66; 43.84)	220,306	2.56	86,052

QALYs – Quality-adjusted life years

Section B.4.13 of the CS details the benefits listed by the company that it believes are not captured in the QALY calculation. These include but are not limited to: productivity losses through early retirement of lost workdays; privately purchased formal care; and additional benefits outside of those associated with wound burden or disease severity, such as differential mortality or complications such as SCC.

5.2.9 Sensitivity analyses

The company presented considerable sensitivity analyses in Section B.4.11 of the CS; however, these analyses were not updated during the clarification process. These analyses have not been repeated by the EAG but where pertinent have been commented upon in Section 5.3 and 5.4.

5.3 Critique of company's submitted economic evaluation by the EAG

5.3.1 Methods for reviewing the company's economic evaluation and health economic model

The EAG checked the implementation of the model cell-by-cell and identified a few minor errors which were corrected by the company during the clarification process. Data used in the model were checked against the source publications where possible and clinical advice was sought where there was debate about the best source to use.

5.3.2 Adherence of the company's model to the NICE Reference Case

The CS has adhered to NICE's Reference Case (see Table 5).

5.3.3 EAG Critique of the modelling performed by the company

The implementation of the modelling performed by the company was generally to a high standard. However, there were key differences between the company's base case and the EAG's preferred analyses related to the population of the model. The main issues identified are detailed in Section 5.3.4.

5.3.4 The main issues identified by the critical appraisal

The main issues are summarised in Box 1 with a more detailed description of the items provided in Sections 5.3.4.1 to 5.3.4.13. The impacts of changes made by the EAG to the ICER are shown in Sections 5.4 and Section 6.

Box 1: Summary of the main issues identified within the company's health economic model

1) Transition probabilities taken from EASE with continuity corrections are preferred to approximations using the mean and variance observed in EASE
2) On discontinuation of BBE, patients are distributed in accordance with the CCM steady state distribution
3) Using one carer for all health states is more aligned with the utility vignettes
4) Using a GLM to estimate utility rather than an OLS model
5) The number of outpatient appointments include patients with JEB-S
6) The average age of people treated with BBE
7) The rate of discontinuation with BBE
8) The distribution between EB subtypes
9) The distribution between health states
10) The appropriateness of continuity corrections
11) The efficacy of BBE in DDEB and JEB
12) The conduct of the structured expert elicitation exercise
13) The capping of utility to preserve face validity

5.3.4.1 The most appropriate transition probabilities to use in the model

The company has used an approach to approximate the movement of patients between health states using the mean change and variance values using data from 12 months of the EASE study. The EAG prefers that the count data from EASE are used as these require no assumptions related to normality of the data or BSAP values within health states, that could distort the transition probabilities.

It is seen that the transition probabilities when using EASE directly (Table 27) appear less favourable to BBE than those using the company's preferred method (Table 21). For example, those patients starting the model in health state 1 remain in health state 1 within the first cycle using the company's approximation approach. However, within EASE, [redacted]% of patients were observed to remain in health state 1, [redacted]% of patients were observed to move to health state 2, and [redacted]% were observed to move to health state 4.

Contrastingly, the transition probabilities when using EASE directly (Table 28) appear more favourable to CCM than those using the company's preferred method (Table 22). For example, for patients starting the model in health state 2 using the company's approximation approach within the first cycle 15.5% remain in health state 2, and 84.5% move to health state 3. However, within EASE, 33% of patients were observed to move to health state 1, [redacted]% remained in health state 2, [redacted]% moved to health state 3, and [redacted]% were observed to move to health state 4.

The company has explored the use of continuity corrections to adjust for low count numbers via two approaches, the first allowing movements only to adjacent health states and the second allowing movement to any health state from any health state. Both approaches are plausible, whilst it is likely that people may only move one health state in a 30-day period, more than 2 health state movements were observed in some patients in EASE. For example, for CCM, patients in health state 1 were observed to be in health state 5 in the next cycle, and patients in health state 6 were observed to move to health state 3, whilst for BBE, patients in health state 1 were observed to be in health state 4 in the next cycle, and patients in health state 6 were observed to move to health state 1.

Table 27: Transition probabilities associated with BBE taken directly from the EASE DBP

Day 0-30						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS2 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS3 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS4 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS5 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS6 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 30-60						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS2 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS3 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS4 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS5 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS6 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 60-90						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS2 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS3 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS4 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS5 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS6 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HS, health state.

Table 28: Transition probabilities associated with CCM taken directly from the EASE DBP

Day 0-30						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS2 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS3 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS4 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS5 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS6 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 30-60						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS2 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS3 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS4 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS5 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS6 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 60-90						
	HS1	**HS2**	**HS3**	**HS4**	**HS5**	**HS6**
HS1 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS2 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS3 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS4 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS5 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS6 (n=[redacted])	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CCM, current clinical management; HS, health state

5.3.4.2 The health state to which patients are assigned following discontinuation of BBE

In the company's base case model, patients who discontinue treatment after 90 days were modelled using the CCM transition probabilities rather than those associated with BBE. However, this had the limitation that after 90 days patients discontinuing BBE were assumed to remain in the same health state until death as the cohort of patients in the CCM arm were assumed to be in steady state. Therefore, patients who discontinued BBE, may have a better health state for the rest of their lives compared to those who had never received BBE. The EAG believes that this is implausible and prefers to distribute patients who discontinue treatment in accordance with the CCM steady state distribution which the

company added the functionality for in the clarification process. Using this approach, patients who discontinue treatment will be assumed to have the same outcomes, from that point on, as people who had received CCM treatment. The EAGs notes that the functionality for redistributing patients according to the steady state of CCM did not work exactly as intended and was slightly favourable to BBE, although as the EAG believes that the impact of this will be small it is comfortable using the company's functionality in exploratory analyses.

5.3.4.3 The most appropriate number of carers

The company has estimated the utility for carer from a vignette study. This vignette explicitly states that '*you are the main caregiver*'. As such, the EAG believes that assuming 1.78 carers in the more severe health states (5 and 6) is not appropriate, as the respondents' answers would likely be changed had they been aware of the additional 0.78 carers. Equally, assuming 0.5 carers in the less severe health states (1 and 2) is not appropriate and the respondents' answers would likely be changed had they been aware that they only needed to be a carer for half the time. As such, in the absence of other data, the EAG has set the number of carers to 1 for each state, acknowledging that this may underestimate the total burden in more severe health states should additional non-'*main carers*' be needed. The EAG notes that the vignettes contain some changes between health states that may be unlikely to be influenced by the use of BBE, which include difficulty in bowel movements, throat stretches, osteoporosis, fused digits, and the ability to eat and drink normally. In its response to clarification question B10,[2] the company states that "*There is no data, or evidence collected in EASE to show an association between wound burden and the specific extra-cutaneous aspects of DEB and JEB, of difficulty in bowel movements, throat stretches, osteoporosis, fused digits, whether people can eat or drink normally (although based on the expert feedback we have received input that a reduction in outpatient visits may be expected with decreased wound burden).*" The company states, however, that "*in the development of the vignettes in the TTO study, clinical experts were fully consulted to validate the states and so the aspects included reflect the opinions of clinical experts as to the expected impact that reducing BSAP and hence reducing wound burden (as a proxy for disease severity), would have. Whilst there is always a risk of some bias dependent on what is included or not included in vignettes (i.e., to make the vignettes sufficiently descriptive but manageable for a member of public to comprehend for the purposes of the TTO exercise), we do not feel this has overly confounded the relative utility values*." The EAG is less confident that the inclusion of extracutaneous aspects of DEB and JEB in the vignettes may not have biased the results, although the magnitude of any bias is unknown. For example, patients in health states 3 and 4 are stated in the vignette to have moderate difficulty with eating and drinking normally whilst patients in health states 1 and 2 are not stated to have any difficulty with eating or drinking. It is expected that having to aid a person with eating and drinking would impact on a carer's utility, and this would

differ between BBE and CCM if the use of BBE moved a patient from health state 3 to health state 2, even though there is no evidence that BBE improves the ability to eat or drink.

The EAG has identified two potential biases in the utility associated with carer utility that work in different directions. The incorporation of extracutaneous factors in the vignettes is favourable to BBE, and the EAG's preference for only one carer in all health states is likely to be unfavourable to BBE. The relative magnitude of these two biases is unknown, and for simplicity in the absence of data, the EAG has assumed these biases cancel out.

5.3.4.4 The use of a GLM rather than an OLS model to estimate patient utility

As described in Section 5.2.5.5.1, the EAG prefers the use of a GLM to the OLS model. The utility values assumed under both assumptions are shown in Table 23.

5.3.4.5 The appropriate number of outpatient appointments per year

In response to additional clarification question 11,[3] the company explains how monthly outpatient visits were calculated. The mean number included JEB-S patients who were excluded from the company model. The reduced the number of estimated outpatient appointments as shown in Table 29 and these values are preferred by the EAG.

Table 29: The impact of removing JEB-S patients when calculating outpatient costs

Health state	Number of outpatient appointments per year including JEB-S patients	Number of outpatient appointments per year excluding JEB-S patients	Change in annual costs of outpatient appointments (£)
1	3.36	2.76	-82.20
2	3.84	3.24	-82.20
3	4.80	4.20	-82.20
4	6.00	5.52	-65.76
5	8.16	7.56	-82.20
6	9.96	9.48	-65.76

5.3.4.6 The age of people treated with BBE

In the company's base case, the average age of patients was 6 months, implying that only incident cases were treated. The EAG believes that the average age of people in the EASE study (16.67 years) is more appropriate to use to represent people who would be treated in England if BBE were recommended. The company's model produced an error when this age was used with a time horizon of 100 years, and so the EAG used a time horizon of 80 years when applying this change.

5.3.4.7 Discontinuation rates

In its model, the company assumed that after the initial 90-day period there would be an annual discontinuation rate of 1%. Data from the EASE OLP indicated that this rate could be much higher, with an observed rate of [redacted] per year. During the clarification process, the EAG asked the company why clinical opinion of 1% per annum was preferred to data from the OLP of EASE where [redacted] of 205 patients ([redacted] discontinued), which was comprised of [redacted] people withdrawing consent, [redacted] due to an AE, and [redacted] for other reasons. The company stated that "*several of the reasons for discontinuation in the EASE trial were linked to trial protocol criteria and would not correspond to treatment cessation in real-world usage: for example, the incidence of SCC or other localised complications led to trial discontinuation, but would not be expected to lead to discontinuation (other than to the area of the body immediately affected, for the duration of the event) in clinical practice. Patient listings also identified discontinuations due to the practicalities of meeting trial criteria in terms of travel to follow-up visits, particularly during the Covid-19 pandemic, that would not apply in a real-world setting. It is also useful to note that discontinuation rates tended to decrease over time in the EASE OLP, so thus maybe more reflective of what would be seen in clinical practice.*" The rate of discontinuations if BBE was used in general practice is unknown, but the EAG has explored a rate of [redacted] as a pessimistic value in a sensitivity analysis.

5.3.4.8 The appropriate distributions amongst EB subtypes

The distribution of patients between EB subtypes in the company's base case was taken from Petrof *et al*.[16] which estimates that 49.10% of the population have DDEB, 26.65% have JEB 21.83% have RDEB and 2.43% have RDEB-S. In clarification question B15,[2] the EAG asked why this source was preferred to the EASE study where 78.48% had RDEB. 11.66% had DDEB, 8.97% had RDEB-S and 0.90% had JEB. The company responded that the data from Petrof *et al*.[16] was "*considered to be most representative of the patient distribution in UK clinical practice, given the longitudinal observation of patients in the UK over a number of years in the study. It is likely that due to the study inclusion/ exclusion criteria, the EASE trial distribution overestimates the number of RDEB-S patients than would be expected in clinical practice.*" Given that the company has assumed that the transition probabilities are identical for RDEB, DDEB and JEB, then it is only the proportion of people with RDEB-S that influences the ICER, which is 2.43% in Petrof *et al*.[16] and 8.97% in EASE.[29] The EAG has kept the company's assumption in its base case and has used the proportions observed in the EASE study in a sensitivity analysis.

5.3.4.9 The appropriate distributions amongst health states

In the company's base case, patients were initially distributed across health states uniformly, with 1/6th of the population in each state. The EAG explored the use of setting the distribution to that of patients, pooled across each arm, observed in in the EASE study. These proportions were 21% in health state 1, 28% in health state 2, 14% in health state 3, 16% in health state 4, 9% in health state 5 and 13% in health state 6. The EAG has kept the company's assumption in its base case and has used the proportions observed in the EASE study in a sensitivity analysis.

5.3.4.10 The appropriate use of continuity correction due to small data sizes

The rationale behind the use of continuity corrections is to avoid a situation where transitions may appear to be highly certain due to a small sample size and to allow potentially plausible observation which were not observed to occur. As an extreme example, if a fair coin was tossed and came down heads, and this was the only observation, it would not be appropriate to assume that all further observations would be heads. When using observed data where the counts are below 5, one approach is to add a continuity correction such that one additional observation is assumed to observed that is uniformly distributed between allowable transitions. In the coin example, this would equate to an updated count of 1.5 heads and 0.5 tails. When there are more data observations, the influence of continuity corrections becomes less.

The company added functionality in its model to explore the use of continuity correction when movement to all possible health states was allowed, or when movements to adjacent health states only were allowed. However, the number added was 1/6th of an observation when all transitions were allowed and when only adjacent movements were possible, 1/8th of an observation for health states 1 and 6, and 3/16th of an observation for the remaining health states. The EAG has changed this to assume one additional observation split equally across all possible transitions. The use of continuity corrections increased the EAG's base case ICER (see Section 6.3).

5.3.4.11 The efficacy of BBE in patients with DDEB and JEB

Clinical opinion provided to the EAG suggested the efficacy of treatment in patients with JEB may not be the same as in patients with DEB. This is possibly shown in Figure 13 which reproduces Figure 12 of the CS, although the EAG acknowledges the small number of patients with JEB. The company provided analyses which looked at the impact on the ICER of using data only for DDEB, but this used the approximation method detailed in Section 5.2.3 which the EAG does not consider to be appropriate (see Section 5.3.4.1). The company's analysis (assuming 12-month data cut off) noticeably reduced the base case ICER from £86,052 to £60,410, which increased to £67,781 when a continuity correction

allowing changes to all health states was applied. No ICERs were provided for the JEB subtype. Given the relatively small patient numbers with DDEB and JEB, it is unclear whether the company's base case results are only generalisable to the RDEB population.

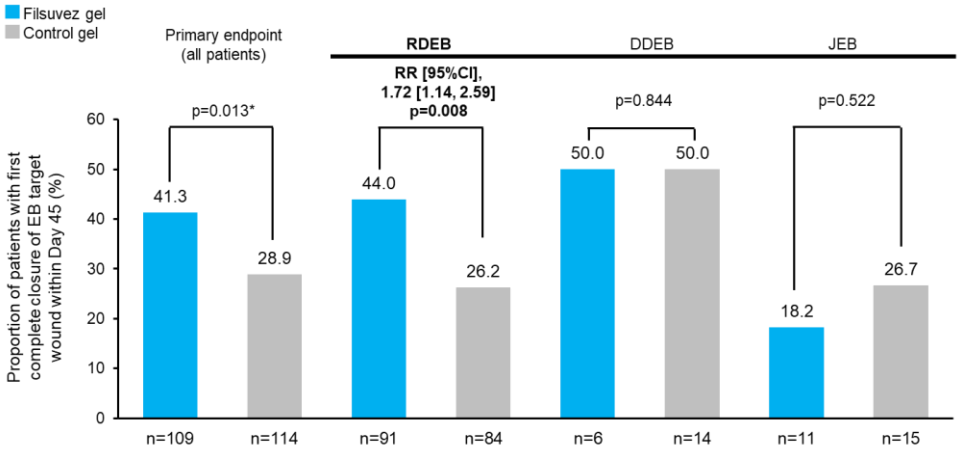


Figure 13: Analysis of EASE primary endpoint by EB subtype (reproduced from Figure 12 of the CS)

5.3.4.12 The conduct of the structured expert elicitation exercise

The EAG agrees with the use of SEE to elicit expert opinion on key model parameters in the case of paucity of clinical evidence. The company chose to follow the IDEA protocol based on its time-efficient property. The EAG has some concerns on the conduct of the elicitation exercises.

There is a key deviation of the company's elicitation process to the IDEA protocol. The IDEA protocol consists of four steps: "Investigate", "Discuss", "Estimate" and "Aggregate".[52] The "Discuss" step should involve "*with assistance of a facilitator, the experts are encouraged to discuss the results, resolve different interpretations of the questions, cross-examine reasoning and evidence, and then provide a second and final private estimate*."[52] The purpose of this discussion step is "*not to reach consensus but to resolve linguistic ambiguity, promote critical thinking, and to share evidence*".[52]

The company's elicitation process lacked the discussion step and experts were not engaged with each other before providing their final estimates. In Stage 2, the anonymised results from all experts from Stage 1 were presented and discussed between the expert interviewed and the interviewer.[3] In Stage 3, experts discussed the aggregated results from Stage 2. In response to additional clarification question 2,[3] the company states that "*Changes between Stage 1 and Stage 2 results mostly involved updating responses where fields were unanswered or not fully addressed during Stage 1 (due to experts not feeling comfortable answering questions outside of their expertise, such as a paediatric clinical expert answering questions relating to adult patients, for example).*" The EAG notes that after examining the

raw Stage 1 and Stage 2 results, there are some substantial changes in the estimates from some experts for some of the questions in addition to updating responses which were not answered in Stage 1. The EAG has concerns in the potential heuristic biases introduced without group discussion before amending the individual answers in Stage 2.

The company originally planned to recruit clinical nurse specialists (CNSs) to the SEE exercises on resource use. However, it was not possible to engage identified CNSs and instead UK-based clinicians were recruited. The EAG agrees that CNSs would be more appropriate to participant in the SEE exercises on resource use.

The EAG does not know what the impact on the ICER would be had the limitations identified in the SEE been removed.

5.3.4.13 The assumptions used to ensure face validity of utility values in PSA

As described in Section 5.2.5.5.1.3, the company capped HRQoL so that the value for patients in a more severe state could not be higher than the value for patients in a less severe state, and similarly the values for carers of patients in a more severe state could not be higher than that of carers of patients in a less severe state. This capping would produce a lower mean value for more severe health states than the value used in the deterministic estimate and the EAG posited that this capping was the reason why the probabilistic estimates generated by the company's model were considerably lower than the deterministic value (for example, the ICER when capping was employed was over £20,000 less than when the cap was removed, with the latter estimate being aligned with the deterministic value). The EAG removed this cap in its PSA (acknowledging that this causes face validity errors in some iterations and could inflate uncertainty) which generated probabilistic results similar to that of the deterministic base case analysis. The EAG did not have time to implement more nuanced methods, but based on its exploratory analysis believes that the deterministic values are an appropriate estimate of the ICER.

5.4 Exploratory analyses undertaken by the EAG

For readability, all analyses presented in this section have been termed exploratory analyses (EA) undertaken by the EAG, however, many were undertaken by the company, but have been listed here as they form either part of the EAG base case or plausible scenario analyses and have been updated from the values presented by the company. The EAG base case makes the following changes from the company's base case:

- Using transition probabilities from the EASE study and assuming steady state in the BBE arm after 90 days
- Distributing patients who discontinue BBE treatment after 90 days according to the steady state distribution for CCM after 90 days
- Assuming one carer per patient for each health state
- Using an alternative estimate of outpatient appointments per health state
- Using an average age of 16.67 years

Exploratory analyses used a rate of discontinuation of [redacted] per year and changing the distribution of patients between health states and EB subtypes to reflect the EASE study.

Further exploratory analyses were undertaken starting from the ERG base case which: changed the number of carers per patient per health state back to that assumed by the company; changed the estimate of patient utility to be derived from the OLS model rather than the GLM; and incorporated of continuity corrections.

Probabilistic estimates have been generated removing the cap on utility (see Section 5.3.4.13)

5.4.1 Alternative transition probabilities used (EA1)

The EAG has explored the impact of using the transition probabilities directly taken from the EASE study for the first 90 days rather than the approximation method applied by the company. Following the first 90-day period, the EAG assumed that there was steady state in both the BBE and CCM arm, rather than 90 days in the CCM arm and 12 months in the BBE arm.

[redacted]

The EAG notes Figure 6 in the company's second response to clarification,[45] which is reproduced in Figure 14 which shows data collected from patients receiving BBE in the DBP and the OLP.

Figure 14: Scatterplot comparing BSAP scores between adjacent visits in the EASE DBP and OLP (reproduced from Figure 6 in the company's second response to clarification)

The EAG believes that assuming a steady state for patients receiving BBE after 90 days is a reasonable simplification given the evolving nature of EB and the data contained in Figure 14. The EAG notes that the company appeared to provide these data not to support a steady state assumption for BBE but to support using data from the 12-month data cut rather than the 24-month data cut, as there were a small number of observations between Day 450 and Day 810 with data less favourable to BBE. If the 24-month data were used in the model rather than the 12-month data, the company's base case ICER increased from £86,052 to £165,973.

5.4.2 Assuming that patients who discontinue BBE are distributed in accordance with the steady state for CCM (EA2)

The EAG has explored the impact of assuming that patients who discontinue BBE after 90 days do not continue to reside in the same health state but were instead redistributed in accordance with the steady state distributions assumed for CCM. This increased the company's base case ICER from £86,052 to £93,341.

5.4.3 Assuming one carer per patient for each health state (EA3)

The EAG has explored the impact of assuming a single carer for patients in each health state rather than assuming an increase in carers as the patients become more severe as in the company's base case. This noticeably increased the company's base case ICER from £86,052 to £101,272.

5.4.4 Using utility values estimated from the GLM rather than the OLS regression (EA4)

The EAG has explored the impact of removing patients with JEB-S from the calculation of mean number of outpatient appointments per year. This markedly decreased the company's base case ICER from £86,052 to £72,651.

5.4.5 Alternative number of outpatient appointments per patient per health state (EA5)

The EAG has explored the impact of removing patients with JEB-S from the calculation of mean number of outpatient appointments per year. This marginally decreased the company's base case ICER from £86,052 to £86,020.

5.4.6 Alternative age of EB patients (EA6)

In its model, the company assumed that the average age of patients was 6 months. The EAG believes that the average age of patients who would be treated in England should BBE receive a positive recommendation is better represented by the average age in the EASE study which was 16.67 years. This did not have a large impact on the company's base case ICER which changed from £86,052 to £86,219.

5.4.7 Alternative discontinuation rate used (EA7)

The EAG has explored a rate of [redacted] per year as a pessimistic value. This decreased the company's base case ICER from £86,052 to £66,981.

5.4.8 Alternative distribution amongst EB subtypes (EA8)

The distribution of patients between EB subtypes in the company's base case was taken from Petrof *et al*.[16] The EAG has performed an exploratory analysis assuming the distribution observed in EASE marginally decreased the company's base case ICER from £86,052 to £86,141.

The ICER was fairly insensitive to changing the distribution such that all patients had RDEB-O, or all patients had RDEB-S, with values of £86,021 and £88,402 respectively.

5.4.9 Alternative distribution amongst health states (EA9)

If the distribution amongst health states were as observed in the EASE study, rather than being distributed uniformly across the six health states the company's base case ICER decreased from £86,052 to £85,387.

The impact of continuity corrections is shown in Section 6.3. The EAG could not assess how assuming different efficacy for EB subtypes would affect the ICER, nor how the ICER would change if limitations associated with the SEE were removed.

6 IMPACT ON THE ICER OF ADDITIONAL ANALYSES UNDERTAKEN BY THE EAG

This section collates the results of the EAG's exploratory analyses described in Section 5.4 and provides the EAG's base case.

6.1 The change in the deterministic ICER following the EAG's exploratory analyses

The changes in the ICER following changes made (in isolation) by the EAG are shown in Table 30. The largest change was when the EAG preferred transition probabilities were used which generated an ICER of £163,241, followed by applying a single carer to each health state which resulted in an ICER of £101,272, using a GLM to estimate patients utility which reduced the ICER to £72,651 applying a discontinuation of [redacted]% per annum which reduced the ICER to £66,981. The EAG was not able to produce ICERs for patients with DDEB and JEB (see Section 5.3.4.9) which could plausibly be less favourable than the ICER for the entire cohort or to adjust for limitations in the SEE (see Section 5.3.4.10). As the use of continuity corrections are only applicable when the data observed from EASE are selected, this amendment is explored having made the changes in the EAG's base case.

Table 30: The impact of the EAG's exploratory deterministic analyses

Exploratory Analysis	Described in Section	Short description	Incremental Costs (£)	Incremental QALYs	Cost per QALY gained (£)
-	-	Company's base case	220,306	2.56	86,052
EA1	5.4.1	Transition probabilities	299,400	1.83	163,241
EA2	5.4.2	Health state post-discontinuation	230,302	2.47	93,341
EA3	5.4.3	Single carer	220,306	2.18	101,272
EA4	5.4.4	Using a GLM	220,306	3.03	72,651
EA5	5.4.5	Outpatient appointments	220,224	2.56	86,020
EA6	5.4.6	Average Age	208,753	2.42	86,219
EA7	5.4.7	Discontinuation rate	167,657	2.50	66,981
EA8	5.4.8	EB subtype	213,813	2.48	86,141
EA9	5.4.9	Initial health states	222,282	2.60	85,387

EA – exploratory analysis; EB - Epidermolysis bullosa; GLM – generalised linear model; OLS – ordinary least squares; QALYs – Quality-adjusted life years

6.2 The EAG's base case ICER

The EAG's base case ICER is shown in Table 31. This combines EA1, EA2, EA3, EA4 EA5 and EA6 as denoted in Table 30. In the EAG's base case, the gain in patient QALYs accounted for 70% of the incremental QALY gain, with the gain in carer QALYs accounting for 30% of the incremental QALY gain. EA7, EA8 and EA9 have been excluded from the EAG's base case as the company states that these have been informed by expert clinical opinion. The company made no claim for a QALY weighting above 1 to be applied, a position that the EAG agrees with.

Table 31: The EAG's deterministic base case results

Treatment	Total costs (£)	Total QALYs (patient; carers)	Incremental Costs (£)	Incremental QALYs	Cost per QALY gained (£)
CCM	1,029,709	53.29 (11.37;41.92)			
BBE	1,327,594	52.31 (10.68; 41.62)	297,885	0.98	302,808

BBE – Birch Bark Extract; CCM – Current Clinical Management; QALYs – Quality-adjusted life years

In probabilistic analyses, the EAG's base case ICER was £304,178 (£297,885 additional costs and 0.98 additional QALYs gained) which was similar to the deterministic estimate.

6.3 Scenario analyses starting from the EAG's base case

The EAGs base case estimate may be unfavourable to BBE as it has assumed one carer in each health state to align with the question asked in the vignette study to generate HRQoL values for carers. However, it is plausible that more carers would be needed for patients in more severe health states, although the extent to which the HRQoL estimates would improve in these states with additional carers is unknown. To inform the committee, the EAG has run its base case removing EA3, which resulted in a deterministic ICER of £185,252 (£297,885 additional costs and 1.61 additional QALYs gained). The EAG notes, however, that the difference in HRQoL between health states may be exaggerated due to the extracutaneous factors that were included in the vignettes and that became more severe as the health states increased that BBE may be unlikely that will help (see Section 5.3.4.3)

Table 32 shows the impact of continuity correction on the EAG's base case ICER and on the EAG's base case where it is assumed that the company's assumption relating to the number of carers per health state is used (0.50 for health states 1 and 2; 1.00 for health states 3 and 4; and 1.78 for health states 5 and 6). In both scenarios, the use of continuity corrections is shown to noticeably increase the ICER indicating that there is considerable uncertainty in the transition probabilities that would be observed if the EASE study had been replicated with a much larger sample size. These analyses produced a range

for the deterministic ICER of £210,345 to £416,314. The lower value is likely to be favourable to BBE due to the inclusion of reduced extracutaneous aspects of EB that were assumed to be improved in less severe health states but where BBE may not have a benefit.

Table 32: Deterministic ICERs from scenario analyses starting from the EAG's deterministic base case results changing the number of carers per patient

	1 carer per patient in each health state	Company's assumption re carers per patient in each health state
No continuity correction (used in the EAG's base case)	£302,808	£210,345
Continuity correction – only adjacent transitions allowed	£359,648	£248,484
Continuity correction – all transitions allowed	£416,314	£284,725

There is also uncertainty in the best method to use for estimating patient utility with the company preferring an OLS regression method and the EAG preferring a GLM. Additional analyses have been run by the EAG where the utility estimate has been derived from the OLS regression model. These results are shown in Table 33. These analyses produced a range for the deterministic ICER of £253,396 to £416,314. The lower value is likely to be favourable to BBE due to the inclusion of reduced extracutaneous aspects of EB that were assumed to be improved in less severe health states but where BBE may not have a benefit.

Table 33: Deterministic ICERs from scenario analyses starting from the EAG's deterministic base case results changing the method for deriving patient utilities.

	Utility derived from the GLM	Utility derived from the OLS
No continuity correction (used in the EAG's base case)	£302,808	£253,396
Continuity correction – only adjacent transitions allowed	£359,648	£302,142
Continuity correction – all transitions allowed	£416,314	£343,175

In an analysis combining the use of different numbers of carers per patient, utility derived from the OLS and no continuity correction, the ICER was £185,252. The EAG believes this represents a lower bound on the ICER.

The EAG also explored the impact of allowing patients in the steady state of the BBE treatment arm to discontinue. This only had a minor impact on the deterministic ICER which increased to £303,166 (incremental costs of £247,257 and incremental QALYs of 0.82) which was expected as in the steady state period the ratio of additional costs to additional QALYs gain is constant for all periods.

The EAG prefers the assumption that patients discontinue treatment as this is more plausible but did not include this within EA1 in Table 30 as, in isolation, counter intuitive results were produced as discontinuation was assumed to result in higher incremental QALYs. This was due to the assumption made by the company that patients remained in the health state from which they discontinued, and slightly more patients were in better health states after discontinuation for the remaining modelling time horizon than if they remained on treatment. When this assumption was amended (as in EA2) the results generated assuming discontinuation from BBE treatment in the steady state period did not lack face validity.

The EAG's best estimate of the ICER is at least £300,000, depending on what form of continuity correction is applied, although this is formed from subjective judgements. The EAG notes that the ICER could potentially be as low as £185,000 or as high as £420,000. This uncertainty could be reduced by: undertaking larger studies which would provide more observations on the transition probabilities for patients using BBE, which could obviate the need for continuity corrections; more research on the number of carers required per health state and the impact on the HRQoL of these carers; and research on the utility of patients with EB.

7 BUDGET IMPACT UPON THE NHS AND PERSONAL SOCIAL SERVICES

The company estimates that at any one time there would be between 150-175 patients using BBE, rising gradually from 152 patients in Year 1 to 161 patients in Year 5 when discontinuation and mortality were accounted for. This represents approximately 23% of the prevalent population which was estimated to be 661 patients in Year 1 and 701 in Year 5.

In clarification question B26,[3] the company was asked why patients would not want BBE if it was recommended and why its estimate was between 150 and 175 patients each year. The company responded that "*These figures were first discussed and agreed at the scoping meeting. They were agreed in consultation with senior clinical experts from two of the specialist centres treating EB patients. They have been verified with both clinicians and by the NICE Topic Selection Oversight Panel (TSOP), as part of their deliberations around Filsuvez gel meeting the HST criteria. There are two factors underpinning these figures. The first is the number of patients presenting with severe forms of EB in each of the four specialist centres in England and, secondly, because of entrenched behaviour regarding the current treatment regime of patients, there is reluctance from patients and carers to adopt new treatment approaches, even if the new treatment is supported by evidence for improved outcomes.*" The EAG has assumed that the company's estimations are correct but notes that the budget impact reported will be proportional to the number of patients treated.

The values presented in Table 41 of the CS are outdated as the cost associated with formal care was revised from £12.50 an hour to £51.00 per hour. [3] The EAG did not identify where in the company's model the budget impact calculations were undertaken and thus approximated this by recording the incremental costs associated with the use of BBE in each of the first five years, by restricting the time horizon to 1, 2 , 3, 4 and 5 years, and subtracting the incremental costs from the previous year. In this analysis the incremental costs in the company's base case were £12,694 in the first year falling to £6806 in the fifth year, with corresponding values of £13,307 and £9894 in the EAG's base case; the EAG notes that these values are discounted.

When accounting for discounting and the anticipated people using BBE, the budget impact in each of years 2-5 in the company's base case is approximately [redacted] and is approximately [redacted] in the EAG's base case. The values are higher in the first year ([redacted] in the company's base case and [redacted] in the EAG's base case) as it takes some time for the benefits of BBE to be realised.

8 OVERALL CONCLUSIONS

The pivotal study (EASE) was a Phase III, randomised, international, multi-centre, double-blinded, RCT initiated in March 2017 and conducted in 51 centres across 26 countries, including two centres in the UK (NCT03068780). EASE is a two-phase efficacy and safety trial with a 90-day DBP, followed by a 24-month, single arm OLP. In the DBP, patients were randomised (stratified by subtype) to receive either BBE gel or a control gel; in the OLP, all patients received the BBE gel. Overall, 223 patients satisfied all eligibility criteria and were randomised: 109 received BBE gel and 114 received the control gel (in the DBP). Of these patients, 100 from the DBP BBE gel group and 105 from the DBP control gel group continued into the 24-month, single arm OLP.

The BBE gel and control gel groups were generally well balanced at baseline in both the DBP and the OLP, with the exception of the potential prognostic factors of wound age and DEB subtype. The proportion of DEB patients with the DDEB and RDEB subtypes in the EASE study differed substantially from the estimated proportions of these subtypes in the UK EB population, based on the data provided in the CS (section B.1.3.2, Table 4).

The EAG agreed with the CS risk of bias assessment that the DBP of the EASE study had some concerns, principally regarding deviation from the protocol, and that the OLP was at moderate risk of bias due to some baseline confounding, discontinuations, some compliance concerns, and the open-label nature of the study.

In the DBP, there was significant difference in favour of BBE gel compared with the control gel for the primary outcome, first target wound closure within 45 days (+/- 7). However, at Day 90, despite some trends in favour of the BBE gel compared with the control gel across some secondary outcomes such as wound closure at Day 90, wound burden, target wound size, itching and pain, none of these differences was statistically significant. The findings for other secondary outcomes, including sleep quality, missed days from school or work, and treatment satisfaction were reported to be similar for both the BBE and control gels. Interpretation of the efficacy findings for subgroups was difficult because of the small numbers of patients with the DDEB and JEB subtypes.

In the OLP, when all participants received BBE gel, the principal analyses focussed on wound burden. The trend was for a slight improvement from baseline to month 24 across different measures of wound burden, with some differences also between those participants who received BBE gel, and those who received the control gel, during the DBP. The reasons for these differences are uncertain. There were no clear trends in incidence of severity levels of target or additional wound infections at 12 and 24

months. There were improvements reported in disease severity using the iscorEB at 12 and 24 months but worsening of quality of life as measured by the EQ-5D VAS at 12 and 24 months. At 3 months, there was either no improvement or a small worsening in the following outcomes: itching, procedural pain, background pain and sleep quality. There was a small improvement in treatment satisfaction.

The frequency of SAEs was not high and, other than wound complications and infections, which might reflect the natural history of EB, no specific type of AE was reported to occur in >10% of patients in any arm or phase of the EASE study. There were no relevant ongoing trials, and no NMA or ITC was conducted due to the absence of any other relevant trials of the intervention or relevant comparators.

The implementation of the modelling undertaken by the company was typically of a high standard, although the EAG preferred alternative assumptions to the company which resulted in a marked increase in the ICER. The modelling assumptions that have the greatest effect on the company's base case ICER are:

- The use of transition probabilities directly from EASE for the first 90 days with both BBE and CCM having steady state distributions after this time point
- Assuming that patients discontinuing BBE treatment after 90 days are distributed in accordance with the steady state distribution associated with CCM
- The assumption of a single carer in each health state
- The method used to generate utility estimates for patients with EB
- The assumed discontinuation rate for patients receiving BBE
- Whether continuity corrections should be applied.

The deterministic EAG base case ICER was £302,808 (£304,178 probabilistic). However, there were three uncertainties: one relating to the number of carer's per health state; one related to the use of continuity corrections; and one related to the method of generating utilities for patients with EB. The impact of these ICERs produced a range in the deterministic ICER of £185,252 to £416,314. The lower value is likely to be favourable to BBE due to the inclusion of reduced extracutaneous aspects of EB that were assumed to be improved in less severe health states but where BBE may not have a benefit.

The EAG's best estimate of the ICER is at least £300,000, although this is formed from subjective judgements. The EAG notes that the ICER could potentially be as low as £185,000 or as high as £420,000.

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10 APPENDICES

Appendix 1: Additional clinical data

Table 34: Quality assessment of the EASE RCT (adapted from CS, Appendix D.1.3, Table 4)

RoB 2 domains and questions	EASE trial assessments CS, Appendix D.1.3, Table 5
Risk of bias arising from the randomisation process	
1.1 Was the allocation sequences random? (Y/ PY/ PN/ N/ NI)	Y – randomisation was conducted according to blinded patient number and the randomisation key was held solely by an independent statistician.
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions? (Y/ PY/ PN/ N/ NI)	Y – randomisation was conducted according to blinded patient number and the randomisation key was held solely by an independent statistician.
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process? (Y/ PY/ PN/ N/ NI)	N – baseline demographics were well balanced between the Oleogel-S10 and control gel arms.
Risk-of-bias judgement (Low/ High/ Some concerns)	LOW RISK
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	
2.1 Were participants aware of their assigned intervention during the trial? (Y/ PY/ PN/ N/ NI)	N – patients were blinded to their assigned intervention during the 90-day double-blind phase, through use of a matched control gel (placebo) as the control arm.
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? (Y/ PY/ PN/ N/ NI)	N – caregivers were blinded to the assigned intervention during the 90-day double-blind phase.
2.3 If Y/ PY to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context? (NA/ Y/ PY/ PN/ N/ NI)	NA
2.4 If Y/ PY to 2.3: Were these deviations likely to have affected the outcome? (NA/ Y/ PY/ PN/ N/ NI)	NA
2.5 If Y/ PY/ NI to 2.4: Were these deviations from intended intervention balanced between groups? (NA/ Y/ PY/ PN/ N/ NI)	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? (Y/ PY/ PN/ N/ NI)	PY – patients who were randomised but not treated were not assigned to any of the analysis sets. The full analysis set included all randomised subjects treated at least once with study medication. At the time of protocol

	development ICH E9 addendum was not effective. Randomisation and treatment were the same day and 100% patients randomised were treated and included in the FAS.
2.7 If N/ PN/ NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised? (NA/ Y/ PY/ PN/ N/ NI)	NA - 100% of patients randomised went on to receive study medication at least once and be included in the FAS.
Risk-of-bias judgement (Low/ High/ Some concerns)	LOW RISK
Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	
2.1 Were participants aware of their assigned intervention during the trial? (Y/ PY/ PN/ N/ NI)	N – patients were blinded to their assigned intervention during the 90-day double-blind phase, through use of a matched control gel (placebo) as the control arm.
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during this trial? (Y/ PY/ PN/ N/ NI)	N – caregivers were blinded to the assigned intervention during the 90-day double-blind phase.
2.3 [If applicable:] If Y/ PY/ NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups? (NA/ Y/ PY/ PN/ N/ NI)	NA
2.4 [If applicable:] Were there failures in implementing the intervention that could have affected the outcome? (NA/ Y/ PY/ PN/ N/ NI)	PY – overall 35% had a major protocol deviation regarding the investigational product, the majority of which involved noncompliance with product administration, and incorrect return of investigational product. This was balanced between the arms - 35% in Oleogel-S10 arm, 38% control gel. Furthermore 7.2% had a major protocol deviation regarding randomisation (mis-stratification), although subjects were included in the correct stratum for all analyses.
2.5 [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes? (NA/ Y/ PY/ PN/ N/ NI)	PY – overall 35% had a major protocol deviation regarding the investigational product, the majority of which involved noncompliance with product administration, and incorrect return of investigational product. This was balanced between the arms - 35% in Oleogel-S10 arm, 38% control gel.
2.6 If N/ PN/ NI to 2.3, or Y/ PY/ NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the	Y – per protocol and completer analysis sets were also used.

effect of adhering to the intervention? (NA/ Y/ PY/ PN/ N/ NI)	
Risk-of-bias judgement (Low/ High/ Some concerns)	SOME CONCERNS
Missing outcome data	
3.1 Were data for outcomes available for all, or nearly all, participants randomised? (Y/ PY/ PN/ N/ NI)	Y
3.2 If N/PN/NI to 3.1: Is there evidence that results were not biased by missing outcome data? (NA/Y/PY/PN/N)	NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? (NA/Y/PY/PN/N/NI)	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value? (NA/Y/PY/PN/N/NI)	NA
Risk-of-bias judgement (Low/ High/ Some concerns)	LOW RISK
Risk of bias in measurement of the outcome	
4.1 Was the method of measuring the outcomes inappropriate? (Y/PY/PN/N/NI)	N – appropriate measures used for all primary and key secondary endpoints.
4.2 Could measurement or ascertainment of the outcomes have differed between intervention groups? (Y/PY/PN/N/NI)	N – blinded trial so the assessments of outcome were unbiased and consistent between intervention groups.
4.3 If Y/PY/NI to 4.1 and 4.2: were outcome assessors aware of the intervention received by study participants? (NA/Y/PY/PN/N/NI)	NA
4.4 If Y/PY/NI to 4.3: Could assessment of the outcomes have been influenced by knowledge of intervention received? (NA/Y/PY/PN/N/NI)	NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessments of the outcomes were influenced by knowledge of intervention received? (NA/Y/PY/PN/N/NI)	NA
Risk-of-bias judgement (Low/ High/ Some concerns)	LOW RISK

Risk of bias in selection of the reported result	
5.1 Were the data that produced the results analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? (Y/PY/PN/N/NI)	Y – the efficacy endpoint results were reported in the same order as laid out in the SAP, with the exception of some secondary endpoints which were "elevated" to key secondary endpoints.
5.2 Are the numerical results being assessed likely to have been selected, on the basis of the results from multiple eligible outcome measurements (e.g., scales, definitions, time points) within the outcome domains? (Y/PY/PN/N/NI)	N - the first key secondary endpoint data were not statistically significant, so key secondary endpoints are supportive only.
5.3 Are the numerical results being assessed likely to have been selected, on the basis of the results from multiple eligible analyses of the data? (Y/PY/PN/N/NI)	N
Risk-of-bias judgement (Low/ High/ Some concerns)	LOW RISK
Overall risk of bias	
Risk-of-bias judgement (Low/ High/ Some concerns)	SOME CONCERNS

Abbreviations: FAS, full analysis set; N, no; NA, not applicable; NA, not applicable; NI, no information; PN, probably no; PY, probably yes; Y, yes.

Table 35: Risk of bias assessment of the EASE OLP using the ROBINS-I tool[34] (modified from Clarification response, A.10, Table 5)

Signalling question	EASE OLP
1: Bias due to confounding	
1.1 Is there potential for confounding of the effect of intervention in the study? (Y/ PY/ PN/ N) If N/PN to 1.1 the study can be considered low risk of bias due to confounding and no further signalling questions need be considered If Y/ PY to 1.1 determine whether there is a need to assess time-varying confounding	N – participants were instructed to continue with their usual wound care, with the addition of the intervention. All patients received Filsuvez gel during this phase.
1.2 Was the analysis based on splitting participants' follow up time according to intervention received? (NA/ Y/ PY/ PN/ N/ NI) If N/ PN answer questions relating to baseline confounding (1.4 to 1.6) If Y/ PY, go to question 1.3	NA
1.3 Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? (NA/ Y/ PY/ PN/ N/ NI) If N/ PN answer questions relating to baseline confounding (1.4 to 1.6) If Y/ PY answer questions relating to both baseline and time-varying confounding (1.7 to 1.8)	NA
Questions relating to baseline confounding only	
1.4 Did authors use an appropriate analysis method that controlled for all the important confounding domains? (NA/ Y/ PY/ PN/ N/ NI)	NA
1.5 If Y/ PY to 1.4: were confounding domains that were controlled for measured validly and reliably by the variable available in this study? (NA/ Y/ PY/ PN/ N/ NI)	NA Y
1.6 Did the authors control for any post-intervention variable that could have been affected by the intervention? (NA/ Y/ PY/ PN/ N/ NI)	NA
Questions relating to baseline and time-varying confounding	
1.7 Did authors use an appropriate analysis method that controlled for all the confounding domains and for time-varying confounding? (NA/ Y/ PY/ PN/ N/ NI)	NA

1.8 If Y/ PY to 1.7: were confounding domains that were controlled for measured validly and reliably by the variables available in this study? (NA/ Y/ PY/ PN/ N/ NI)	NA
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	LOW
2: Bias in selection of participants into the study	
2.1 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? (Y/ PY/ N/ PN/ NI) If N/ PN go to 2.4	N - participants were randomised at the beginning of the DBP, before intervention was given. In the OLP, all participants were assessed within their prior allocation groups (prior Filsuvez gel or prior control gel) and no additional participants were recruited. ***EAG: PY**
2.2 If Y/PY to 2.1: were the post-intervention variable that influenced selection likely to be associated with the intervention? (NA/ Y/ PY/ PN/ N/ NI)	NA **EAG: N**
2.3 If Y/PY to 2.2: were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? (NA/ Y/ PY/ PN/ N/ NI)	NA
2.4 Do start of follow-up and start of intervention coincide for most participants? (Y/ PY/ N/ PN/ NI)	Y
2.5 If Y/ PY to 2.2 and 2.3, or N/ PN to 2.4: were adjustment techniques used that are likely to correct for the presence of selection biases? (NA/ Y/ PY/ PN/ N/ NI)	NA
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	LOW
3: Bias in classification of interventions	
3.1 Were intervention groups clearly defined? (Y/ PY/ N/ PN/ NI)	Y – based on prior allocation at DBP baseline
3.2 Was the information used to define intervention groups recorded at the start of the intervention? (Y/ PY/ N/ PN/ NI)	Y
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of outcome? (Y/ PY/ N/ PN/ NI)	N – allocation was randomly assigned ahead of the DBP, but open-label for all participants during OLP
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	LOW

4: Bias due to deviations from intended interventions	
4.1 Were there deviations from the intended intervention beyond what would be expected in usual practice? (Y/ PY/ N/ PN/ NI)	N ***EAG: PN**
4.2 If Y/ PY to 4.1: were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome? (NA/ Y/ PY/ N/ PN/ NI)	NA
4.3 Were important co-interventions balanced across intervention groups? (Y/ PY/ N/ PN/ NI)	There were no important co-interventions
4.4 Was the intervention implemented successfully for most participants? (Y/ PY/ N/ PN/ NI)	Y – all patients in the OLP received the Filsuvez gel intervention
4.5 Did study participants adhere to the assigned intervention regimen? (Y/ PY/ N/ PN/ NI)	Y – high treatment compliance observed (99% in both groups) ***EAG: PY**
4.6 If N/ PN to 4.3, 4.4, or 4.5: was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? (NA/ Y/ PY/ N/ PN/ NI)	NA
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	LOW ***EAG: Moderate**
5: Bias due to missing data	
5.1 Were outcome data available for all, or nearly all, participants? (Y/ PY/ N/ PN/ NI)	N – due to discontinuations through the long OLP (2 years) not all participants were included in analyses at each time point
5.2 Were participants excluded due to missing data or intervention status? (Y/ PY/ N/ PN/ NI)	Y – participants who had discontinued were not included in analyses
5.3 Were participants excluded due to missing data on other variables needed for the analysis? (Y/ PY/ N/ PN/ NI)	N
5.4 If PN/ N to 5.1, or Y/ PY to 5.2 or 5.3: are the proportion of participants and reasons for missing data similar across interventions? (NA/ Y/ PY/ N/ PN/ NI)	Y – discontinuation rates similar between arms (26% in prior control gel group and 31% in prior Filsuvez gel group).
5.5 If PN/ N to 5.1, or Y/ PY to 5.2 or 5.3: is there evidence that results were robust to the presence of missing data? (NA/ Y/ PY/ N/ PN/ NI)	NI
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	MODERATE – discontinuations consistent with the extended phase length means there is

	a risk of bias through missing data at the later endpoints
6: Bias in measurement of outcomes	
6.1 Could the outcomes measure have been influenced by knowledge of the intervention received? (Y/ PY/ N/ PN/ NI)	Y – this phase was open-label so participants and investigators knew that active intervention was being received
6.2 Were the outcomes assessors aware of the intervention received by study participants? (Y/ PY/ N/ PN/ NI)	Y – open-label
6.3 Were the methods of outcome assessment comparable across intervention groups? (Y/ PY/ N/ PN/ NI)	Y – methods were the same between groups
6.4 Were any systematic errors in measurement of the outcomes related to intervention received? (Y/ PY/ N/ PN/ NI)	N
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	MODERATE – owing this phase of the trial being open-label
7: Bias in selection of the reported result	
Is the reported effect estimate likely to be selected on the basis of the results, from…..	
7.1 …multiple outcome measurements within the outcome domain? (Y/ PY/ N/ PN/ NI)	N – order of analysis of endpoints predefined in SAP
7.2 …multiple analyses of the intervention-outcome relationships? (Y/ PY/ N/ PN/ NI)	N – analyses predefined
7.3 …different subgroups? (Y/ PY/ N/ PN/ NI)	N – both FAS and subgroup data presented
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	LOW
Overall risk of bias	
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	MODERATE – open-label trial phase with a long follow-up period leading to discontinuations.
Abbreviations: DBP, double-blind phase; FAS, full analysis set; N, no; NA, not applicable; NI, no information; OLP, open-label phase; PN, probably no; PY, probably yes; ROBINS-I, Risk Of Bias In Non-Randomized Studies - of Interventions; SAP, statistical analysis plan; Y, yes. *EAG = where EAG responses differ from CS	

Table 36: Characteristics of participants in EASE across treatment groups at DBP baseline and OLP baseline (modified from CS, B.2.3.2, Table 10)

		EASE DBP[30, 32]			EASE OLP[30]		
		BBE gel (n= 109)	**Control gel (n=114)**	**All subjects (N=223)**	**Previously BBE gel (n=100)**	**Previously control gel (n=105)**	**All subjects (n=205)**
Demographics							
Age, years	**Mean (SD)**	16.8 (13.89)	16.5 (14.57)	16.7 (14.21)	16.8 (14.38)	15.8 (13.94)	16.3 (14.13)
	Median (range)	13.0 (1-71)	12.0 (0[a]-81)	12.0 (0[a]-81)	12.0 (1-71)	12.0 (0[a]-81)	12.0 (0[a]-81)
Age groups, n (%)	**≤4 years**	7 (6.4)	10 (8.8)	17 (7.6)	7 (7.0)	9 (8.6)	16 (7.8)
	4 to <12 years	42 (38.5)	43 (37.7)	85 (38.1)	40 (40.0)	41 (39.0)	81 (39.5)
	12 to <18 years	25 (22.9)	29 (25.4)	54 (24.2)	22 (22.0)	28 (26.7)	50 (24.4)
	≥18 years	35 (32.1)	32 (28.1)	67 (30.0)	31 (31.0)	27 (25.7)	58 (28.3)
Gender, n (%)	**Male**	68 (62.4)	66 (57.9)	134 (60.1)	63 (63.0)	63 (60.0)	126 (61.5)
	Female	41 (37.6)	48 (42.1)	89 (39.9)	37 (37.0)	42 (40.0)	79 (38.5)
Geographic region, n (%)	**Europe**	48 (44.0)	55 (48.2)	103 (46.2)	NR	NR	NR
	South America	33 (30.3)	35 (30.7)	68 (30.5)	NR	NR	NR
	Rest of world	21 (19.3)	17 (14.9)	38 (17.0)	NR	NR	NR
	United States	7 (6.4)	7 (6.1)	14 (6.3)	NR	NR	NR
Race, n (%)	**White**	95 (87.2)	91 (79.8)	186 (83.4)	86 (86.0)	83 (79.0)	169 (82.4)
	Black or Af/Am	1 (0.9)	2 (1.8)	3 (1.3)	1 (1.0)	2 (1.9)	3 (1.5)
	Asian	4 (3.7)	7 (6.1)	11 (4.9)	4 (4.0)	6 (5.7)	10 (4.9)
	Am/Ind or Ala/nat	0	1 (0.9)	1 (0.4)	0 (0)	1 (1.0)	1 (0.5)
	Unknown	1 (0.9)	1 (0.9)	2 (0.9)	1 (1.0)	1 (1.0)	2 (1.0)
	NA[b]	4 (3.7)	8 (7.0)	12 (5.4)	4 (4.0)	8 (7.6)	12 (5.9)
	Other[c]	4 (3.7)	4 (3.5)	8 (3.6)	4 (4.0)	4 (3.8)	8 (3.9)
BMI (kg/m^2)	**Mean (SD)**	16.05 (4.979)	16.31 (5.037)	16.18 (4.999)	16.21 (5.128)	16.29 (5.099)	16.25 (5.101)
EB subtype, n (%)	**RDEB**	**91 (83.5)**	**84 (73.7)**	**175 (78.5)**	**83 (83.0)[d]**	**77 (73.3)[d]**	**160 (78.0)**
	RDEB, generalised severe	62 (56.9)	62 (54.4)	124 (55.6)	55 (55.0)	58 (55.2)	113 (55.1)
	RDEB, generalised intermediate	23 (21.1)	16 (14.0)	39 (17.5)	22 (22.0)	13 (12.4)	35 (17.1)
	RDEB, localised	3 (2.8)	4 (3.5)	7 (3.1)	3 (3.0)	4 (3.8)	7 (3.4)
	RDEB, other	3 (2.8)	2 (1.8)	5 (2.2)	3 (3.0)	2 (1.9)	5 (2.4)

		EASE DBP[30, 32]			EASE OLP[30]		
		BBE gel (n= 109)	**Control gel (n=114)**	**All subjects (N=223)**	**Previously BBE gel (n=100)**	**Previously control gel (n=105)**	**All subjects (n=205)**
	DDEB	6 (5.5)	14 (12.3)	20 (9.0)	6 (6.0)	12 (11.4)	18 (8.8)
	JEB JEB, generalised severe JEB, generalised intermediate JEB, localised JEB, other	**11 (10.1)** 0 8 (7.3) 1 (0.9) 2 (1.8)	**15 (13.2)** 2 (1.8) 9 (7.9) 0 4 (3.5)	**26 (11.7)** 2 (0.9) 17 (7.6) 1 (0.4) 6 (22.7)	**10 (10.0)[d]** 0 (0) 8 (8.0) 1 (1.0) 1 (1.0)	**15 (14.3)[d]** 2 (1.9) 9 (8.6) 0 (0) 4 (3.8)	**25 (12.2)** 2 (1.0) 17 (8.3) 1 (0.5) 5 (2.4)
	EBS	1 (0.9)	1 (0.9)	2 (0.9)	1 (1.0)	1 (1.0)	2 (1.0)
	Kindler	0	0	0	0	0	0
Method of diagnosis n (%)	**Genetic mutation identified**	67 (61.5)	62 (54.4)	129 (57.8)	70 (70.0)	65 (61.9)	135 (65.9)
	Clinical diagnosis only	25 (22.9)	24 (21.1)	49 (22.0)	13 (13.0)	14 (13.3)	27 (13.2)
	Immunofluorescence mapping or electron microscopy	16 (14.7)	25 (21.9)	41 (18.4)	16 (16.0)	24 (22.9)	40 (19.5)
	Other	1 (0.9)	3 (2.6)	4 (1.8)	1 (1.0)	2 (1.9)	3 (1.5)
Wound characteristics							
Age of target wound/ days	**Mean (SD)**	124.3 (327.44)	126.4 (459.99)	125.4 (399.54)	128.9 (340.19)	132.5 (476.77)	130.7 (414.78)
	Median (range)	39.0 (21-2920)	32.0 (21-4745)	35.5 (21–4745)	39.5 (21-2920)	32.0 (21-4745)	36.0 (21-4745)
Size of target wound/ cm^2	**Mean (SD)**	18.99 (8.640)	19.41 (10.104)	19.20 (9.398)	18.84 (8.348)	19.81 (10.292)	19.34 (9.384)
	Median (range)	16.00 (10.0-45.6)	15.45 (10.0-49.5)	15.60 (10.0-49.5)	16.00 (10.0-45.6)	15.60 (10.0-49.5)	15.80 (10.0-49.5)
Total BSAP[e], n (%)	**Mean (SD)**	12.06 (9.967)	12.18 (12.215)	12.12 (11.143)	7.41 (6.238)	8.30 (7.552)	7.85 (6.916)
	<10%	58 (53.2)	71 (62.3)	129 (57.8)	54 (54.0)	65 (61.9)	119 (58.0)
	10-25%	38 (34.9)	27 (23.7)	65 (29.1)	35 (35.0)	26 (24.8)	61 (29.8)
	>25%	13 (11.9)	15 (13.2)	28 (12.6)	11 (11.0)	13 (12.4)	24 (11.7)
	Missing	0	1 (0.9)	1 (0.4)	0 (0)	1 (1.0)	1 (0.5)

		EASE DBP[30, 32]			EASE OLP[30]		
		BBE gel (n= 109)	**Control gel (n=114)**	**All subjects (N=223)**	**Previously BBE gel (n=100)**	**Previously control gel (n=105)**	**All subjects (n=205)**
Total wound burden/ EBDASI[f], n (%)	**Mean (SD)**	19.6 (11.26)	19.6 (12.55)	19.6 (11.91)	16.5 (9.41)	15.8 (8.81)	16.2 (9.10)
	Mild	101 (92.7)	109 (95.6)	210 (94.2)	NR	NR	NR
	Moderate	7 (6.4)	4 (3.5)	11 (4.9)	NR	NR	NR
	Severe	0	0	0	NR	NR	NR
	Missing	1 (0.9)	1 (0.9)	2 (0.9)	NR	NR	NR

Abbreviations: Af/AM=African American; Am/Ind, American or American Indian; Ala/nat=Alaska Native; BMI=body mass index; BSAP, body surface area percentage; cm2, square centimetre; DEB, dystrophic epidermolysis bullosa; DDEB, dominant dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; EB, epidermolysis bullosa simplex; EBDASI, Epidermolysis Bullosa Disease Activity Score Index; EBS, epidermolysis bullosa simplex; JEB, junctional epidermolysis bullosa; kg/m2, kilogram per square metre; N / n, number of subjects; NA, not applicable; RDEB, recessive dystrophic epidermolysis bullosa; SD, standard deviation.

[a] six months

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

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

[d] Self-calculated values

[e] BSAP measured as total body surface area affected by EB partial-thickness wounds based on "Lund and Browder" chart.

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

Table 37: Summary of clinical efficacy results for other secondary outcomes from EASE OLP (adapted from CS, B.2.6.2, Table 13)

Study name	**EASE OLP (24 months)[30]**								
Timepoint	**Month-3**			**Month-12**			**Month-24**		
Analysis type	**Full analysis set**								
Intervention	**Former BBE gel**	**Former control gel**	**All patients**	**Former BBE gel**	**Former control gel**	**All patients**	**Former BBE gel**	**Former control gel**	**All patients**
Size of study group	100	105	205	100	105	205	[redacted]	[redacted]	[redacted]
Name	**Maximum severity of target wound infection from OLP Day 0 based on AE reporting of PTs for wound infection**								
Incidence, n (%)	NR	NR	NR	4 (4.0)	3 (2.9)	7 (3.4)	[redacted]	[redacted]	[redacted]
Severity, n (%)							[redacted]	[redacted]	[redacted]
Mild	NR	NR	NR	2 (50.0)	0	2 (28.6[a])	[redacted]	[redacted]	[redacted]
Moderate				0	3 (100.0)	3 (42.9[a])			[redacted]
Severe				2 (50.0)	0	2 (28.6[a])			
Life-threatening				0	0	0			
Death				0	0	0			
Missing				0	0	0			
Name	**Maximum severity of additional wound infection from OLP Day 0 based on AE reporting of PTs for wound infection**								
Incidence, n (%)	NR	NR	NR	0	3 (2.9)	3 (1.5)	[redacted]	[redacted]	[redacted]
Severity, n (%)							[redacted]	[redacted]	[redacted]
Mild	NR	NR	NR	0	3 (100.0)	3 (100.0)		[redacted]	[redacted]
Moderate				0	0	0			
Severe				0	0	0			
Life-threatening				0	0	0			
Death				0	0	0			
Missing				0	0	0			
Name	**Change from OLP Day 0 in itching (assessed using Itch Man Scale for patients aged 4-13 years and Leuven Itch Scale for patients aged 14 years and over)**								
Mean change in Itch Man scale (SD)	n=31 0.3 (1.13)	n=36 0.00 (1.03)	n=67 0.1 (1.08)	NR	NR	NR	[redacted]	[redacted]	[redacted]
***P*-value[e]**	0.396		NA	NR		NA	[redacted]		[redacted]

Study name	**EASE OLP (24 months)[30]**								
Timepoint	**Month-3**			**Month-12**			**Month-24**		
Analysis type	**Full analysis set**								
Intervention	**Former BBE gel**	**Former control gel**	**All patients**	**Former BBE gel**	**Former control gel**	**All patients**	**Former BBE gel**	**Former control gel**	**All patients**
Size of study group	100	105	205	100	105	205	[redacted]	[redacted]	[redacted]
Leuven Itch scale Domain	n= 32-36	n=24-26	n=56-62	NR	NR	NR	[redacted]	[redacted]	[redacted]
Frequency	6.25 (21.856)	1.92 (18.605)	4.44 (20.508)						
Severity[f]	1.99 (20.689)	0.60 (18.362)	1.41 (19.605)						
Duration	-0.98 (30.133)	-8.33 (17.720)	-4.02 (25.802)						
Consequence	1.47 (12.244)	0.28 (9.390)	0.98 (11.078)						
Distress[f]	0.14 (17.909)	-2.46 (21.796)	-0.94 (19.469)						
Surface area	-0.72 (14.926)	-1.92 (12.056)	-1.24 (13.664)						
***P*-value[d]**							[redacted]		[redacted]
Frequency	0.728		NA	NR		NA			
Severity[f]	0.651								
Duration	0.412								
Consequence	0.748								
Distress[f]	0.578								
Surface area	0.346								
Name	**Change from OLP Day 0 in <u>procedural pain</u> (assessed using Wong Baker Faces for patients aged ≥4 years of age and FLACC for those <4 years of age)**								
Mean change in Wong-Baker FACES score (SD)	n=66 0.2 (2.48)	n=63 0.2 (2.74)	n=129 0.2 (2.60)	NR	NR	NR	[redacted]	[redacted]	[redacted]
***P*-value[e]**	0.723		NA	NR		NR	[redacted]		[redacted]
Mean change in FLACC score (SD)	n=6 -0.50 (2.51)	n=6 2.83 (3.43)	n=12 1.2 (3.35)	NR	NR	NR	[redacted]	[redacted]	[redacted]
***P*-value**	NE		NA	NR		NR	[redacted]		[redacted]
Name	**Change from OLP Day 0 in background <u>pain</u> (assessed using Wong Baker Faces for patients aged ≥4 years of age and FLACC for those <4 years of age)**								
Mean change in Wong-Baker FACES score (SD)	n=67 0.3 (2.41)	n=62 0.4 (2.38)	n=129 0.3 (2.39)	NR	NR	NR	[redacted]	[redacted]	[redacted]

Study name	EASE OLP (24 months)[30]								
Timepoint	Month-3			Month-12			Month-24		
Analysis type	Full analysis set								
Intervention	Former BBE gel	Former control gel	All patients	Former BBE gel	Former control gel	All patients	Former BBE gel	Former control gel	All patients
Size of study group	100	105	205	100	105	205	[redacted]	[redacted]	[redacted]
P-value[e]	0.698		NA	NR		NR	[redacted]		[redacted]
Mean change in FLACC score (SD)	n=6 -1.0 (1.67)	n=6 1.0 (2.19)	n=12 0.0 (2.13)	NR	NR	NR	[redacted]	[redacted]	[redacted]
P-value	NE		NA	NR		NR	[redacted]		[redacted]
Name	Change from OLP Day 0 in impact of wounds on sleep quality (Likert Scale) in patients aged ≥14 years								
Mean (SD)	n=36 -0.2 (2.40)	n=26 0.2 (2.42)	n=62 0.0 (2.39)	NR	NR	NR	[redacted]	[redacted]	[redacted]
LS mean (SE)	-0.22 (0.44)	-0.01 (0.46)	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
95% CI of LS mean	-1.10, 0.67	-0.92, 0.90	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
Difference in LS means (SE)	-0.20 (0.57)		NA	NR		NA	[redacted]		[redacted]
95% CI of difference in LS means	-1.34, 0.93		NA	NR		NA	[redacted]		[redacted]
P-value[g]	0.720		NA	NR		NA	[redacted]		[redacted]
Name	Number of days missed from school or work during the past 14 days								
Mean [days] (SD)	n=41 1.5 (2.75)	n=45 1.9 (3.99)	n=86 1.7 (3.44)	NR	NR	NR	[redacted]	[redacted]	[redacted]
Proportion who had missed days, n (%)	15 (36.6)	17 (37.8)	32 (37.2)	NR	NR	NR	[redacted]	[redacted]	[redacted]
Name	Response to treatment (TSQM) before wound dressing changes in patients aged ≥4 years								
LS mean (SE)	4.75 (0.20)	4.71 (0.20)	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
95% CI of LS mean	4.35, 5.15	4.30, 5.12	NR	NR	NR	NR	[redacted]	[redacted]	[redacted]
Difference in LS means (SE)	0.04 (0.25)		NA	NR		NA	[redacted]		[redacted]
95% CI of difference in LS means	-0.47, 0.55		NA	NR		NA	[redacted]		[redacted]

Study name	EASE OLP (24 months)[30]								
Timepoint	Month-3			Month-12			Month-24		
Analysis type	Full analysis set								
Intervention	Former BBE gel	Former control gel	All patients	Former BBE gel	Former control gel	All patients	Former BBE gel	Former control gel	All patients
Size of study group	100	105	205	100	105	205	[redacted]	[redacted]	[redacted]
P-value	0.870		NA	NR		NA	[redacted]		[redacted]
Name	Disease Severity using the iscorEB Score by Visit (using LOCF)								
Mean CFB in total iscorEB score (SD)	NR	NR	NR	n=4 -8.0 (30.06)	n=5 11.6 (30.13)	n=9 2.9 (29.99)	[redacted]	[redacted]	[redacted]
95% CI mean	NR	NR	NR	-55.8, 39.8	-25.8, 49.0	-20.2, 25.9	[redacted]	[redacted]	[redacted]
Name	HRQoL by Visit using the EQ-5D scale VAS (using LOCF)								
Mean CFB in EQ-5D-Y/ EQ-5D-Y proxy (SD)	NR	NR	NR	n=3 -6.7 (15.28)	n=4 7.5 (22.17)	n=7 1.4 (19.52)	[redacted]	[redacted]	[redacted]
95% CI mean	NR	NR	NR	-44.6, 31.3	-27.8, 42.8	-16.6, 19.5	[redacted]	[redacted]	[redacted]
Mean CFB in EQ-5D-5L (SD)	NR	NR	NR	n=0 - (--)	n=1 -5.0 (--)	n=1 -5.0 (--)	[redacted]	[redacted]	[redacted]
95% CI mean	NR	NR	NR	--, --	--, --	--, --	[redacted]	[redacted]	[redacted]
Mean CFB in EQ-5D-Y/ EQ-5D-Y proxy/ EQ-5D-5L (SD)	NR	NR	NR	n=3 -6.7 (15.28)	n=5 5.0 (22.00)	n=8 0.6 (18.21)	[redacted]	[redacted]	[redacted]
95% CI mean	NR	NR	NR	-44.6, 31.3	-27.8, 42.8	-16.6, 19.5	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; ANCOVA, analysis of covariance; BSAP, body surface area percentage; CFB, change from baseline; CI., confidence interval; EB, epidermolysis bullosa; EBDASI, epidermolysis bullosa disease activity and scarring index; EQ-5D-Y, EuroQol 5-dimension Youth; EQ-5D-5L, EuroQol 5-dimension 5-level; FLACC, face, legs, activity, cry, consolability scale; LOCF, last observation carried forward; LS, least squares; n, number; NE, not estimable; NR, not reported; OLP, open label phase; PTs, preferred terms; PTW, partial-thickness wound; SD, standard deviation; SE, standard error; TBSA, total body surface area.

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

[d] Parameter and model estimates based on an analysis of covariance (ANCOVA) on the change from baseline with Treatment group, EB Subtype and Target Wound Size class as fixed effects and Total BSAP at baseline as a covariate.

[e] Parameter and model estimates based on a 2-sided Wilcoxon Rank Sum test using the van Elteren extension stratified by EB subtype and target wound size class.

[f] Scaled-up values used for these domains (values recorded with an incorrectly sized scale were converted to a common scale and multiplied by 10 as: Scaled-up subscore = [(recorded answer*10)/actual VAS length]*10. Actual VAS length used as provided by the study clinical team).

[g] Parameter and model estimates based on an ANCOVA on the change from baseline with treatment group and EB Subtype as fixed effects and baseline W-QoL Scale score as a covariate.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

EAG report – factual accuracy check and confidential information check

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 2 March 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 10. Issue 1 of Table 1 reads “The company has used an approximation method to estimate transition probabilities between the modelled health states and assumes that these apply for a patient’s lifetime for birch bark extract.” Page 70 – “After 90 days, the company’s base case assumed that the cohort of patients receiving CCM would have reached a steady state and that the distribution of patients across health states would remain unchanged. However, for the BBE arm patients continued to transition between health states using the described method for approximating transitions until the end of the time horizon.”	Suggested wording: “The company has used an approximation method to estimate transition probabilities between the modelled health states and **assumes that transitions between health states apply for the first 12 months before reaching a steady state** for birch bark extract.”	The current wording suggests that trial-based transitions are extrapolated indefinitely in the company submission (CS) approach, whereas the CS base case (and key scenarios) assume a steady state after 12 months in the BBE arm. This is seen as an important clarification since the current wording may be construed as suggesting that the CS approach extrapolates improvements beyond the trial period to a potentially extreme level in the absence of longer-term evidence, whereas the steady state rule applied in the CS base case in fact constrains any such effect beyond the period observed directly in the EASE OLP.	Changes have been made on page 10, page 70, and page 93 as requested.

Page 94 - The EAG has explored the impact of using the transition probabilities directly taken from the EASE study for the first 90 days rather than the approximation method applied by the company. Following the first 90-day period, the EAG assumed that there was steady state in both the BBE and CCM arm, rather than just in the CCM arm. While the company model allows for open-label transition probabilities to be apply to BBE patients over any user-specified period, this period is limited to 12 months before assuming a steady state in the company base case.			

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 10. Issue 6 of Table 1 (but please note that this point regarding discontinuations may also apply to other scenarios): Under the EAG adaptation made for scenario EAG1 (BBE steady state after 90 days), transitions from on to off treatment continue to be applied, while transitions to alternative severity states cease. Please note that this contrasts with (and is potentially overridden by) the CS approach, whereby the steady state time point selected in DASHBOARD cell E35 prohibits further movement in terms of treatment status as well as severity.	Highlighted to EAG for information / consideration as appropriate.	Highlighted as a potential area of inconsistency between EAG and company approaches when exploring scenarios.	Thank you for highlighting this. We did intend that discontinuation occurred in the steady state period. This only slightly increases the ICER and has been noted after the EAG base case. This was not formally incorporated in EAG EA1 as the results in isolation were counter intuitive, with more QALYs being produced when patients discontinue due to the assumption in the company base case that patients remain in that health state. When added to the EAG's base case the results had face validity and our approach seems less likely to cause unnecessary confusion / delay in the committee.

Should the intention be for discontinuations to continue indefinitely in EA1, EA6 and other scenarios, please note that this assumption will only apply if 'All time points' are selected in DASHBOARD E35, without further adaptation.			

Issue 3

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG Response**
Page 12. Table 2 – an ICER of £163,241 (not £163,251) was found by the company when attempting to reproduce EA1 scenario. Also applies to Table 30 (page 97).	Amend to £163,241 if correction is appropriate	Company was unable to replicate estimate	This typo has been corrected

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 23. The description of the inclusion criteria on age of population in the SLR versus the decision problem, the EASE trial and submission is currently a little misleading.	The PICOS for the SLR included adults or children from birth with DEB (RDEB or DDEB) or JEB – this comment could be added for completeness, alongside existing descriptions of population age relating to the EASE trial which included patients from 21 days (revised down from ≥4 years of age). The decision problem population was from 6 months of age, in line with the marketing authorisation.	This section appears under the 4.1.2 Inclusion criteria within the methods of the review, but does not currently make clear the population inclusion criteria from the systematic review, in terms of age.	Not an error, but text added: 'whereas the SLR criteria indicated from birth'.

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Pages 28-31, Table 8. Formatting of bullets in the table is incorrect e.g., Concomitant medications section listed as appendices rather than bullets.	Correction to bullets style to make clear.	Reference to the appendices is incorrect and could be misleading.	Formatting error, thank you. Bullets have now been reinstated.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 60. The EAG report states “The report did not distinguish between adverse events (AEs) and treatment-related AEs”. This is incorrect, the Company Submission did make the distinction.	Comment to be removed or revised to include values that were provided in the Company Submission where AEs (treatment-emergent) and treatment-related AEs were both reported.	(TE)AEs and TRAEs, including those that were Serious AEs and Serious TRAEs, were both reported in the Company Submission, page 77-80, Table 14.	Error: Text under 4.4 deleted.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 62. The percentage of participants overall in the OLP who experienced pyrexia as an AE is reported incorrectly in the text. N.B. the value reported in Table 20 is correct.	The value should be [redacted] rather than [redacted]	Incorrect value reported in the text.	Error, thank you, corrected to [redacted]

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 94 – Caption for Figure 14 reads 'Scatterplot comparing BSAP scores between adjacent visits in the EASE OLP..'. Please note that the scatterplot (originally provided in a company clarification document) reflects visits from the DBP (up to day 90) and OLP (beyond day 90) visit data. Across all time points, the scatterplots are filtered on patients randomised to Filsuvez gel in the DBP, as correctly described on page 93.	Suggest amending to 'Scatterplots comparing BSAP scores between adjacent visits in the EASE OLP and DBP.'	Clarification around figure description.	This has been changed to '… EASE DBP and OLP'

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Page 98. Text reads 'The EAG's base case ICER is shown in **Error! Reference source not found.**. This combines EA1, EA2, EA3, EA4 and EA5 as denoted in **Error! Reference source not found.**.' The EAG base case incorporates EA1 to EA6, as described in Table 2 (page 12) and confirmed by the EAG model.	Suggest amending to 'The EAG's base case ICER is shown in **Error! Reference source not found.**. This combines EA1, EA2, EA3, EA4, EA5 and EA6 as denoted in **Error! Reference source not found.**.'		This has been changed, as has the following text to read that 'EA7, EA8 and EA9 have been excluded' – These were previously EA6, EA7 and EA8.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG Response
Page 79. Usage of colours for redacting AIC and CIC. Number of tubes used ([redacted]) should be	Change highlighting from yellow to blue to indicate CIC.	The mean number of tubes used per month across the DBP and 24-month OLP was [redacted].[30]	This has been done. We have also marked the cost of a year of treatment as CIC.

highlighted as CIC, not AIC.			
Page 34, Figure 2, should be highlighted as AIC	Redact Figure 2 to be AIC		This has been done.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **13 April 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Amryt Pharma DAC
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Key issues for engagement

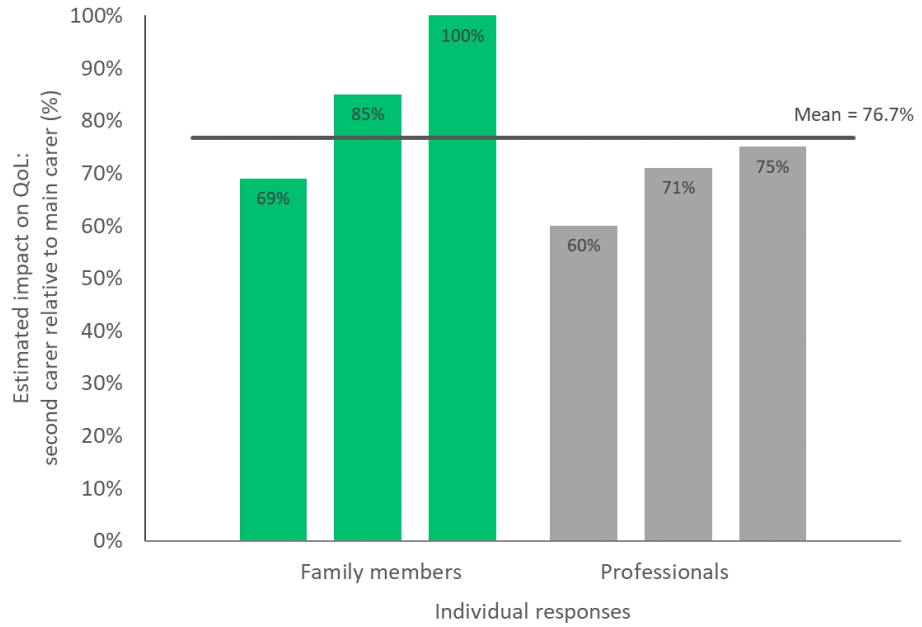
All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Use of approximation method to estimate transition probabilities. (See 5.3.4.1 of EAG report)	Yes	The company submission approach approximates transition probabilities based on mean change in BSAP observed in the EASE trial. This reflects an assumption, based on EASE DBP and OLP study data, that reductions in overall BSAP among patients treated with Filsuvez gel are not achieved fully until 12 months of use. If this assumption is accepted, scenarios in which a steady state is applied at 90 days would underestimate the treatment effect. To support the company assumption, new evidence is provided from a study of a cohort of DEB patients in real world clinical practice using Filsuvez gel in line with the label (Torres-Pradilla 2023, provided as a slide pack accompanying this response document). Pooled data from this cohort demonstrate an ongoing reduction in mean BSAP from baseline to 12 months after initial exposure, with mean BSAP levels maintained at the a steady state over the subsequent 12-month period (see extract below). We provide this additional evidence to support the company approach to extrapolation beyond the EASE DBP. **Figure:** [redacted]

		 Rates of BSAP reduction beyond the 90-day EASE RCT are derived from OLP visits conducted at 12-month intervals. A straight-forward transition approach was not found to be sufficiently sensitive for changes in BSAP observed during the OLP to be captured in terms of aggregate health states, particularly when interpolating between visits. Estimating transitions according to mean change and variance was adopted as a solution following discussions with experts during a multistakeholder panel, where it was raised that this methodology had been used in previous NICE guidance for visual acuity (NG82). The approach ensured that changes in BSAP observed at the cohort level in the EASE study could be reflected in the model irrespective of the frequency of visits or magnitude of change. Tests for normality around change in BSAP were conducted to assess adherence to underlying assumptions of this approach as discussed in the EAG report.

		The company agrees that transition rates are an area of uncertainty to which the company approach is one of several pragmatic options, each with limitations. However, it believes that the imposition of steady state assumptions at 90 days would be overly pessimistic in terms of capturing the benefits of treatment fully. A hybrid approach, applying conventional transition matrices to both arms to day 90 (as applied in EAG1) and transitions derived using the mean reduction approach (the company approach) between day 90 and month 12 been provided as a model scenario and result in a reduced ICER relative to the base company analysis.
Health state distribution of people in the model after discontinuation at 90 days. (See section 5.3.4.2 of EAG report)	No	The company agrees with the EAG as to the appropriateness of their suggested approach, whereby patients discontinuing Filsuvez gel are assumed to resolve to a BSAP state consistent with the comparator arm.
Number of carers modelled (See section 5.3.4.3 of EAG report)	Yes	The company accepts the EAG suggestion that carer utility estimates derived from TTO study responses cannot automatically be assumed to be generalisable to second carers, due to the framing of the vignettes around the main carer. To help address this uncertainty, new evidence is provided using responses to a short questionnaire hosted by DEBRA UK exploring the input of second unpaid carers in higher-severity patients and the burden/quality of life impact to second carers relative to patients' main carer. An overview of responses (N=7 family members and professionals working with EB patients) is provided as a slide pack. Mean results suggest that the decrement corresponding to second carers would be approximately 77% of that of the main carer. This supports the original submission assumption that disutilities are applicable to second carers, albeit at a lower rate that has been reflected in updated model assumptions. **Figure: Summary of Q2 responses by respondent type**

		 **Source: THE/DEBRA UK questionnaire** As the ongoing study is small, further exploration of carer HRQoL/ utility impact covering the impact on additional carers is an area for future research.
Use of ordinary least squares (OLS) or generalised linear model (GLM) regression (See section 5.4.4 of EAG report)	No	The company agrees with the EAG's assessment that utility estimates derived from a GLM provide a superior statistical and visual fit to cross-sectional EASE data and would be appropriate to use in base estimates.
Discontinuation rate used in the model (See section 5.3.4.7 of EAG report)	No	The company approach assumes that discontinuation rates will be lower than observed in EASE due to trial protocols that would not be generalisable to real-world practice based on clinical expert opinion.

		In light of uncertainties, a discontinuation rate of 1% was applied as a cautious base assumption rather than rates more in line with the EASE study that would favour cost-effectiveness results but may not be appropriate to clinical practice. Should such scenarios be considered, the company agrees with the EAG interpretation that [redacted] would appear to be an appropriate upper estimate of discontinuation.
Use of a continuity correction in the model (Section 5.3.4.10)	No	The company agrees with the EAG assessment that continuity corrections should be explored in conjunction with transition estimates and functionality is provided to apply this in all model scenarios.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Appropriate number of outpatient appointments per year	Sections 5.3.4.5 and 5.4.5	No	The company accepts and agrees with the EAG's recommendation to exclude JEB-S patients when calculating numbers of outpatient appointments for internal consistency.
Additional issue 2: The age of people treated with BBE	Sections 5.3.4.6 and 5.4.6	No	The company accepts and agrees with the EAG's preference to use EASE baseline age to represent the expected profile of 'day 1' patients. The company considers cost-effectiveness at the minimum licensed age to also be of importance in exploring cost-effectiveness at the earliest stages of intervention, which may relate to clinical practice in the future. However, the results are comparable in either case.
Additional issue 3: The appropriate distribution amongst EB subtypes	Sections 5.3.4.8 and 5.4.8	No	The company accepts and agrees with the EAG's discussion around the potential importance of distributions between EB types and maintains that Petrof *et al* is likely to provide the most reliable source of evidence around relative prevalence. As discussed in section 5.3.4.8, this is not a key driver

			due to the assumed generalisability of treatment effects across DEB and JEB subgroups.
Additional issue 4: The appropriate distribution amongst health states	Sections 5.3.4.9 and 5.4.9	No	The company accepts and agrees with the EAG's highlighting of the importance of exploring baseline health state membership in scenario analyses.
Additional issue 5: The efficacy of BBE in patients with DDEB and JEB	Section 5.3.4.11	No	The company agrees with the validity of EAG's suggestion to explore efficacy evidence specific to subgroups but maintains that due to the small numbers of JEB patients observed, this analysis is only feasible in relation to a DDEB-only subgroup. In the absence of any clinical rationale for a difference in effectiveness, a pooled approach is considered by the company to be the most appropriate in the base case analysis.
Additional issue 6: The conduct of the structured expert elicitation exercise	Section 5.3.4.12	No	The company accepts the limitations identified by the EAG in relation to the SEE including the reliance upon UK clinicians rather than CNSs as proxy respondents for resource use questions and the limited opportunity for group discussion across experts during the process and considers this an area for potential evidence to be generated.
Additional issue 7: The assumptions used to ensure face validity of utility values in the PSA	Section 5.3.4.13	No	The company accepts the limitations raised by the EAG regarding the capping of health-state utility estimates in the PSA approach and its assessment that the lifting of this rule may provide more reliable estimates.

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
EA1	Reduction in BSAP to 12 months in Filsuvez arm, based on mean change	[No change but additional supportive evidence provided]	N/A
EA2	Post-discontinuation health states determined using comparator transitions (i.e. no change if after 90 days)	Post-discontinuation health state aligned with comparator arm 90-day distribution. Consistent with EA2.	Revised ICER (in isolation): £93,341 Change relative to company base case before TE: +£7,289
EA3	Utility decrement for additional (second) carer assumed to be equal to that of 'main carer'	Utility decrement for additional (second) carer assumed to be 77% of the decrement applied to the 'main carer', based on DEBRA survey estimates.	Revised ICER (in isolation): £87,289 Change relative to company base case before TE: +£1,237
EA4	OLS used to estimate health state utility scores	GLM used to estimate health state utility scores. Consistent with EA4.	Revised ICER (in isolation): £72,651 Change relative to company base case before TE: -£13,401

EA5	Outpatient appointments calculated including data from JEB patients	Outpatient appointments calculated excluding data from JEB patients	Revised ICER (in isolation): £86,020 Change relative to company base case before TE: -£32
EA6	Patients aged 6 months (as per license) at model baseline	Patients aged 16.7 (as per EASE baseline age) at model baseline	Revised ICER (in isolation): £86,219 Change relative to company base case before TE: +£167
Company's base case following technical engagement (EA2,4,5,6 plus reduction in disutility applied to second carers in response to EA3)	Incremental QALYs: 2.75	Incremental costs: £218,129	Company revised base-case ICER: £80,199 Change relative to company base case before TE: -£5,854

Sensitivity analyses around revised base case

Company's base case following technical engagement, observed transitions to 90 days followed by mean change to 12 months	ICER: £62,288

An exploration of the quality of life impact of additional EB carers

Questionnaire design and results

13/04/2023

Tolley Health Economics

A bespoke approach to Health Technology Assessment

Background

- Tolley Health Economics (THE) have developed a cost-effectiveness analysis submitted to NICE to support an HST submission for Filsuvez gel in the treatment of Epidermolysis Bullosa (EB).
- The model estimates the impact of treatment on lifetime costs and the quality of life (in terms of quality-adjusted life years (QALYs)) of EB patients and their informal carers. The model assumes that for more severe patients, up to two informal carers may be routinely involved in patients' care.
- Carer utility values for each DEB/ JEB patient health state were elicited from a time trade off study in the general public, where respondents were asked to trade time in different health states from the perspective of the patient or the "main caregiver".
- For patients that are expected to receive care from two caregivers, no assessment has been made directly of the utility values corresponding to the second carer. This slide pack provides an overview of a short questionnaire developed by THE to inform utility estimates applicable to additional carers to address evidence gaps and inform ongoing evidence generation around the impact of EB and EB treatment.

Methods

- A short online questionnaire was developed by THE and piloted with representatives from DEBRA UK, a support group for patients living with EB, their carers and health professionals.
- Upon finalisation of the materials, the survey was rolled out to members of DEBRA to complete via a link (hosted by SurveyMonkey) on the members area of the DEBRA website.
- The final survey included two core questions, both in relation to the carer vignette used in the earlier TTO exercise to describe care of patients with the high EB severity in terms of body surface area percentage (BSAP).
    - Respondents were asked to consider the appropriateness of the assumption that more than one carer would be involved in providing unpaid care.
    - In relation to circumstances where a second caregiver was involved, respondents were asked to estimate the quality of life impact of the second carer relative to the 'main' carer. Responses were collected using a sliding scale where 0% indicates that the secondary carers quality of life is not impacted at all, and 100% means that their quality of life is impacted by at least as much as the main caregiver.

Results

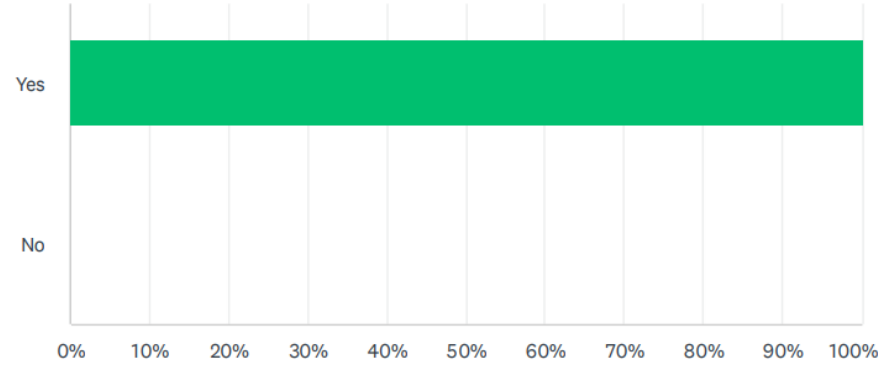
- A link to the survey was loaded to the members page of the DEBRA website on 30th March 2023, with a request for responses by the 5th April. The survey link was kept live by DEBRA beyond this date to accommodate additional responses up to the deadline for new evidence to inform the technical engagement process.
- Results to all questions are presented in slides 5-9.
  - Key questions (Q1 and Q2) had been responded to by six individuals at the point of analysis (13th April 2023). All were either friends or family members of a patient with EB (n=3) or had professional experience with EB (n=3).
  - All respondents agreed that there would typically be at least one second carer involved in the management of an EB patient, with an overall average HRQoL impact of 77% (range 60%-100%) relative to the main carer.

Results

EB multiple carer questionnaire

Q1 For a patient with the level of EB severity described, is it reasonable to assume that more than one person would typically be involved in providing unpaid care? By 'unpaid care', we mean regular help with aspects of EB care (for example changing dressings and bandages) provided by a friend or family member.

Answered: 6 Skipped: 1

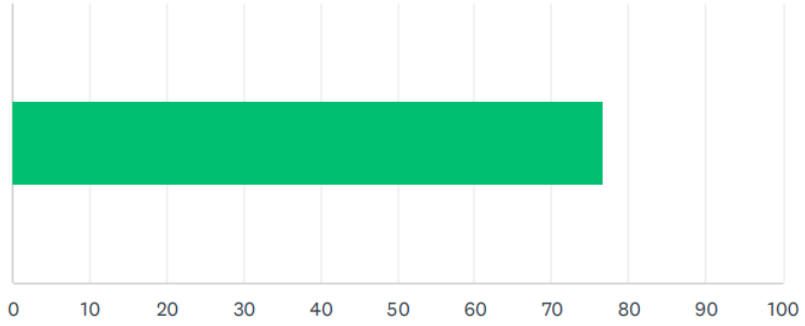


ANSWER CHOICES	RESPONSES	
Yes	100.00%	6
No	0.00%	0
TOTAL		6

Results

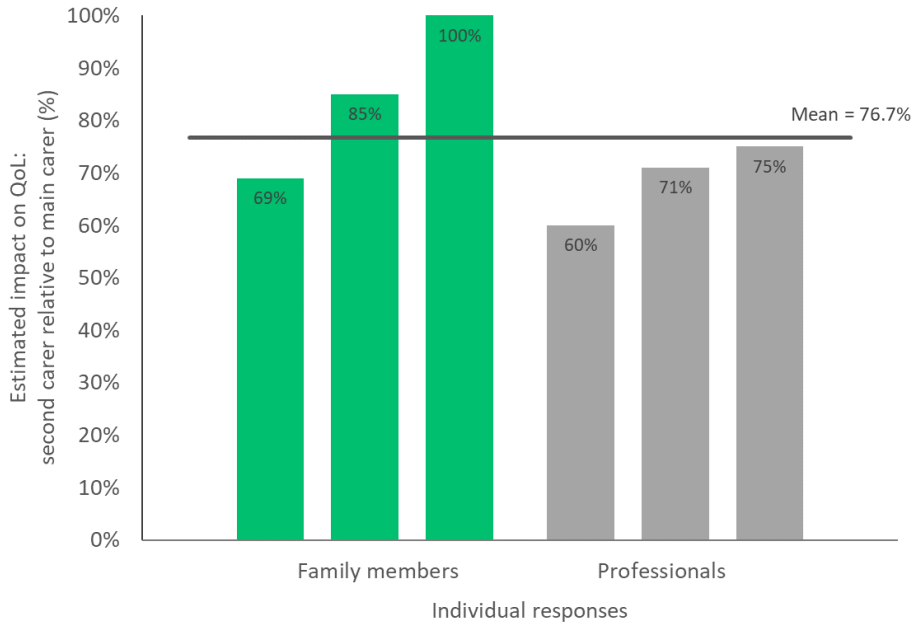
Q2 In the following question, please assume that two unpaid carers are involved in the patient's care.How much do much do you think the quality of life of the second carer is likely to be impacted by caring for someone with EB, relative to the person that was referred to as the 'main' carer? Please respond using the slider below, or by typing a number into the box next to it.Examples: 100% would mean the second carer's quality of life is affected by at least as much as the main carer. 0% would mean the second carer's quality of life is not affected at all.

Answered: 6 Skipped: 1



ANSWER CHOICES	AVERAGE NUMBER	TOTAL NUMBER	RESPONSES
	77	460	6
Total Respondents: 6			

Summary of Q2 responses by respondent type



Results

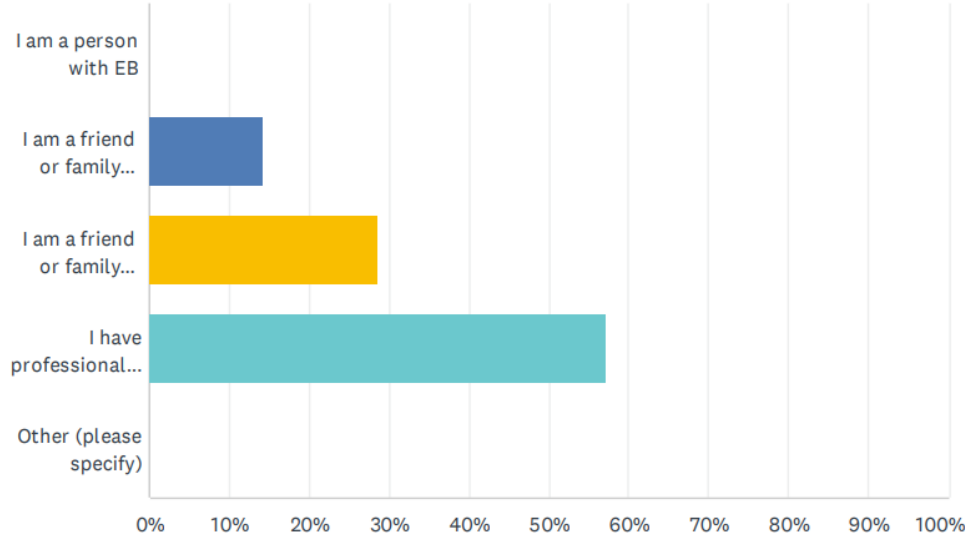
Q3 Additional comments (optional)

Answered: 0 Skipped: 7

Results

Q4 What is your relationship to EB?

Answered: 7 Skipped: 0



ANSWER CHOICES	RESPONSES	
I am a person with EB	0.00%	0
I am a friend or family member of someone with EB (I provide informal care)	14.29%	1
I am a friend or family member of someone with EB (I do not provide informal care)	28.57%	2
I have professional experience with EB	57.14%	4
Other (please specify)	0.00%	0
TOTAL		7

Appendix: Survey questions

Appendix 1 – Survey questions

Thank you for taking the time to help us with this questionnaire.

Who is carrying this out?

DEBRA UK is conducting this research. DEBRA is the national charity and patient support organisation for people living with the incredibly painful genetic skin blistering condition, epidermolysis bullosa (EB), also known as butterfly skin. The results of the research will be used by DEBRA and selected partners, where appropriate, for the express purpose of raising awareness of EB and of DEBRA's key activities, and when lobbying for support.

Why is this being carried out?

To help understand the potential impact of treatments for dystrophic and junctional epidermolysis bullosa (EB), this questionnaire builds on a series of studies that explore how living with EB affects the quality of life of patients and their informal (unpaid) carers. Specifically, this questionnaire builds on an earlier study that looked at the quality of life of EB patients and their 'main' informal carers.

In this questionnaire we hope to understand more about carer impact when patients need help from more than one person. Your opinion as someone with experience of EB and the EB community is greatly valued regardless of whether this applies to your situation personally.

How long will it take?

The questionnaire should take no longer than 5 to 10 minutes to complete.

Appendix 1 – Survey questions

Background

Carer quality of life was explored in a recent study. This used a 'time trade-off' (TTO) approach, which is a way of measuring how much people think their quality of life would be affected if they were a patient or informal carer in various different scenarios.

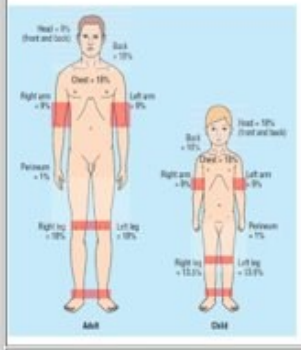
Each scenario described a different hypothetical patient with EB, or a person caring for someone with EB. The scenarios explored different levels of EB severity, in terms of the body surface area percentage (BSAP) covered by surface wounds as well as other complications and the need for support with dressing changes or other care.

The scenario relating to a carer of a person with the highest level of EB severity that was explored is described below. Please read this carefully before answering the questions.

Appendix 1 – Survey questions

Wounds and other symptoms

• You are the main caregiver of a person with wounds covering 25% or more of their body. These wounds cover a significant area of their limbs and a significant area of their chest and abdomen (see diagram). The person develops blisters easily and has a lot of skin crusting, scabbing or erosions on their body.



Disease management

• You dress the person's wounds daily, so that they heal. The process takes 4 or more hours daily.
• The person with EB has severe acute (temporary) skin pain or discomfort with itching, especially when dressings are changed.
• You regularly administer treatment for pain, itch and nutritional supplements to the person with EB. They require a high dose of painkillers (daily) for their wounds.

Impact on your life

• The person with EB is unable to eat or drink normally– you aid their feeding multiple times a day. They are unable to sleep well and your sleep will be very impacted.
• You accompany the person with EB to their frequent medical visits and in-hospital treatment for anaemia; you are unable to work. Due to their inability to move around or use their hands, you must always aid the person with EB to adjust to their daily activities.
• Often, you experience negative emotions (such as anxiety or frustration) due to the nature and burden of the condition.

Appendix 1 – Survey questions

1. For a patient with the level of EB severity described, is it reasonable to assume that more than one person would typically be involved in providing unpaid care?

By 'unpaid care', we mean regular help with aspects of EB care (for example changing dressings and bandages) provided by a friend or family member.

- ◯ Yes
- ◯ No

Comments (optional)

Appendix 1 – Survey questions

2. In the following question, please assume that **two** unpaid carers are involved in the patient's care.

How much do much do you think the quality of life of the **second carer** is likely to be impacted by caring for someone with EB, relative to the person that was referred to as the **'main' carer?**

Please respond using the slider below, or by typing a number into the box next to it.

Examples:

- *100% would mean the second carer's quality of life is affected by the same amount as the main carer.*
- *0% would mean the second carer's quality of life is not affected at all.*

3. Additional comments (optional)

Appendix 1 – Survey questions

Thank you for taking the time to complete this questionnaire. If you are able to tell us your experience relating to EB or caring for someone with EB, that will help us to understand our responses even more.

4. What is your relationship to EB?

- ◯ I am a person with EB
- ◯ I am a friend or family member of someone with EB (I provide informal care)
- ◯ I am a friend or family member of someone with EB (I do not provide informal care)
- ◯ I have professional experience with EB
- ◯ Other (please specify)

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically availabel from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **13 April 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating epidermolysis bullosa and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Anna Martinez
2. Name of organisation	Great Ormond Street
3. Job title or position	Consultant
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with epidermolysis bullosa ? ☐ A specialist in the clinical evidence base for epidermolysis bullosa or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	
8. What is the main aim of treatment for epidermolysis bullosa ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Help wounds heal, reduce inflammation, treat complications, no treatment or cure exists so we manage complications, try and reduce progression.

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Wound closure that stays closed longer than when using a placebo because in children wounds heal but reopen, so they will all close under the age of 10yrs.
10. In your view, is there an unmet need for patients and healthcare professionals in epidermolysis bullosa?	Yes – in all aspects of care, wound heal, infection, itch, pain management, cancer, inflammation.
11. How is epidermolysis bullosa currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, national & international best practice guidelines.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes in England as national centres.
• What impact would the technology have on the current pathway of care?	The birch bark may speed up wound closure but it was disappointing that no better than placebo at day 90.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The birch bark will be additional to current ward care
• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	All settings. Home, community, hospital – patients/carers apply
• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Quick training on how much to apply & how – not difficult
13. Do you expect the technology to provide clinically meaningful benefits compared with current care?	I am not sure, data from the open label 24 month ease extension study should have more information to inform this and we need this.

• Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	I think it is unlikely to increase length of life It may improve skin care/help heal when applied but placebo did that at day 90
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	?
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	None that would cause barriers bar tubes that are small so they would need lots of them if treating large areas.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	None that I am aware of but be good to know BSA wounds affected at the start
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	None

18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	The day 45 wound closure vs placebo was significant but not sustained – if it improves wound healing & therefore reduces inflammation long term it may help to some degree I do not believe it is a step change Yes improves wound care if 24 month extension open label data shows this
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Minor/not significant
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes Wound healing – yes - No
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	We have not seen results of 24 month open label ease extension yet
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this	

treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	In the UK not that I am aware of. No No No

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Use of approximation method to estimate transition probabilities. (See 5.3.4.1 of EAG report)	?
Health state distribution of people in the model after discontinuation at 90 days. (See section 5.3.4.2 of EAG report) **Is there likely to be a continuing effect of**	?

birch bark extract gel once treatment has been discontinued?	
Number of carers modelled (See section 5.3.4.3 of EAG report) **How many carers would you expect to see for the health states described in Table 25 of the company submission?** **How would you expect the impact on carer quality of life to change in the different health states and if additional carers were present?**	Same number of carers will be needed – no change anticipated in my view
Use of ordinary least squares (OLS) or generalised linear model (GLM) regression (See	?

section 5.4.4 of EAG report)	
Discontinuation rate used in the model (See section 5.3.4.7 of EAG report)	?
Use of a continuity correction in the model (Section 5.3.4.10)	?
Are there any important issues that have been missed in EAR?	/

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **13 April 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	DEBRA
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Use of approximation method to estimate transition probabilities. (See 5.3.4.1 of EAG report)	Yes/No	We are not health economics experts and are therefore unable to provide a meaningful response
Health state distribution of people in the model after discontinuation at 90 days. (See section 5.3.4.2 of EAG report)	Yes/No	We are not health economics experts and are therefore unable to provide a meaningful response
Number of carers modelled (See section 5.3.4.3 of EAG report)	Yes/No	We are not health economics experts and are therefore unable to provide a meaningful response
Use of ordinary least squares (OLS) or generalised linear model (GLM) regression (See section 5.4.4 of EAG report)	Yes/No	We are not health economics experts and are therefore unable to provide a meaningful response
Discontinuation rate used in the model (See section 5.3.4.7 of EAG report)	Yes/No	We are not health economics experts and are therefore unable to provide a meaningful response

Use of a continuity correction in the model (Section 5.3.4.10)	Yes/No	We are not health economics experts and are therefore unable to provide a meaningful response

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Appropriate number of outpatient appointments per year	Sections 5.3.4.5 and 5.4.5	Yes/No	We are not experts on this and therefore unable to provide a meaningful response
Additional issue 2: The age of people treated with BBE	Sections 5.3.4.6 and 5.4.6	Yes/No	We are not experts on this and therefore unable to provide a meaningful response
Additional issue 3: The appropriate distribution amongst EB subtypes	Sections 5.3.4.8 and 5.4.8	Yes/No	We are not experts on this and therefore unable to provide a meaningful response
Additional issue 4: The appropriate distribution amongst health states	Sections 5.3.4.9 and 5.4.9	Yes/No	We are not experts on this and therefore unable to provide a meaningful response
Additional issue 5: The efficacy of BBE in patients with DDEB and JEB	Section 5.3.4.11	Yes/No	We are not experts on this and therefore unable to provide a meaningful response
Additional issue 6: The conduct of the structured expert elicitation exercise	Section 5.3.4.12	Yes/No	We are not experts on this and therefore unable to provide a meaningful response
Additional issue 7: The assumptions used to ensure face validity of utility values in the PSA	Section 5.3.4.13	Yes/No	We are not experts on this and therefore unable to provide a meaningful response

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Technical engagement response form

About you

Table 1 About you

Your name	Drs [redacted], [redacted], [redacted] and Profs [redacted] and [redacted], on behalf of the British Association of Dermatologists (BAD) Therapy & Guidelines sub-committee
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	British Association of Dermatologists (the BAD)
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Use of approximation method to estimate transition probabilities. (See 5.3.4.1 of EAG report)	~~Yes~~/No	We agree that the EAG's approach appears reasonable.
Health state distribution of people in the model after discontinuation at 90 days. (See section 5.3.4.2 of EAG report)	~~Yes~~/No	BBE does not appear to be disease-modifying, therefore, we agree that the EAG's approach appears reasonable.
Number of carers modelled (See section 5.3.4.3 of EAG report)	~~Yes~~/No	Real-world clinical practice suggests that 1 carer per adult patient is appropriate, however, 2 carers per paediatric patient might be more appropriate.
Use of ordinary least squares (OLS) or generalised linear model (GLM) regression (See section 5.4.4 of EAG report)	~~Yes~~/No	This is not within our area of expertise.
Discontinuation rate used in the model (See section 5.3.4.7 of EAG report)	~~Yes~~/No	We agree with the use of the EASE study data rather than the company's estimation.

Use of a continuity correction in the model (Section 5.3.4.10)	~~Yes~~/No	This is not within our area of expertise.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Appropriate number of outpatient appointments per year	Sections 5.3.4.5 and 5.4.5	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: The age of people treated with BBE	Sections 5.3.4.6 and 5.4.6	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 3: The appropriate distribution amongst EB subtypes	Sections 5.3.4.8 and 5.4.8	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa. A Single Technology Appraisal.
EAG response after company's response to Technical Engagement

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	17/04/2023

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Declared competing interests of the author
Neither author has a conflict of interest to declare.

1. BACKGROUND

This report details the response of the External Assessment Group (EAG) to the company's response to Technical Engagement (TE).[1] This report should be read in conjunction with the EAG's main report[2] which critiques the company submission on Birch Bark Extract (BBE) in the treatment of epidermolysis bullosa (EB).

In TE, the company provided additional information related to some of the key issues identified by the EAG and agreed with the proposed EAG changes for some key issues. As a result, the EAG believes that there is only one outstanding difference between the company's base case and the EAG's base case, albeit a difference that has a substantial impact on the incremental cost-effectiveness ratio (ICER). In this report, all ICERs are reported in terms of cost per quality-adjusted life year (QALY) of Birch Bark Extract (BBE) compared to current clinical management (CCM).

Table 1 reproduces the key issues from the EAG report, using the short-hand notation of the key issues used in Table 30 of the EAG report. This tables also details whether the EAG now considers each issue to be resolved after TE.

In addition to the key issues identified by the EAG, the company has amended its model to incorporate EAG preferences that had only a minor impact on the ICER. These include removing severe junctional EB (JEB) patients when calculating the number of outpatient appointments and increasing the age of the cohort to 16.67 years. The EAG is content with these changes. Due to small numbers, the efficacy (and hence cost-effectiveness of BBE) is uncertain in the JEB subgroup, which could not be resolved at TE. Both the company and the EAG's ICERs are pooled for both patients with JEB and with dystrophic EB.

The EAG and company base cases remain likely to be moderately favourable to BBE due to the inclusion of reduced extracutaneous aspects of EB in less severe Body Surface Area Percentage (BSAP) health states, but where BBE may not have a benefit. This would overestimate the increase in utility of improving BSAP health state due to the use of BBE. As an example, patients in BSAP health states 3 and 4 are stated in the vignette to have moderate difficulty with eating and drinking normally whilst patients in health states 1 and 2 are not stated to have any difficulty with eating or drinking. It is plausible that BBE can improve BSAP health state from 3 to 2, but there is no evidence that BBE improves the ability to eat or drink.

Table 1: The EAG's key issues

Short description	Resolved after TE?	Comments
Transition probabilities	No	The company has amended its model such that the actual data from the EASE study is used for the initial 90 days. The approximation method is then used to the end of year 1 when steady state is assumed. The EAG prefers that steady state is assumed at 90 days with no use of the approximation method.
Health state post-discontinuation	Yes	The company has amended its model to align with the EAG's preferred approach.
Single carer	Yes	Following further evidence received at TE and an amendment to the model, the EAG is content that the company's approach is reasonable.
Using a GLM	Yes	The company has amended its model to align with the EAG's preferred approach.
Discontinuation rate	Yes	The company and the EAG agree with using 1% discontinuation per annum in the base case although both note that this is uncertain. A scenario analysis using a discontinuation rate of [redacted]% per year, as observed in EASE, has been applied to the EAG base case although the change in the ICER is slight.
Continuity Corrections	Partly	Neither the company nor the EAG has used continuity corrections in their base cases. However, both agree that the use of continuity corrections should be explored, and these increase the ICER. Scenario analyses have been undertaken using continuity corrections applied to the EAG base case which markedly increase the ICER.

2. THE COMPANY'S BASE CASE ICER

The results generated when using the company's revised base case are shown in Table 2.

Table 2: The company's base case

Treatment	Total costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	Cost per QALY gained (£)
CCM	1,061,671	50.74			
BBE	1,279,800	53.46	218,129	2.72	80,199

3. ADDITIONAL ANALYSES UNDERTAKEN BY THE EAG

This section describes the rationale for the one change in the company's base case made by the EAG which relates to the time at which steady state was assumed in the BBE arm. In TE, the company provided additional data on the change in BSAP in [redacted] patients treated in Columbia who had received long-term BBE treatment.[3] These data are reproduced in Figure 1 and the company states they are supportive of steady state being reached at 12 months rather than 90 days.

Figure 1: Additional data provided by the company on the change in BSAP

The EAG's view that steady state can plausibly be assumed from day 90 has not been changed as the new data are on a small number of patients and considerably more patients are included in the open-label phase (OLP) of the EASE study. The data from OLP of the EASE study reproduced in Figure 2 show that the assumption of steady state from day 90 appears reasonable with slightly more data points above the line of equality between day 90 and day 450 (indicating that the BSAPs had improved) whilst more data points lie below the line of equality between day 450 and day 810 (indicating that the BSAPs had worsened). Data on the changes in BSAP of patients between day 90 and day 810 would be informative.

Figure 2: Scatterplot comparing BSAP scores between adjacent visits in the EASE OLP (reproduced from Figure 6 in the company's second response to clarification)

In addition to individual data on BSAP, plots of mean Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) and mean BSAP for the cohort were evaluated. Figure 3 shows data on mean EBDASI and Figure 4 shows data on mean BSAP, both excluding OLP visit windows; the conclusions are similar if these were included.

The EAG cautions against using the approximation method put forward by the company as it was seen to poorly match the data within EASE and relies on the change in BSAP being normally distributed. If the distribution was normal then

the majority of the changes would be grouped closely around zero with only a small proportion of patients having large changes (either improving or worsening); Figure 2 suggests that this is not the case as there are many points with large changes. If scenario analyses were conducted using a longer time to steady state than the 90 days assumed by the EAG then using the actual transitions observed within the EASE OLP would be preferable as these would not rely on an assumption of a normal distribution.

Figure 3: EBDASI improvements throughout the EASE OLP for patients receiving BBE

Figure 4: BSAP improvements throughout the EASE OLP for patients receiving BBE

Having reviewed additional data provided by the company and from stakeholders the EAG has changed its perspective on the disutility associated with carers. The EAG believes that the following company assumptions are reasonable: (i) that the number of carers required increases as the severity of the patient increases (0.50 for health states 1 and 2; 1.00 for health states 3 and 4; and 1.78 for health states 5 and

6) and (ii) that where additional carers are needed in those health states where BSAP is ≥19% (health states 5 and 6) that the second carer would have 77% of the disutility of that estimated for the main carer.

The data for the disutility estimate came from a survey of seven people (six respondents) where the BSAP was estimated to be ≥25%. Clinical stakeholders suggested that "*Real-world clinical practice suggests that 1 carer per adult patient is appropriate, however, 2 carers per paediatric patient might be more appropriate.*" and most patients ([redacted]% in the CCM arm from the model) would be in health states 1 to 4. Given this new information, the EAG has maintained the assumption used in the company's base case.

4. ICERS GENERATED BY THE EAG

The results generated when using the EAG's base case are shown in Table 3. This is likely to be moderately favourable to BBE due to the inclusion of reduced extracutaneous aspects of EB in less severe BSAP health states but where BBE may not have had an impact.

Table 3: The EAG's base case

Treatment	Total costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	Cost per QALY gained (£)
CCM	1,029,709	51.88			
BBE	1,327,662	53.20	297,954	1.32	225,781

The functionality to run probabilistic sensitivity analyses appears to have been removed in the company's model after TE. However, as the model was previously shown to be relatively linear when the company's restriction on utilities was removed this was not deemed by the EAG to be a major limitation.

4.1 Scenario analyses starting from the EAG's base case

Table 4 shows the impact of continuity correction on the EAG's base case ICER. In both scenarios, the use of continuity corrections is shown to noticeably increase the ICER producing a range in the deterministic ICER of £225,781 (the EAG base case) to £306,598.

Table 4: Deterministic ICERs starting from the EAG's deterministic base case when assuming the use of continuity corrections

Scenario	ICER
No continuity correction (used in the EAG's base case)	£225,781
Continuity correction – only adjacent transitions allowed	£266,911
Continuity correction – all transitions allowed	£306,598

The EAG also explored the impact of increasing the discontinuation rate per year to [redacted]% as observed in the EASE study. This had a small impact on the ICER reducing it to £220,809 (£261,430 additional costs and 1.18 additional QALYs). Allowing patients to discontinue BBE treatment whilst in the steady state also had a minor impact on the ICER, increasing it to £226,056 (£247,313 additional costs and 1.09 additional QALYs).

5. OVERALL CONCLUSIONS

The EAG's base case ICER is over £225,000 and could be much higher depending on whether a continuity correction is applied. However, this value would likely be lower if steady state in the BBE arm was assumed to happen later than 90 days but was 90 days in the CCM arm. The EAG has concerns that a key assumption underpinning the company's approximation approach is incorrect and would prefer the use of observed transition from the EASE OLP where longer times to steady state are assumed.

There remains uncertainty in the decision problem which could be reduced by undertaking larger studies of longer duration which would provide more observations on the transition probabilities for patients using BBE and the timepoint at which steady state is assumed to have been reached. However, such studies could not feasibly be conducted within the timescales of this appraisal.

6. REFERENCES

1. Amryt Pharma DAC. Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]. Technical engagement response form. 2023.
2. Stevenson M, Carroll C, Ren S, Rawdin A, Ren S, Clowes M. Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa. A Single Technology Appraisal.: School of Health and Related Research (ScHARR); 2023.
3. Torres-Pradilla M. EB: Broadening the horizon.; 2023.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with Recessive Dystrophic Epidermolysis Bullosa. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your evaluation in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Patient expert statement

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Your response should not be longer than 15 pages.

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Patient expert statement

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with dystrophic and junctional epidermolysis bullosa

Table 1 About you, dystrophic and junctional epidermolysis bullosa, current treatments and equality

1. Your name	[redacted]
2. Are you (please tick all that apply)	☐ A patient with dystrophic and junctional epidermolysis bullosa? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with dystrophic and junctional epidermolysis bullosa? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	DEBRA UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☒ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience

Patient expert statement

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

	☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with dystrophic and junctional epidermolysis bullosa? **6a. How many many carers/ hours of care do you receive per week?7**	
7a. What do you think of the current treatments and care available for dystrophic and junctional epidermolysis bullosa on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for dystrophic and junctional epidermolysis bullosa (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of Birch bark extract over current treatments on the NHS please describe these.	

For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Birch bark extract help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of Birch bark extract over current treatments on the NHS please describe these. For example, are there any risks with Birch bark extract? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from Birch bark extract or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering dystrophic and junctional epidermolysis bullosa and Birch bark extract? Please explain if you think any groups of	

people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

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Patient expert statement

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Patient expert statement

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with dystrophic and junctional epidermolysis bullosa

Table 1 About you, dystrophic and junctional epidermolysis bullosa, current treatments and equality

Patient expert statement

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

NICE National Institute for Health and Care Excellence

1. Your name	James Hinchcliffe
2. Are you (please tick all that apply)	☑ A patient with dystrophic and junctional epidermolysis bullosa? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with dystrophic and junctional epidermolysis bullosa? ☑ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Debra / Genetic Alliance
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing

Patient expert statement

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

5. How did you gather the information included in your statement? (please tick all that apply)	☑ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with dystrophic and junctional epidermolysis bullosa? **6a. How many many carers/ hours of care do you receive per week?7**	Recessive Dystrophic Epidermolysis Bullosa Pruriginosa (RDEB) is a rare, debilitating, genetic skin disorder which inhibits the body's ability to secure the epidermis to underlying dermis. And thus rendering the skin extremely fragile and prone to ulceration and full-thickness separation with long-term deterioration. The specific form of EB I have is a combination of over powering itch and very fragile skin: a volatile mix. The areas that are affected – the whole of my lower body from the chest down and both forearms – roll through a cycle of pain, healing, itching and deterioration. My life is dominated by daily care, chronic pain and an itchiness best likened to the sensation of hundreds of tiny insects burrowing beneath the skin. I require a nurse and a carer daily. I have an alternating daily regime of a full change: 6-8 hours, interspaced with a partial change: 4-5 hours. So 10-13 hrs over 2 days or 70-91 hrs per fortnight. The final total comes to about 35-45.5 hours a week. Put another way, it takes a full-time job to keep me alive.

7a. What do you think of the current treatments and care available for dystrophic and junctional epidermolysis bullosa on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	There has been a revolution in dressings during my lifetime and the current available options are light-years ahead of what my mother had to use to care for me as a child. But these only treat symptoms, not the causes of RDEB. To be blunt, most of my friends with RDEB are no longer alive to speak for themselves. I am reluctant to speak for them because but for an unusual period of 'dormancy' in teenage- and early adult-hood, the treatments in question might not have sufficed to permit my participation here either. Despite that reluctance, I would have to say that, at best, they would likely agree with my assessment.
8. If there are disadvantages for patients of current NHS treatments for dystrophic and junctional epidermolysis bullosa (for example, how they are given or taken, side effects of treatment, and any others) please describe these	▶ The amount of care required to maintain current treatment is excessive. ▶ RDEB carries with it an increased risk of SCC (Squamous Cell Carcinoma [skin cancer]). ▶ Infections - Staphylococcus Aureus [including MRSA], Streptococcus and Pseudomonas - of the skin are a constant threat, including the potential for sepsis. ▶ Other skin damage eg. maceration, resulting from inability of the dressings to wick moisture away from wounds.

9a. If there are advantages of Birch bark extract over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does Birch bark extract help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	I have not yet had the opportunity to test this treatment.
10. If there are disadvantages of Birch bark extract over current treatments on the NHS please describe these. For example, are there any risks with Birch bark extract? If you are concerned about any potential side effects you have heard about, please describe them and explain why	See 9(a)
11. Are there any groups of patients who might benefit more from Birch bark extract or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	The diversity of symptoms amongst EB sufferers (or even just those with RDEB) both limits my corresponding knowledge on other patients and inhibits a helpful response. However, in the interests of completeness, I will make a couple of short comments. The limited life expectancy amongst Junctional patients reduces success rate. But it also, paradoxically, increases the impetus to trial any potential treatment.

12. Are there any potential equality issues that should be taken into account when considering dystrophic and junctional epidermolysis bullosa and Birch bark extract? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	None that spring to mind.
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Patient expert statement

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- The final total comes to about 35-45.5 hours a week. Put another way, it takes a full-time job to keep me alive.
- The areas that are affected – the whole of my lower body from the chest down and both forearms – roll through a cycle of pain, healing, itching and deterioration.
- To be blunt, most of my friends with RDEB are no longer alive to speak for themselves.
- The amount of care required to maintain current treatment is excessive.

Thank you for your time.

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The information that you provide on this form will be used to contact you about the topic above.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]

Company response to committee request for additional analyses

June 2023

File name	Version	Contains confidential information	Date
ID1505 birch bark extract committee scenarios company response [redacted].docx	1	yes	23/06/2023

Purpose

Following the NICE committee meeting on June 8th 2023, this document is submitted alongside an adjusted CE model in response to a request from NICE for additional analyses as outlined by email on June 12th and discussed at a subsequent video meeting with the EAG and NICE on June 15th.

The additional analyses are based on the EAG base case, with EASE 24-month open-label data added as outlined below. Unless otherwise stated, all other assumptions align with the EAG base case. An updated version of the Excel model (v1.5) with these changes included has been uploaded.

Following review of the model, we hope to proceed as discussed under a Chair's action. We gratefully acknowledge the collaborative way of working with NICE and the EAG to find a way forward that is acceptable to all stakeholders to work towards hopefully securing routine commissioning.

Background

Box 1: Summary of committee request

"As the current version of the model does not have the functionality to implement the committee preferred base case, we kindly request that an additional analysis which uses the EASE observed transition probabilities up to day 810 to calculate health state transitions in the BBE arm, before the steady state assumption is applied.

"The committee preferences were:

- To use the EASE observed trial data to calculate transition probabilities for the CCM arm up to 90 days
- To use the EASE observed trial data to calculate transition probabilities for the BBE arm up to 810 days
- To not apply continuity corrections to the committee base case, and account for the uncertainty posed by unobserved transitions in its consideration of the ICER threshold and its decision making."

Following the HST evaluation committee meeting for Filsuvez gel (birch bark extract, BBE), on 8th June 2023, correspondence was received from NICE on 13th June 2023 detailing additional analyses requested by the appraisal committee (excerpt above).

In preparing its response, the company identified that no observations corresponding to patients in health state 5 and 6 at Day 450 were available at the following visit (Day

810). Consequently, applying transition probabilities based on 450-810 directly in the model without a continuity correction or some other form of adjustment to inform ongoing transitions for these patients would not be possible. An equivalent limitation had not been encountered in Day 0 to Day 90 estimates since each health state had at least one exit observation per visit.

Figure 1: Sankey diagram illustrating observed transitions between Day 90, Day 450 and Day 810 visits

A video call between NICE, EAG and company representatives was held on 15th June 2023 to identify and align on the most suitable approach and assumptions to meet the committee's request. The company, NICE and the EAG agreed that the company provide the following two scenarios, both exploring the use of EASE observed data between Day 90 and Day 810:

Committee scenario 1: Annual transition probability matrices (TPMs) for days 90 to 450 and days 450 to 810, based on EASE observed data, are used to estimate BBE health state membership at Day 450 and Day 810. Continuity corrections are applied, but only to rows of the TPMs that are entirely unpopulated from observed data. Model

cycles between days 90, 450 and 810 are interpolated linearly, accounting for mortality and discontinuation rates.

Committee scenario 2: BBE health state membership at days 450 and 810 is derived directly from the cross-sectional distribution of EASE patients at the corresponding time points. As above, model cycles between days 90, 450 and 810 are interpolated linearly, accounting for mortality and discontinuation rates. This approach avoids using transitions and the corresponding requirement for patient-level observations to be made at adjacent visits. However, since estimates are independent of prior health state, the approach cannot be used in conjunction with scenarios in which align baseline health state distributions are assumed to differ substantially from the EASE population.

In both approaches, a steady state is assumed beyond day 810 in the BBE arm. No changes have been made to the CCM arm in either scenario (steady state assumptions apply from 90 days).

Results

Cost-effectiveness results for both scenarios are shown in the table below, alongside estimates from the company and EAG base cases ([redacted]% PAS discount applied in all analyses). Scenarios corresponding to each result have been stored within the updated model v1.5 and can be loaded from the model DASHBOARD sheet.

ICERs for both analyses using 24-month EASE data fall below the company and EAG base case estimates. When applying scenario 1 with a continuity correction to <u>all</u> transition matrices (including day 0 to day 90 visits in either arm), the ICER result is comparable to the company base case at £80,460 per QALY gained.

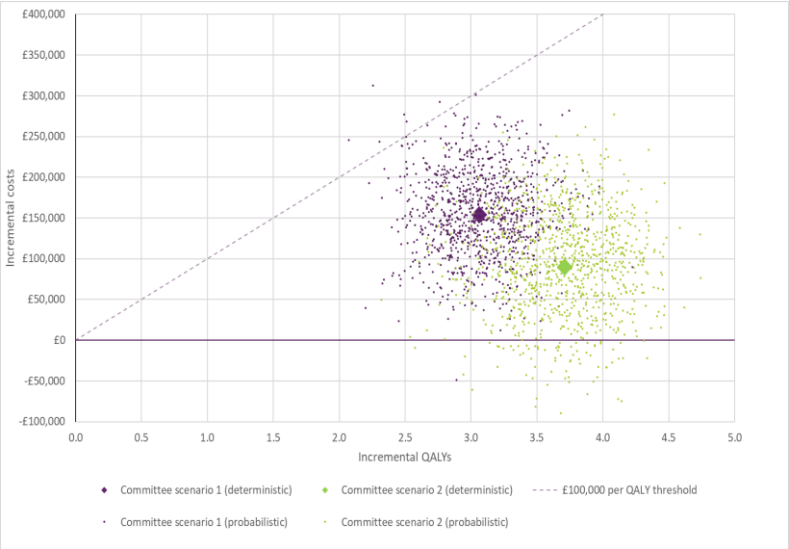
Table 1: Comparison of cost-effectiveness results according to company, EAG and committee scenarios ([redacted]% PAS discount assumed)

		Company (post TE)	EAG (post TE)	Committee scenario 1	Committee scenario 2
Costs	BBE	£1,279,800	£1,327,662	**£1,183,662**	**£1,119,478**
	CCM	£1,061,671	£1,029,709	**£1,029,709**	**£1,029,709**
	Incremental	£218,129	£297,954	**£153,954**	**£89,769**
QALYS	BBE	53.46	53.20	**54.94**	**55.59**

	CCM	50.74	51.88	**51.88**	**51.88**
	Incremental	2.72	1.32	**3.06**	**3.71**
ICER		£80,199	£225,781	**£50,291**	**£24,186**

It was also noted that the probabilistic sensitivity analysis (PSA) should be reinstated so that the alignment between probabilistic and deterministic results can be verified. Plotted results are shown below, demonstrating alignment between deterministic and PSA results.

Figure 2: Scatterplot showing probabilistic and deterministic results from committee scenarios 1 & 2 on a cost-effectiveness plane (1,000 iterations, no constraint on utility estimates by adjacent health state values)



Confidential until published

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa. A Single Technology Appraisal.
EAG additional analysis post NICE Appraisal Consultation Document

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Declared competing interests of the author
Neither author has a conflict of interest to declare.

1 Introduction

This document should be read in conjunction with the initial External Assessment Group (EAG) report[1] and the EAG's response to technical engagement[2] which provide more details on the EAG's critique of the model and additional analyses undertaken by the EAG prior to the first ACM.

In June 2023, the NICE HST appraisal committee (henceforth referred to as the Committee) met to appraise the use of birch bark extract (BBE) for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa compared with current clinical management (CCM). The Committee requested further analyses to be undertaken by the company which was sent to the EAG on the 26th of June 2023.[3]

The Committee's request, as summarised by the company, is shown in Box 1.

Box 1: Summary of committee request (reproduced from the company's additional analyses)

"As the current version of the model does not have the functionality to implement the committee preferred base case, we kindly request that an additional analysis which uses the EASE observed transition probabilities up to day 810 to calculate health state transitions in the BBE arm, before the steady state assumption is applied.

"The committee preferences were:

- To use the EASE observed trial data to calculate transition probabilities for the CCM arm up to 90 days
- To use the EASE observed trial data to calculate transition probabilities for the BBE arm up to 810 days
- To not apply continuity corrections to the committee base case, and account for the uncertainty posed by unobserved transitions in its consideration of the ICER threshold and its decision making."

Section 2 details the analyses undertaken by the company which comprised of four scenarios: the EAG's base case; the company's base case; Committee's Scenario 1; and Committee Scenario 2 and the results generated from these analyses. These results are provided as incremental cost-effectiveness ratios (ICERs), expressed in terms of the incremental cost per quality-adjusted life year (QALY) gained. Section 3 details the EAG's summary of the advantages and disadvantages of each of the four scenarios presented by the company. Section 4 provides analyses of the drivers of the differences in the ICERs of each of the four methods. Section 5 provides exploratory analyses undertaken by the EAG whilst Section 6 summarises the EAG's conclusions based on the new analyses presented.

All reported ICERs have assumed a price reduction of [redacted]% in the cost of BBE. This value is unchanged from the company's initial submission.

2 The analyses run by the company

The company produced results for four scenarios:

- The EAG's base case
- The company's base case
- Committee Scenario 1
- Committee Scenario 2

The EAG's base case and the company's base case remain as reported in previous documents.[1, 2]

The company ran two scenarios which attempt to address the request from the Committee which were discussed in advance with NICE and the EAG. The reason for the two scenarios is that at some time points there were Health States (HS) in which there were no transition data for patients, as no patient providing data was in that HS, meaning that transition probabilities could not be generated. The company addressed this in the two scenario analyses as now detailed. Further information on these scenarios can be found in the company's response to the Committee's request.[3] The EAG believes that the company has correctly implemented its intended analyses.

Committee Scenario 1.
The company used the observed transitions from the EASE study but where there were no data at a particular time point it assumed that patients had an equal chance of moving to any of the HSs.

Committee Scenario 2.
The company used the state occupancy within the EASE study at day 450 and day 810 and interpolated state occupancy for cycles between these time points.

The results generated by the company are shown in Table 1. The ICERs from the Committee scenarios are noticeably lower than both the EAG's base case and the company's base case; the reasons for these differences are discussed in Section 3.

Table 1: The ICERs generated by the company

	Costs BBE (£)	QALYs BBE	Costs CCM (£)	QALYs CCM	Inc Costs (£)	Inc QALYs	ICER (£)
EAG's base case	1,327,662	53.20	1,029,709	51.88	297,954	1.32	225,781
Company's base case	1,279,800	53.46	1,061,671	50.74	218,129	2.72	80,199
Committee's Scenario 1	1,183,662	54.94	1,029,709	51.88	153,954	3.06	50,291
Committee's Scenario 2	1,119,478	55.59	1,029,709	51.88	89,769	3.71	24,186

BBE – birch bark extract; CCM – current clinical management; QALYs – quality-adjusted life years; Inc – incremental; ICER – incremental cost-effectiveness ratio

3 The advantages and disadvantages of each of the four scenarios

This section details the EAG's view of the advantages and disadvantages of each scenario when compared with the other scenarios.

2.1 The EAG's base case

Advantages:

The EAG's base case has the advantage that it uses data from a time point where there was a large proportion of patients providing data, meaning that the aggregate data are likely to be robust. This is detailed in Section 4. As noted in Section 4 there is also evidence to suggest that there could be a steady state between day 60 and day 90 as assumed in the EAG's base case.

Disadvantages:

If a steady state occurs later than day 90 and BBE continues to provide an improvement in a patient's HS, the EAG's base case would be unfavourable to BBE.

2.2 The company's base case

Advantages:

None compared with other scenarios.

Disadvantages:

The company's base case assumed an approximation method to estimate transition probabilities which resulted in the HS occupancy within the model being discrepant with the observed data. Patients who discontinued BBE treatment were assumed to remain in the HS that they were in before discontinuing BBE, meaning that on average, patients who had discontinued BBE a number of years previously and had been receiving current clinical management (CCM) were in better HSs than those who never received BBE.

2.3 Committee Scenario 1

Advantages:

This scenario uses longer-term data on BBE and assumes that a steady state occurs at day 810 as requested by the Committee. When no data are available for a particular HS, transition probabilities assume a continuity correction where transition to all HS was possible.

Disadvantages:

There was a marked increase in the number of patients who did not provide data at later time points, and as detailed in Section 4, this may be due to informative censoring. Where there were no data from the EASE study at a particular time point the company assumed that patients had an equal chance of moving to any of the HSs. This may be favourable to BBE as the HSs without data are the most severe and data within the EASE study showed that a patient in a severe HS was more likely to remain in a severe HS, for example HS5 or HS6, than transition to a less severe HS, for example HS1 or HS2.

2.4 Committee Scenario 2

Advantages:

This scenario uses longer-term data on BBE and assumes that a steady state occurs at day 810 as requested by the Committee. State occupancy levels were set to the observed EASE values at day 450 and day 810 with the value for interim cycles interpolated to assume a linear change.

Disadvantages:

There was a marked increase in the number of patients who did not provide data at later time points, and as detailed in Section 4, this may be due to informative censoring.

4 The drivers of the differences in the ICERs between the four scenarios

4.1 *Costs per annum and utility data by HS*

As presented in Figure 1, the costs and utilities change markedly by HS, with an increase in cost between HS1 and HS6 of £111,845 per annum and a decrease in utility of 0.49. Therefore, state occupancy will be a large driver of cost-effectiveness.

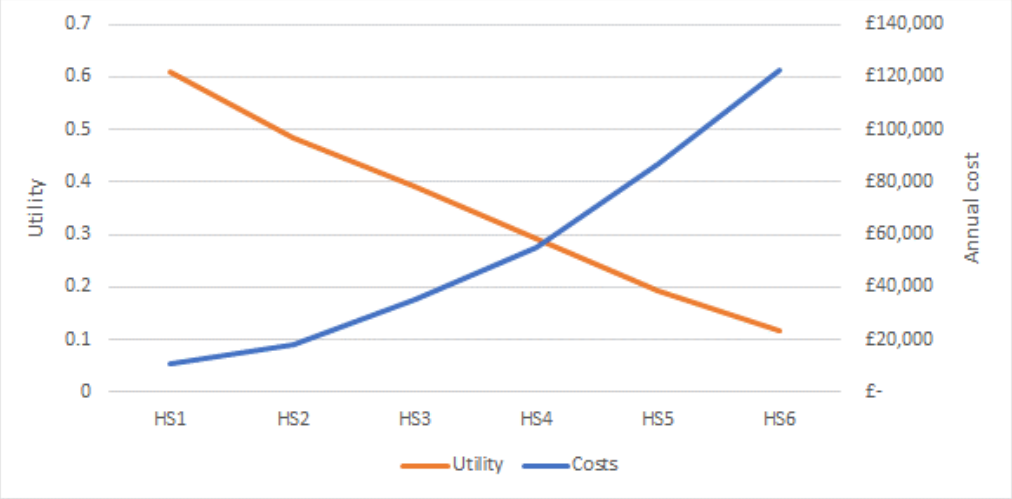

Figure 1: Costs and QALYs associated with each HS

4.2 Assumed HS occupancy

The EAG has generated the proportions of patients in each HS for patients receiving BBE, shown in Figure 2 and the proportions of patients in each HS for patients receiving CCM, shown in Figure 3. These proportions have been calculated for the entire cohort and therefore the number receiving BBE and the number receiving CCM sum to unity for each scenario. There are more discontinuations in the Committee Scenario 1 and 2 as discontinuations continue until day 810.

Figure 2: Distribution of patients receiving BBE by HS at day 810

Figure 3: Distribution of patients receiving CCM by HS at day 810

Figure 2 shows that in Committee Scenario 1 and 2 the proportions of patients receiving BBE that are in the less severe HSs are much higher than in the EAG's or company's base case. For example, the proportion of patients in HS1 and HS2 are [redacted]% in Committee Scenario 1 and [redacted]% in Committee Scenario 2 but only [redacted]% in the EAG's base case and [redacted]% in the company's base case. The proportion of patients in the more severe HSs (HS5 and HS6) also differ, being [redacted]% in the EAG's base case, [redacted]% in the company's base case, [redacted]% in Committee Scenario 1 and [redacted]% in Committee Scenario 2.

Figure 3 shows that within the CCM group the proportions amongst the HSs are similar for the EAG's base case, Committee Scenario 1 and Committee Scenario 2, (although there are more discontinuations

in Committee Scenario1 and Committee Scenario 2) but are markedly different in the company's base case. This is due to the assumption in the company's base case that patients discontinuing BBE remain in the HS from which they discontinued, whereas the other scenarios apportion patients according to the steady state distribution of CCM.

4.3 Observed HS occupancy from the EASE study

The observed distributions within the EASE study of patients in the BBE arm by HS by time point are shown in Figure 4. The EAG highlights that the distributions are relatively similar between day 60 and day 90 although it is plausible that patients are improving at day 90 as the distribution is more favourable at day 90 than at day 60. The EAG also highlights the reduced number of patients contributing to the distributions at later time points, with approximately [redacted] patients providing data for the first 90 days and [redacted] patients providing data at day 450 and [redacted] patients providing data at day 810. If this represents informative censoring, for example, that the severity of a patient's HS may directly influence whether a patient participated in a clinical assessment to provide relevant data, then the data at day 450 and day 810 may be biased in favour of BBE. We henceforth refer to patients who did not provide relevant data at a fixed time point as 'missing patients'.

Figure 4: Observed HS occupancy in the EASE study

4.4 Investigating the possibility of informative censoring.

The EAG used data provided by the company from the EASE study to explore whether the increased number of missing patients at later time points could be due to informative censoring. A summary of the proportions of patients missing patients conditional on time point and on HS is provided in Table 2. These values have been calculated for each HS by subtracting the division of the number of people with data at the later time point by the number of people with data at the earlier time point from unity. For

example, if there were 30 people in HS2 at day 30 and only 20 people starting in HS2 had data from day 30 to day 60 this would equate to a 33% missing patients proportion, calculated as 1- (20/30).

Table 2: The proportions of missing patients in the EASE study based on time point and HS

	HS1	HS2	HS3	HS4	HS5	HS6
Day 30 to day 60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 60 to day 90	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 90 to day 450	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Day 450 to day 810	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*See main text for further information

Table 2 shows that during the randomised controlled period of EASE (up to day 90) the proportions of missing patients is low with no clear pattern. Negative numbers have been generated which indicates that more people were assumed to start in a particular HS at a certain time (for example day 60) than ended in that HS in the previous period, for example, day 60 to day 90. This can be seen in Figure 4 where the number of patients was [redacted] at day 60 and [redacted] at day 90.

As the data move to the open-label period, the proportions of missing patients increase noticeably, with a potential pattern in that higher proportions of missing patients occur in the more severe health states. For example, between day 450 and day 810, the proportions of missing patients in HS1 to HS4 was below [redacted], whilst the proportion of missing patients was [redacted]% in both HS5 and HS6. Between day 90 and day 450, the missing patients proportion was highest in HS5 and [redacted]

.

This pattern indicates potentially informative censoring with higher values for missing patients in the more severe health states (HS5 and HS6). If this were correct this would mean that the observed distributions are favourable for BBE with a higher proportion of patients with lower disease severity being observed than is truly the case.

5 Crude analyses undertaken by the EAG to explore the impact of potentially informative censoring

The EAG undertook an analysis using Committee Scenario 2 exploring the impact of potentially informative censoring. Committee Scenario 2 was used as the EAG could more easily overwrite the state occupancy values, although the EAG would expect similar ICERs were Committee Scenario 1 used. It was assumed that known missing patients in HS5 and HS6 were assumed to be in HS5 or HS6 at day 810 with the number of patients in HS1 to HS4 unchanged at day 810 – this scenario is denoted EAG1. Based on the observed EASE transition probabilities this would result in an additional [redacted] patients in HS5 and [redacted] extra patient in HS6. In EAG1, these were added to the number of patients in HS5 and HS6 at day 810 in Committee Scenario 2, [redacted] and [redacted] respectively, resulting in [redacted] people in HS5 and [redacted] people in HS6. EAG 2 assumes that that missing patients in HS5 and HS6 are included in the observed state occupancy levels at day 810, resulting in [redacted] people in HS5 and [redacted] people in HS6 at day 810. In both EAG1 and EAG2, the proportion of patients who had discontinued BBE were assumed to remain constant for simplicity. No adjustments were made for missing patients in HS1 to HS4 and the uncertainty and direction of change in the ICER of this omission is unknown.

The distributions between HS at day 810 used in Committee Scenario 2 and in the EAG's exploratory analyses for people with RDEB, DDEB and JEB are shown in Table 3. The relative changes in patients with RDEB-S are similar to those shown in Table 3.

Table 3: The distributions between HS at day 810 in Committee Scenario 2 and in the EAG's exploratory analyses

HS	Committee Scenario 2	EAG 1	EAG 2
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
6	[redacted]	[redacted]	[redacted]

Distributions are of the entire cohort. The remaining [redacted] patients have discontinued treatment

In EAG1, the ICER increased to £144,183 from the Committee Scenario 2 value of £24,186; in EAG2, the ICER increased to £52,082. This indicates the possible impact on the ICER of informative censoring assuming that patients continue to receive BBE. If missing patients also discontinue BBE treatment then the ICER would be expected to be close to the £24,186 value.

6 Conclusion

The Committee's request resulted in the company implementing two methods that gave much lower ICERs (£24,186 and £50,291) than seen previously as the company's base case ICER was £80,199 and the EAG's base case ICER was £225,781.

The EAG has concerns, however, that the observed data may be subject to informative censoring with those patients receiving BBE who are in the more severe HS more likely to be missing patients than those in better HSs. This biases the ICER in favour of BBE although the magnitude of the bias is unknown and will be largely affected on whether missing patients are continuing with BBE treatment, and therefore incurring the costs of treatment, or whether these people have discontinued BBE treatment. If patients are continuing on BBE treatment then the acquisition costs of BBE would be incurred along with a possible benefit; if patients have discontinued BBE treatment than the anticipated incremental costs and QALYs would be similar to patients receiving CCM. Without further data on what happened to missing patients, the EAG is unable to provide a precise estimate of the ICER. However, the EAG has undertaken crude analyses based on Committee Scenario 2 assuming that missing patients in HS5 and HS6 remain on BBE treatment and in HS5 and HS6. The ICER for these analyses ranged between £52,082 and £144,183 dependent on the additional number of patients added to HS5 and HS6 at day 810. The EAG does not know whether the more pessimistic EAG1 or more optimistic EAG2 is more likely to be correct.

The analyses undertaken by the EAG to address informative censoring are simplistic. More formal methods to address this problem typical involve the use of inverse probability weighting[4] although such approaches could not be undertaken by the EAG within the timescales of the appraisal.

Whilst the ICERs generated in EAG1 and EAG2 may be plausible, the ICER could be considerable higher if steady state had been reached at day 90 and changes in the distribution across HSs beyond that point is caused solely by a reduced number of patients and informative censoring. In this case, the ICER would be that generated in the EAG base case which is £225,781. If further data were available at a time point between day 90 and day 450 this could support or refute the assumption that steady state had been reached at day 90.

7 References

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Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa. A Single Technology Appraisal.
EAG additional analysis post NICE Appraisal Consultation Document

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The author has a conflict of interest to declare.

1 Introduction

This document should be read in conjunction with an addendum produced by ScHARR following the NICE HST meeting held in June 2023.[1] Within this document a scenario (EAG1) was produced which generated an ICER of £144,183.

NICE requested that the EAG recalculate the ICER for EAG1 following a change in PAS. For previous calculations, a price reduction of [redacted]% in the cost of BBE was assumed, however this has since been increased to [redacted]%.

2 The analysis run by the EAG

The EAG has repeated the EAG1 scenario at the new price for BBE. These results are shown in Table 1.

Table 1: The results generated by EAG1 using the new PAS.

	Costs BBE (£)	QALYs BBE	Costs CCM (£)	QALYs CCM	Inc Costs (£)	Inc QALYs	ICER (£)
EAG1	[redacted]	53.73	1,029,709	51.88	[redacted]	1.85	[redacted]

BBE – birch bark extract; CCM – current clinical management; QALYs – quality-adjusted life years; Inc – incremental; ICER – incremental cost-effectiveness ratio

[1] Stevenson M, Ren S. Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa. A Single Technology Appraisal. EAG additional analysis post NICE Appraisal Consultation Document. July 2023.