

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

[Access the **final scope** and **final stakeholder list** on the NICE website.](#)

- 1. Company submission from Krystal Biotech:**
 - a. Full submission
 - b. Summary of Information for Patients (SIP)
- 2. Clarification questions and company responses**
 - a. Clarification response b15
 - b. Clarification response b15 update
- 3. Patient group, professional group, and NHS organisation submissions from:**
 - a. Cure EB
 - b. Debra UK
 - c. British Association of Dermatologists
- 4. External Assessment Report** prepared by School of Health and Related Research (SchARR)
- 5. External Assessment Report – factual accuracy check**
- 6. Technical engagement response from company**
 - a. Technical engagement appendix
 - b. SEE report
- 7. Technical engagement responses and statements from experts:**
 - a. Dr Anna Martinez and Professor Jemima Mellerio, consultant dermatologists – clinical experts, nominated by British Association of Dermatologists and Cure EB
 - b. Claire Mather, director of member services – patient expert, nominated by DEBRA UK
 - c. Sohana Collins – patient expert, nominated by Cure EB
 - d. Natasha Hersham – patient expert, nominated by Cure EB
- 8. Technical engagement responses from stakeholders:**
 - a. British Association of Dermatologists
 - b. Chiesi Ltd
 - c. NHS England

9. **External Assessment Report critique of company response to technical engagement** prepared by School of Health and Related Research (SchARR)
10. **Managed access committee briefing**

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**

Single technology appraisal

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

Company evidence submission

April 2025

File name	Version	Contains confidential information	Date
		Yes	

Contents

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE	1
Single technology appraisal	1
Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]	1
Company evidence submission.....	1
List of figures	5
List of tables	6
Abbreviations	9
1 Decision problem, description of the technology and clinical care pathway	11
1.1 Decision problem	11
1.2 Description of the technology being evaluated.....	14
1.3 Health condition and position of the technology in the treatment pathway	16
1.3.1 Disease overview	18
1.3.2 Clinical presentation and disease.....	19
1.3.3 Disease inheritance and severity	20
1.3.4 Epidemiology of DEB in the UK.....	21
1.3.5 Burden of disease	21
1.3.6 Clinical pathway of care	33
1.4 Equality considerations	39
2 Clinical effectiveness.....	40
2.1 Identification and selection of relevant studies.....	40
2.2 List of relevant clinical effectiveness evidence.....	40
2.3 Summary of methodology of the relevant clinical effectiveness evidence..	42
2.3.1 Summary of study design and methodology	42
2.3.2 GEM-3 study design and methodology	49
2.3.3 GEM-1 study design and methodology	52
2.3.4 EASE study design and methodology.....	55
2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence	57
2.4.1 GEM-3 overview.....	57
2.4.2 GEM-1 overview.....	59
2.4.3 EASE overview.....	60
2.5 Critical appraisal of the relevant clinical effectiveness evidence	61
2.6 Clinical efficacy results of the relevant studies.....	63
2.6.1 GEM-3 clinical efficacy results	64
2.6.2 GEM-1 clinical efficacy results	67
2.6.3 EASE: clinical efficacy results	72
2.6.4 Subsequent treatments used in the relevant studies	74
2.7 Subgroup analysis	74
2.8 Meta-analysis.....	75
2.9 Indirect and mixed treatment comparisons	75

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

2.9.1	Uncertainties in the indirect and mixed treatment comparisons	78
2.10	Adverse reactions	78
2.10.1	GEM-3 safety findings	78
2.10.2	GEM-1 safety findings	79
2.10.3	GEM-3 OLE safety findings	80
2.10.4	EASE safety findings	82
2.10.5	EASE OLP safety findings	83
2.11	Ongoing studies	83
2.12	Interpretation of clinical effectiveness and safety evidence	83
3	Cost-effectiveness	85
3.1	Published cost-effectiveness studies	85
3.2	Economic analysis	86
3.2.1	Patient population	87
3.2.2	Model structure	89
3.2.3	Intervention technology and comparators	102
3.3	Clinical parameters and variables	104
3.3.1	Replication of birch bark extract model as described in HST28	104
3.3.2	Transition probabilities	110
3.3.3	Natural History	115
3.3.4	Clinical manifestations	115
3.3.5	Mortality	117
3.3.6	B-VEC discontinuation	119
3.3.7	Birch bark extract discontinuation	119
3.4	Measurement and valuation of health effects	120
3.4.1	Health-related quality-of-life data from clinical trials	120
3.4.2	Mapping	121
3.4.3	Health-related quality-of-life studies	121
3.4.4	Adverse reactions	122
3.4.5	Health-related quality-of-life data used in the cost-effectiveness analysis	122
3.5	Cost and healthcare resource use identification, measurement and valuation	125
3.5.1	Cost and healthcare resource use identified in the SLR	126
3.5.2	Intervention and comparators' costs and resource use	126
3.5.3	Concomitant medication costs	128
3.5.4	Clinical manifestation costs	130
3.5.5	Health-state unit costs and resource use	131
3.5.6	Adverse reaction unit costs and resource use	132
3.5.7	Miscellaneous unit costs and resource use	132
3.6	Severity	133
3.7	Uncertainty	134
3.8	Managed access proposal	134
3.9	Summary of base-case analysis inputs and assumptions	134

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

3.9.1	Summary of base-case analysis inputs.....	134
3.9.2	Assumptions	136
3.10	Base-case incremental cost-effectiveness analysis results	137
3.10.1	Cost-effectiveness results	137
3.11	Sensitivity analyses.....	138
3.11.1	Probabilistic sensitivity analysis	138
3.11.2	Deterministic sensitivity analysis.....	141
3.11.3	Scenario analysis	143
3.12	Subgroup analysis	146
3.13	Validation	146
3.14	Interpretation and conclusions of economic evidence.....	146
	References.....	149

List of figures

Figure 1.1: Absent or reduced COL7 disrupts dermal–epidermal adhesion	18
Figure 1.2: Skin fragility and blistering observed in people with DEB	20
Figure 1.3: Tumorigenesis in EB due to blistered and chronically inflamed skin	25
Figure 1.4: Patient-reported and carer-reported complications in people with EB....	28
Figure 1.5: Impact of epidermolysis bullosa on life decisions of carers	31
Figure 1.6: Impact of epidermolysis bullosa on life decisions of people with the condition	32
Figure 1.7: Importance of needs for people with DEB	36
Figure 1.8: Mechanism of action of B-VEC	37
Figure 1.9: Anticipated clinical pathway of care for patients with DEB in the UK	38
Figure 2.1: Overview of the phase 3 GEM-3 study design	49
Figure 2.2: Overview of the phase 1 and phase 2 GEM-1 study design	53
Figure 2.3: Study design of EASE (NCT03068780)	56
Figure 2.4: Wound closure in patients with RDEB following topical B-VEC or placebo	68
Figure 2.5: Molecular correction of COL7 and anchoring fibrils after topical B-VEC therapy	71
Figure 2.6: Proportion of patients with first complete closure of EB wound by visit..	72
Figure 2.7: Evaluation of itch using the Itch Man Scale in patients ≥ 4 –13 years	73
Figure 2.8: Subgroup analyses for complete wound closure at 6 months in GEM-3	74
Figure 2.9: Subgroup analyses of the primary efficacy endpoint in EASE.....	75
Figure 3.1: Model design.....	90
Figure 3.2: Probability of survival among patients with EB according to age and EB type	118
Figure 3.3: Mortality by health state and age adopted in the model	119
Figure 3.4: Distribution of results of PSA simulations in the cost-effectiveness plane for the comparison to BSC	139
Figure 3.5: Distribution of results of PSA simulations in the cost-effectiveness plane for the comparison to BBE	139
Figure 3.6: Cost-effectiveness acceptability curve for the comparison to BSC	141
Figure 3.7: Cost-effectiveness acceptability curve for the comparison to BBE.....	141
Figure 3.8: Results of the one-way sensitivity analysis for the comparison to BSC	142
Figure 3.9: Results of the one-way sensitivity analysis for the comparison to BBE	143

List of tables

Table 1.1: The decision problem	12
Table 1.2: Technology being evaluated.....	14
Table 1.3: Characteristics of wounds in DEB	22
Table 1.4: Frequency of signs/symptoms in severe DEB	22
Table 1.5: Devastating multiorgan complications of severe DEB	23
Table 1.6: Impact of DEB on daily activities of people with the condition, DEBRA study.....	29
Table 1.7: Mean daily time spent on activities of daily living among patients with DEB and their carers, DEBRA study	32
Table 2.1: Clinical effectiveness evidence: GEM-3 and GEM-1	40
Table 2.2: Clinical effectiveness evidence: EASE	41
Table 2.3: Summary of methodology for randomised controlled trials – GEM-3	42
Table 2.4: Summary of methodology for randomised controlled trials – GEM-1	44
Table 2.5: Summary of methodology for randomised controlled trials – EASE	47
Table 2.6: GEM-3: Demographic and baseline characteristics (ITT population)	50
Table 2.7: Summary of eligibility criteria and treatment randomisation for GEM-1 ...	54
Table 2.8: GEM-1: Demographic and baseline characteristics (safety and ITT populations).....	54
Table 2.9: Analysis of primary and secondary endpoints in GEM-3	58
Table 2.10: Analysis of primary and secondary endpoints in GEM-1	59
Table 2.11: Statistical analysis summary for the EASE trial	61
Table 2.12: Quality assessment results for GEM-3	62
Table 2.13: Quality assessment results for GEM-1	62
Table 2.14: Quality assessment results for EASE	63
Table 2.15: GEM-3: Primary and key secondary endpoint analyses (imputed data)	64
Table 2.16: GEM-3: Supplementary analyses for durability of wound closure (imputed data)	65
Table 2.17: GEM-3: Secondary endpoint analysis for pain severity during wound dressing changes	66
Table 2.18: GEM-1: Primary endpoint analysis for wound closure (observed data)	69
Table 2.19: GEM-1: Primary endpoint analysis for time to and durability of wound closure (observed data).....	70
Table 2.20: GEM-3: Summary of AEs	78
Table 2.21: GEM-1: Summary of AEs	79
Table 2.22: GEM-3 OLE: Summary of AEs	80
Table 2.23: GEM-3 OLE: AEs reported for at least 5% of patients by system organ class and preferred term (safety population)	81
Table 2.24: EASE: summary of AEs.....	82
Table 3.1: Summary list of published cost-effectiveness studies	86
Table 3.2: Baseline distribution and characteristics of patients in GEM-3 according to age subgroups	88
Table 3.3: Features of the economic analysis	91
Table 3.4: Data sources used in the patient-level simulation to estimate transitions between health states	92
Table 3.5: Number of wounds per health state at risk of reopening	94
Table 3.6: Definitions of model health states according to UK clinical experts.....	100

Table 3.7: Distribution of the cohort at baseline across the health states according to Bruckner <i>et al.</i> (2020).....	101
Table 3.8: Distribution of the cohort at baseline across the health states according to the Bruckner population	102
Table 3.9: BBE model inputs.....	106
Table 3.10: Conversion from health states used in the BBE NICE submission to B-VEC health states	107
Table 3.11: BBE model inputs (mapped to four health states)	107
Table 3.12: BBE transition probabilities from HST28, mapped to four health states	108
Table 3.13: BSC transition probabilities from HST28, mapped to four health states	108
Table 3.14: Comparison of current model base case settings to settings used to replicate BBE Company Submission model	109
Table 3.15: Comparison of model results from reproducing BBE model within current CEM	110
Table 3.16: B-VEC transition probabilities based on simulated data	111
Table 3.17: BSC transition probabilities based on simulated data	113
Table 3.18: Clinical manifestations of DDEB by disease severity	115
Table 3.19: Per-cycle probability of developing reversible clinical manifestations by health state.....	117
Table 3.20: Per-cycle rate of developing irreversible clinical manifestations by health state	117
Table 3.21: Sources of mortality according to health state, DEB subtype, and model start age	118
Table 3.22: HRQoL according to the different approaches	123
Table 3.23: BBE NICE submission utility values	124
Table 3.24: Utility values by B-VEC model health state based on the BBE NICE submission	124
Table 3.25: Base case carers' utility values.....	125
Table 3.26: Number of B-VEC vials used per cycle by health state, by year and by age subgroup according to the patient-level simulation.....	128
Table 3.27: B-VEC cost per cycle (£) by health state, by year and by age subgroup	128
Table 3.28: Percentage of patients using concomitant medication per health state	130
Table 3.29: Clinical manifestations costs	131
Table 3.30: Outpatient costs by health state (per cycle).....	132
Table 3.31: Dressing and formal care costs by health state	132
Table 3.32: Absolute and proportional QALY shortfall threshold values for disease severity and the respective inferred willingness to pay threshold	133
Table 3.33: Absolute and proportional QALY shortfall threshold values for disease severity and the respective inferred willingness to pay threshold	134
Table 3.34: Summary of variables applied in the economic model	134
Table 3.35: Assumptions and justifications for model inputs	136
Table 3.36: Base-case results.....	138
Table 3.37: Results of base case incremental cost-effectiveness analysis	138
Table 3.38: Comparison of the base case and PSA results – comparison to BSC	140
Table 3.39: Comparison of the base case and PSA results – comparison to BBE.	140

Table 3.40: Percentage change in base case results of comparison to BSC following lower and upper variation in the 10 most influential model parameters	142
Table 3.41: Percentage change in base case results of the comparison to BBE following lower and upper variation in the 10 most influential model parameters ...	143
Table 3.42: Scenario analyses explored	144
Table 3.43: Results of the scenario analysis	145

Abbreviations

Term	Definition
AE	adverse event
AIC	akaike information criterion
AMED	allied and complementary medicine database
BBE	birch bark extract
BIC	bayesian information criterion
BIM	budget impact model
BNF	British National Formulary
BSA	body surface area
BSC	best supportive care
B-VEC	beremagene geperpavec
CE	cost-effectiveness
CEM	cost effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
COL7A1	collagen type VII alpha 1 chain
DALYs	disability-adjusted life years
DBP	double blind period
DDEB	dominant dystrophic epidermolysis bullosa
DEB	dystrophic epidermolysis bullosa
EAG	evidence assessment group
EB	epidermolysis bullosa
EBDASI	Epidermolysis Bullosa Disease Activity and Scarring Index
EMA	European Medicines Agency
EQ-5D	EuroQol 5-Dimensions
EQ-5D-Y	EuroQol 5-Dimensions Youth
EU	European Union
FDA	Food and Drug Administration
FLACC-R	Faces, Legs, Activity, Cry, Consolability Revised
QOLEB	Epidermolysis Bullosa Quality of Life Instrument
HCRU	healthcare resource use
HRQoL	health-related quality of life
HST	Highly Specialised Technology
HSV-1	herpes simplex virus type 1
ICER	incremental cost-effectiveness ratio
IGA	investigator global assessment analysis
ITC	indirect treatment comparison
ITT	intent to treat
iscorEB	Instrument for Scoring Clinical Outcomes of Research for Epidermolysis Bullosa
JEB	junctional epidermolysis bullosa
KEB	Kindler epidermolysis bullosa
LYs	life years
mITT	modified intent-to-treat
NA	not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	net monetary benefit
OLE	open label extension
OR	odds ratio
PASS	post-authorisation safety study
PFU	plaque-forming unit
PICOS	Population, Intervention, Comparator, Outcome, Study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
RCT	randomised controlled trial
RDEB	recessive dystrophic epidermolysis bullosa
SCC	squamous cell carcinoma
SD	standard deviation

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Term	Definition
Skindex-29	29-Item Skindex instrument
SLR	systematic literature review
SmPC	summary of product characteristics
SMC	Scottish Medicines Consortium
SoC	standard of care
SSRI	selective serotonin reuptake inhibitors
TCA	tricyclic depressants
TEAE	treatment-emergent adverse event
TGF- β	transforming growth factor- β
TP53	tumour suppressor gene p53
TSP1	thrombospondin 1
TTO	time trade-off
US	United States
VAS	visual analog scale
WHO	World Health Organization
WTP	Willingness to pay
YHEC	York Health Economics Consortium

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

1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. Table 1.1 summarises the statement of the decision problem.

Table 1.1: 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 with dystrophic epidermolysis bullosa	As per final scope issued by NICE	NA
Intervention	Beremagene geperpavec	Vyjuvek® (beremagene geperpavec [B-VEC])	Throughout this submission, the intervention is abbreviated to B-VEC.
Comparator(s)	- Established clinical management without B-VEC (including, but not limited to, treatments that can help ease and control infections, pain, and other aspects of epidermolysis bullosa) - BBE (NICE final scope issued in February 2025) [ID3959])	As recommended by NICE, comparisons were made with B-VEC and BSC, and B-VEC with Filsuvez® (BBE) gel.	- Comparators align with the recommendations from NICE. - There was substantial heterogeneity between studies for B-VEC and BBE in terms of study design and patient population that would likely bias results and cannot be corrected for through an ITC approach. In particular, frequency of the application of placebo treatment differed between trials (which precludes the use of the placebo arms as a common comparator), and concomitant topical medications were permitted in at least one BBE study. This is further described in Section 2.9.
Outcomes	The outcome measures to be considered include: - Proportion of complete wound closure - Time to wound closure - Duration of wound closure - Percentage of BSA with wounds - Pain - Change in itching - Incidence of squamous cell carcinoma - Mortality - Adverse effects of treatment - Health-related quality of life	- Percentage of the surface area of wound healed - Change in total body wound burden - Time to wound closure - Duration of wound closure - Percentage of body surface area with wounds - Pain - Change in itching - Incidence of SCC - Mortality (surrogate) - Adverse effects of treatment - HRQoL	NICE suggested that "Percentage of the surface area of wound healed" and "change in total body wound burden" should be merged into a single outcome, "percentage of body surface area with wounds." The rationale for separating these outcomes is that the first outcome (interpreted as a change in wound size over time) is less relevant as the treatment aims to promote durable wound closure). The mortality outcome will be assessed through surrogate endpoints, given the long timeframe needed to collect direct evidence on mortality.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per	As per final scope issued by NICE.	NA

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	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 evidence allows, the following subgroups will be considered: • Dominant dystrophic epidermolysis bullosa (DDEB) • Recessive dystrophic epidermolysis bullosa (RDEB)	Aligning with the final scope issued by NICE, subgroup data are reported for: • Dominant dystrophic epidermolysis bullosa (DDEB), • Recessive dystrophic epidermolysis bullosa (RDEB), and additionally, • Paediatric patients with dystrophic epidermolysis bullosa, • Adult patients with dystrophic epidermolysis bullosa.	Given that B-VEC is indicated for all patients with DEB, starting at birth,¹ paediatric and adult patient subgroups should additionally be considered. Treatment of newborns can potentially prevent the devastating sequelae of DEB (such as fibrosis and scarring, deformities like mitten hands and feet, SCC, and reduce the risk for early mortality).
Special considerations including issues related to equity or equality	• Guidance will only be issued in accordance with the marketing authorisation. • Where the wording of the therapeutic indication does not include specific treatment	NA	NA

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.		
BBE=birch bark extract; BSA=body surface area; BSC=best supportive care; B-VEC=beremagene geperpavec; DDEB=dominant dystrophic epidermolysis bullosa; DEB=dystrophic epidermolysis bullosa; HRQoL=health-related quality of life; ITC=indirect treatment comparison; MHRA=Medicines and Healthcare products Regulatory Agency; NA=not applicable; NHS=National Health Service; NICE=National Institute for Health and Care Excellence; RDEB= recessive dystrophic epidermolysis bullosa; SCC=squamous cell carcinoma			

1.2 Description of the technology being evaluated

A summary of the product characteristics (SmPC) is shown in Appendix A.

Table 1.2 summarises beremagene geperpavec (B-VEC), the technology being evaluated.

Table 1.2: Technology being evaluated

UK approved name and brand name	Vyjuvek (beremagene geperpavec [B-VEC]) ¹
Mechanism of action	B-VEC is a gene therapy based on an engineered, replication-defective herpes simplex virus 1 (HSV-1) encoded with COL7A1 gene, addressing the underlying genetic cause of dystrophic epidermolysis bullosa. Upon cutaneous application to the wounds, beremagene geperpavec can transduce both keratinocytes and fibroblasts. Once in the nucleus, transcription of the encoded human COL7A1 is initiated. The resulting transcripts allow for production and secretion of COL7 by the cell in its mature form. These COL7 molecules arrange themselves into long, thin bundles that form anchoring fibrils. The anchoring fibrils hold the epidermis and dermis together and are essential for maintaining the integrity of the skin. DEB is caused by mutations in the <i>COL7A1</i> gene, which results in reduced or absent levels of biologically active COL7. Upon cutaneous application to the wounds, B-VEC can transduce both keratinocytes and fibroblasts. Following entry of B-VEC into the cells, the vector genome is deposited in the nucleus. Once in the nucleus, transcription of the encoded human <i>COL7A1</i> is initiated. The resulting transcripts allow for production and secretion of COL7 by the cell in its mature form. These COL7 molecules arrange themselves into long, thin bundles that form anchoring fibrils. The anchoring fibrils hold the epidermis and dermis together and are essential for maintaining the integrity of the skin.
Marketing authorisation/CE mark status	On 28 February 2025, B-VEC received a positive opinion from the EU CHMP for the treatment of patients from birth with DEB with mutation(s) in the <i>collagen type VII alpha-1-chain (COL7A1)</i> gene (defined in Section 1.3.1)² B-VEC was also approved by the FDA on 19 May 2023 “for the treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene.”³

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

UK approved name and brand name	Vyjuvek (beremagene geperpavec [B-VEC])¹
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	B-VEC is indicated for the treatment of wounds in patients with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene, from birth. Restrictions: Medicinal product subject to restricted medical prescription.
Method of administration and dosage	Preparation and administration: Treatment with B-VEC should be initiated by healthcare professionals experienced in the management of DEB patients. The recommended dose of B-VEC gel is based on age: • Patients above 3 years: maximum weekly dose of 4×10^9 PFU, with the total administration volume of 2 mL. • Patients from birth to 3 years: maximum weekly dose of 2×10^9 PFU, with the total administration volume of 1 mL). After mixing under aseptic conditions, B-VEC can be stored for 7 days at 2 to 8°C. Anticipated interval between courses of treatment: B-VEC gel is applied cutaneously to wound(s) once a week. It may not be possible to apply B-VEC gel to all the wounds at each treatment visit. B-VEC is applied to wounds until they are closed before selecting new wound(s) to treat, and previously treated wounds if they re-open should be prioritised for weekly treatment. If a dose is missed, B-VEC gel should be administered as soon as possible, and weekly dosing should be resumed thereafter. Anticipated dose adjustments: The treatment volume applied may vary as the wounds decrease or increase in size.
Additional tests or investigations	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. Diagnostic tests include a skin biopsy and blood sampling from the child and family for mutation analysis.⁴ Given that B-VEC is indicated for the treatment of patients with mutations in the COL7A1 gene, genetic testing is required for initiation of treatment.
List price and average cost of a course of treatment	The list price is £21,500 per vial of B-VEC.
Patient access scheme (if applicable)	Not applicable.
B-VEC=beremagene geperpavec; CHMP=Committee for Medicinal Products for Human Use; COL7=type VII collagen; COL7A1=collagen type VII alpha 1 chain; DEB=dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; PFU=plaque-forming units Source: Krystal biotech (SmPC)¹	

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

Dystrophic epidermolysis bullosa (DEB)

- DEB is a rare, inherited, debilitating skin fragility disorder that can lead to lifelong complications, early mortality, and has a devastating impact on the patients' health-related quality of life (HRQoL).⁵⁻⁷
- DEB is characterised by marked skin fragility and manifests as painful blistering and scarring of the skin following minimal trauma and friction.⁷⁻¹⁰
- DEB is caused by mutations in the *COL7A1* gene encoding type VII collagen (COL7),^{10,11} and typically presents at birth or within the first year of life, with serious and potentially life-threatening disease manifestations accumulating over a person's lifetime.^{9,12,13}
- As a result of impaired COL7, persistent blistering, impaired wound closure, reblistering, and complications from extensive scarring lead to cumulative morbidities and long-term complications.^{9,14-17}
- DEB can lead to premature death, particularly in people with more severe forms of the disease who may die in their third or fourth decade, predominantly due to SCC.^{7,18}
- Pain, comorbidities and complications associated with DEB impact all aspects of daily life, leading to substantial decrements in HRQoL.⁵⁻⁷
- People with DEB experience a wide range of extracutaneous manifestations that interfere with daily functioning and require lifelong management.^{6,7}
- DEB leaves families and carers of people with DEB often experiencing chronic emotional and psychological distress.^{6,7,19,20}

Current treatment options and clinical pathway of care

- Current standard of care (SoC), which is limited to the management of symptoms and secondary complications, inadequately addresses DEB.^{6,21}
- Wound care for individuals with DEB is time-consuming, often requiring several hours a day and assistance from one or two carers.⁷ The burden intensifies with the severity of the disease, as wounds become increasingly painful, prone to infection, and require constant attention, including multiple dressing changes daily.^{6,7,22} This painful routine, which causes significant emotional distress, is compounded by the need to carefully handle dressings to avoid further skin damage, making it a distressing experience for patients and carers.^{6,8,23}
- There are no approved curative or NICE-recommended targeted corrective therapies for DEB.
- Birch bark extract (BBE) gel for cutaneous application is the first EB-specific treatment to receive marketing approval in the UK and Europe and received a positive recommendation from NICE, via Highly Specialised Technology (HST) evaluation, in September 2023 (HST28).²⁴ However, while BBE marked a much-needed shift in the treatment paradigm for patients with DEB as the first licensed and NICE recommended intervention for DEB and JEB, unmet need remains. For those who are treated, acceleration in wound closure may be experienced but a sustained effect on wound closure has not been demonstrated, and BBE does not offer a corrective mechanism of action.²⁵⁻²⁸

Unmet need

- DEB is a lifelong, debilitating disease that typically presents from a very young age, and has a profound impact on patients, their carers, and other family members.^{6,9,12,13,20}

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

- Patients with DEB experience a lot of pain and discomfort starting at birth or very early in life and can expect their lives to be substantially shortened.^{9,12,13}
- DEB can be life-changing for both patients and their carers, given that the high symptom and treatment burden can interfere with the ability to engage in normal activities such as attending school or working.^{6,7,19,20,22}
- Currently, BBE gel is the only treatment option available to patients with DEB; however, this therapy is not corrective or curative and has shown limited clinical efficacy.²⁷
- In the absence of a cure, the cornerstone of DEB management is wound care,²⁹ which places a high burden on patients and their carers.³⁰
- The substantial treatment burden, which can include multiple hours per day spent on wound care, can lead people with DEB and their carers to make difficult life decisions, such as deciding not to work, reducing their working hours, or dropping out of school.⁶
- People with DEB want to be healed of all skin alterations, free of itching and pain, and able to lead a normal everyday life.³¹
- In the NICE appraisal of BBE for treating epidermolysis bullosa (HST28), the NICE committee concluded that epidermolysis bullosa has extensive and severe effects on quality of life.²⁴
- Given the devastating impact of DEB on many aspects of life,^{8,19,20,31} there is a high unmet need for a targeted corrective therapy that reduces the number and severity of wounds and breaks the cyclical nature of wounding, closure, and reblistering, to prevent the debilitating and potentially life-threatening consequences of living with DEB.

B-VEC

- B-VEC is a replication-defective, herpes simplex virus 1 (HSV-1)–based, topical, redosable gene therapy designed to restore the structural stability of the skin for directly treated wounds.^{32,33}
- B-VEC addresses the root cause of DEB via delivery of the *COL7A1* gene and functional correction of COL7 expression.³²
- Repeated topical application of B-VEC results in full-length COL7 protein expression, normalised anchoring fibril formation, and durable and consistent wound closure.^{32,33}
- Treatment with B-VEC leads to significant improvement in the number of wounds with complete and durable closure (Section 2.6).
- B-VEC is anticipated to be the first topical and redosable gene therapy with marketing authorisation for the treatment of patients with DEB supported by data from two placebo-controlled trials.^{32,33}

Anticipated place of B-VEC in therapy

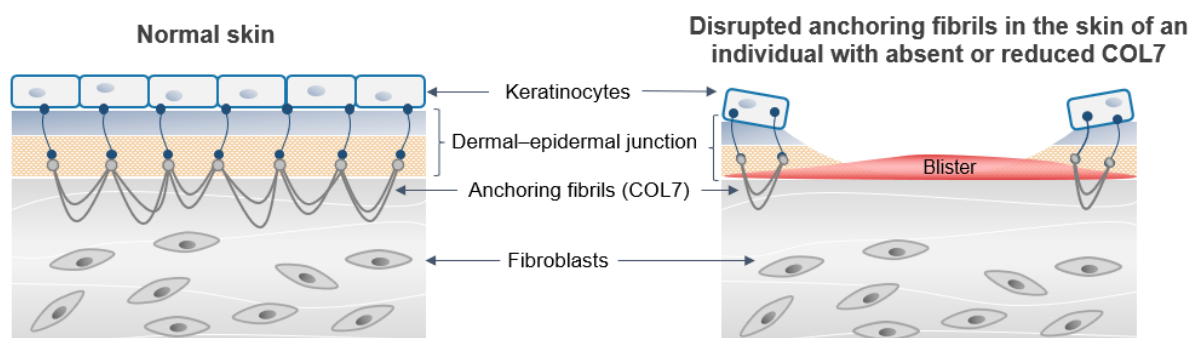
- Based on input from UK clinical experts with experience in DEB and the advantages that B-VEC provides in terms of durable and consistent wound closure, B-VEC is expected to be used in addition to supportive care measures to treat wounds in patients with RDEB and DDEB.

1.3.1 Disease overview

DEB is an inherited, debilitating, skin fragility disorder that is caused by mutations in the COL7A1 gene, leading to skin fragility, blistering and scarring following minimal trauma and friction.^{8,10,32}

Epidermolysis bullosa (EB) encompasses a group of disorders with skin fragility as a common feature.^{8,10} There are four subtypes of EB, with each subtype representing a distinctive disease, caused by unique and specific pathogenic gene variants and associated protein abnormalities, leading to a different plane of cleavage within the skin, and different clinical manifestations that necessitate different treatment approaches. Dystrophic epidermolysis bullosa (DEB), one of the subtypes of EB, is a lifelong, chronic, inherited skin fragility disorder.^{8,10,34} DEB is caused by mutations in the collagen type VII alpha 1 chain (*COL7A1*) gene encoding COL7, resulting in absent or abnormally formed anchoring fibrils at the basement membrane zone.^{10,14,35} Anchoring fibrils engage with collagen fibrils in the dermis to provide the foundational anchor between the epidermis, the outer layer of skin, and the underlying dermis.¹⁴ COL7 is the main component of anchoring fibrils, and approximately 30%–35% of normal COL7 is necessary to maintain adequate dermal–epidermal adhesion.^{36–38} Conditions such as DEB that are characterised by absent or reduced COL7 result in impaired dermal–epidermal adhesion, leading to skin fragility, spontaneous or minimal friction-induced blister formation, and subsequent scarring (Figure 1.1).^{14,39,40}

Figure 1.1: Absent or reduced COL7 disrupts dermal–epidermal adhesion



COL7=type VII collagen.

The skin is the body's primary defence barrier, protecting against desiccation (water loss), infection, and damage to internal structures.⁴¹ Damage to the skin initiates a rapid, efficient, and coordinated reparative response known as wound healing or closure.^{14,41} Disruption of the reparative process, as seen in DEB, can delay or prevent the closure of wounds, and result in scar formation.¹⁴ Wounds may remain unhealed for long periods and inflammation and scarring create an environment that

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

favours further tissue damage, potentially leading to highly disabling and potentially life-threatening disease complications.^{14,39,40} Skin fragility is a hallmark of DEB because of absent or reduced COL7. Skin and mucous membranes blister or shear away in response to minimal everyday friction and trauma. Repeated blistering leads to microbial colonisation, infection, and inflammation that result in an altered wound closure response, chronic wound development, and scar formation.^{14,35}

1.3.2 Clinical presentation and disease

DEB is characterised by marked skin fragility that causes painful blistering and scarring of the skin following minimal trauma and friction.⁷⁻¹⁰ Approximately 80% of people with DEB exhibit signs by the end of the first year of life,¹³ with continuous cycles of blistering, altered wound healing and reopening leading to serious complications that accumulate over a person's lifetime.^{9,12,13}

The hallmark of DEB is mechanical fragility of the skin that causes frequent blistering or erosions in response to minor trauma or friction of the skin surface.^{13,17} Acute or chronic wounds can occur at various body sites, especially in areas prone to friction, such as hands and feet, and, in severe forms of the disease, cover a substantial proportion of the body. Recurrent wounds heal but can easily blister again, while chronic wounds remain open for 8 weeks or longer. The mucosa and adnexal structures of the skin may also be affected, leading to involvement of intraoral soft tissue, dental abnormalities, nail dystrophy, and secondary alopecia.¹⁷ Additionally, corneal and eyelid erosions may lead to severe impairment of visual acuity.

Patients with DEB experience impaired wound healing or closure, and consequently, wounds can remain unhealed for long periods, leading to a high wound burden and making wound management complex.⁷ Continuous cycles of blistering and altered wound closure in the same area can lead to persistent ulcerations, and over time, to chronic ulcers accompanied by fibrosis and scarring.¹⁴ In severe forms, fibrosis that is caused by the chronic injury and inflammation can lead to joint contractures and webbing of fingers and toes and mitten deformities, which substantially limit joint function and mobility.^{14,17}

The presence of wounds, as well as the loss of collagen VII from secondary lymphoid organs are associated with an increase in bacterial colonisation and increased susceptibility to bacterial infections.¹⁷ The intermittent blistering, impaired wound closure with inflammation, high bacterial load, infections, and subsequent fibrosis of the skin create a microenvironment that promotes mutagenesis of keratinocytes, and facilitate the growth, progression, and metastasis of established squamous cell carcinomas.¹⁷

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

DEB typically presents at birth or within the first year of life, with serious and potentially life-threatening disease manifestations accumulating over a person's lifetime (Figure 1.2).^{9,12,13} Approximately 57%–71% of people with DEB exhibit signs at birth, while ~80% exhibit signs by the end of the first year of life.¹³ Delayed onset of symptoms into adolescence can be observed in people with a milder subtype.⁴² Skin fragility and blistering persist throughout life, leading to an accumulation of serious and potentially life-threatening disease complications requiring lifelong management.^{7,13,18}

Figure 1.2: Skin fragility and blistering observed in people with DEB



DEB=dystrophic epidermolysis bullosa.
Illustration adapted from: Wilkinson *et al.* (2020)⁴¹

1.3.3 Disease inheritance and severity

There are no DEB-specific, objective measures or scales available to assess disease severity. However, disease severity is related to the body surface area (BSA) that is affected by wounds: the larger the BSA that is affected by wounds, the greater the disease severity.²²

DEB is inherited in an autosomal dominant (DDEB) or autosomal recessive (RDEB) pattern. The recessive form tends to be more severe and is associated with a higher mortality rate,¹¹ but there is considerable phenotypic overlap between the major clinical subtypes.^{10,13} Severity may be assessed based on the distribution of clinical features (localised vs. generalised), cutaneous versus extracutaneous disease involvement and severity of this involvement.⁴³ However, there is currently no standardised measure for defining disease severity in DEB. Burden of disease studies often classify patients by severity, but mostly do so based on patient or carer perceptions. There are no objective measures or scales available specific to DEB. Available measures of the extent, impact, or severity of disease, specific to EB include:

- The EB Disease Activity and Scarring Index (EBDASI), a clinician-reported assessment of the extent of disease involvement (i.e., number of affected sites in the skin, scalp, mucous membrane, nail, and epithelialised surfaces) and extent of damage across affected areas.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

- The Instrument for Scoring Clinical Outcomes for Research of EB (iscorEB), a clinician-reported and patient-reported assessment of skin, mucosal, and internal organ involvement, laboratory abnormalities, complications/procedures, pain, itch, and impact on essential functions, daily activity, and mood.⁴⁴
- The Quality of Life in Epidermolysis Bullosa (QOLEB) questionnaire, a patient-reported EB-specific quality-of-life instrument validated in adults with EB. QOLEB contains 17 questions capturing the psychological and functional impact of the disease with respect to activities of daily living.

Disease severity is related to the body surface area (BSA) that is affected by wounds: the larger the BSA that is affected by wounds, the greater the clinical complications, symptoms, impairment, and, consequently, the disease severity.²² Hence BSA or the proportion of BSA affected by DEB wounds may be used as a proxy measure for disease severity.

1.3.4 Epidemiology of DEB in the UK

It is estimated that there are 617 prevalent patients with DEB in England.⁴⁵

Analysis of the National Health Service (NHS) EB service registry database revealed that, as of March 2021, there were 2,361 people in England and Wales living with EB.¹¹ DEB, which is caused by *COL7A1* gene mutations, has a prevalence of 10.7 per million (or 0.535 per 50,000) population and an incidence of 26.1 live births per million (or 1.305 per 50,000) population. Using these EB registry data, it is estimated there are 617 prevalent patients and 15 incident patients with DEB in England.⁴⁶

1.3.5 Burden of disease

1.3.5.1 Clinical burden

DEB is associated with a substantial clinical burden that starts at birth^{9,10} and progressively worsens over a patient's lifetime.^{7,9,13} People with DEB experience severe complications that can lead to devastating multiorgan consequences, including hand and foot deformities, oesophageal strictures, failure to thrive, blindness, increased risk of cutaneous SCC and premature death.^{7,9,13,47,48,49}

Wound closure in RDEB is hindered by chronic anaemia, delayed growth, and general weakness, with anaemia affecting severe cases due to

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

inflammation and iron loss. Growth impairment, starting early in life, is linked to high energy demands, poor food intake, and nutrient deficiencies, further complicating closure.^{48,49}

Persistent reblistering, closure, and scarring

People with DEB experience marked skin fragility, blistering, and scarring of the skin and mucous membranes.⁷⁻¹⁰ DEB is characterised by generalised skin blistering from birth.^{9,10} Healing of blisters is associated with milia formation, atrophic scarring, and nail dystrophy.⁹ Wounds associated with DEB are commonly categorised as either recurrent or chronic (Table 1.3).⁷

Table 1.3: Characteristics of wounds in DEB

Recurrent	Chronic
Tend to be small-to-medium in size (<7.5 cm diameter)	Tend to be larger (66.3 cm ² vs. 44.7 cm ² ; p<0.01) and more painful (4.31 vs. 3.59 out of 10; p=0.05) than recurrent wounds
Tend to heal (21% within 1 week; 75% within 1–3 weeks)	Tend to remain open for 8 weeks or longer
Blister easily	Sometimes never heal
DEB=dystrophic epidermolysis bullosa Source: Eng <i>et al.</i> (2021) ²² ; Tang <i>et al.</i> (2021) ⁷	

Blistering can also occur at mucous membranes:^{9,10,13}

- Oral involvement can lead to fusion of the tongue to the floor of the mouth (ankyloglossia) and progressive reduction in the size of the mouth (microstomia).
- Oesophageal blistering that recurs and causes erosions can lead to progressive difficulties swallowing (dysphagia) secondary to narrowing (stricture) of the oesophagus.

People with severe forms of DEB experience multiple, chronically open wounds, disfiguring complications, and devastating multiorgan consequences, many of which appear at an early age (Table 1.4 and Table 1.5).⁷⁻¹⁰ For instance, debilitating hand and foot deformities occur in 30% of people with severe DEB by age 2, and in all people (100%) by age 20.⁹ Oesophageal strictures occur in 10% of people with severe DEB by age 2, and in approximately 90% by age 35.^{7,9,13}

Table 1.4: Frequency of signs/symptoms in severe DEB

Sign/symptom	Frequency (%)
Generalised skin blistering at birth	100
Nail dystrophy and loss	100
Progressive scarring leading to debilitating hand and foot deformities (pseudosyndactyly)	13–71
Oral lesions	79–100
DEB=dystrophic epidermolysis bullosa	

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Table 1.5: Devastating multiorgan complications of severe DEB

Consequence	Frequency (%)
Oesophageal strictures	51–86
Corneal blisters or scarring	51–68
Leading to corneal complications (e.g., abrasion, pannus)	63–100
Anaemia	50–100
Ankyloglossia and microstomia contributing to impaired intake of nutrition	50–72
Impaired vision	40
Growth retardation	34
Failure to thrive	25–39
Blindness	6.5
DEB=dystrophic epidermolysis bullosa Source: Fine <i>et al.</i> (2004) ⁵⁰ ; Fine (2010) ⁹ ; Pfendner and Lucky (2018) ¹³ ; Tang <i>et al.</i> (2021) ⁷ ; Tong <i>et al.</i> (1999) ⁴⁷	

Persistent blistering, impaired wound closure, reblistering, and complications from extensive scarring create an environment that promotes bacterial infection.^{9,14,15,17} Such changes in the skin microenvironment, together with mutational changes in the tumour suppressor gene, *TP53*, and other cancer-related genes that drive tumour development following chronic exposure of damaged skin to ultraviolet radiation, can result in the development of aggressive epithelial cancers.⁵¹

Wound closure is further impeded by chronic anaemia, delayed growth, and general weakness. Anaemia is prevalent in severe DEB cases, affecting 68% of RDEB patients,⁴⁹ and is typically present in the first year of life.⁴⁸ This anaemia stems from chronic inflammation and iron loss due to extensive blistering and mucosal involvement, leading to reduced oxygen delivery to tissues and consequently hindering wound closure.^{48,49}

RDEB patients also show weight impairment, which may start at 12–18 months old.⁴⁸ Growth impairment is caused by increased energy demand, decreased intake due to oesophageal stenosis, tooth decay and pain, and impaired nutrient absorption.⁴⁸ Remer *et al.* (2020) showed that low weight in RDEB was significantly correlated with reduced levels of haemoglobin, iron, vitamin D, zinc, and albumin, along with elevated C-reactive protein and a lack of COL7.⁴⁸

Fatal consequences of bacterial infections

Bacterial infections can have fatal consequences in individuals with severe forms of DEB.^{9,15} Approximately 12% die of chronic renal failure due to poststreptococcal glomerulonephritis or renal amyloidosis. People with DEB have a 4.5% cumulative risk of developing potentially fatal dilated cardiomyopathy by age 20, of which 30% eventually die as a consequence.⁹

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

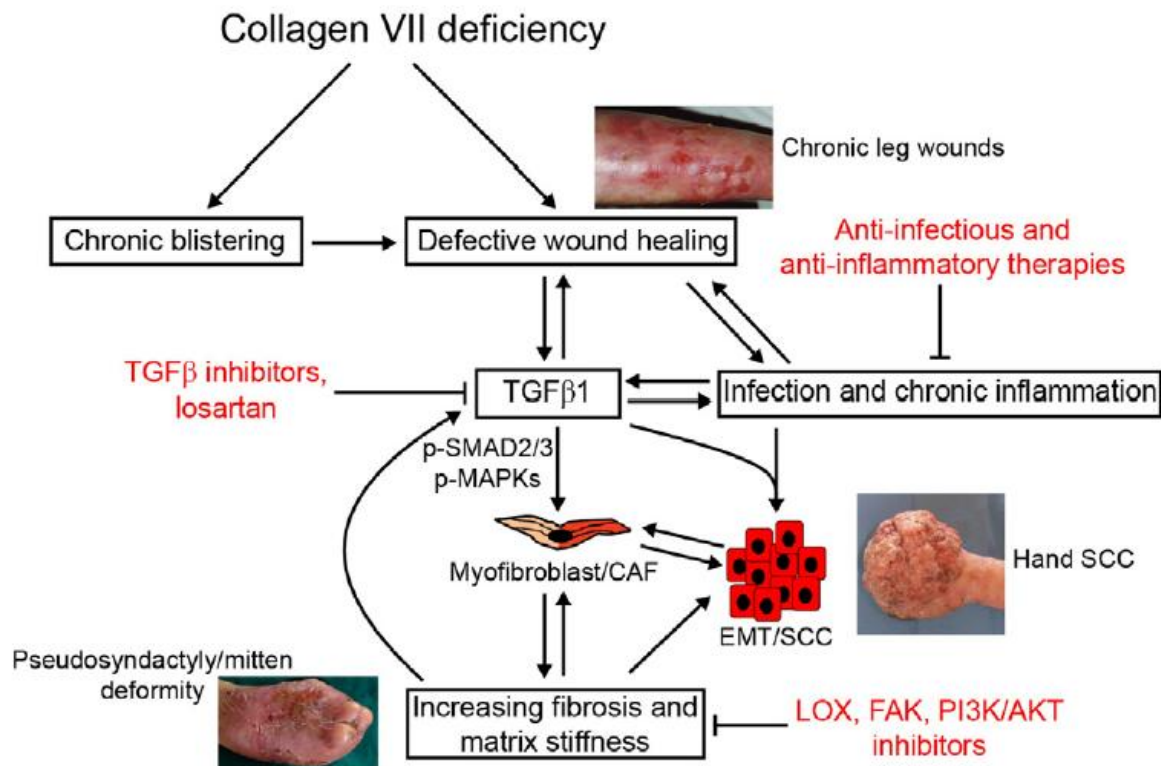
Squamous cell carcinoma as a frequent cause of premature death in DEB

People with DEB are at an increased risk of developing cutaneous SCC and regular monitoring is required from a young age. Rates of occurrence of SCC are 47% by age 65 in less severe forms of DEB and in excess of 90% by age 55 in more severe forms of DEB. SCC is more prevalent and clinically more aggressive in DEB than in the general population, which may be a direct consequence of COL7 deficits.^{9,39,52-55} As described in Section 1.3.1, mutations in the COL7A1 gene result in impaired skin integrity—leading to chronic blistering and defective wound closure.⁵⁵

Thrombospondin 1 (TSP1) induces transforming growth factor- β (TGF- β) signalling, which results in increasing fibrosis and matrix stiffness, and subsequently, SCC. COL7 binds TSP1 and prevents it from inducing downstream TGF- β signalling.^{54,55} On the other hand, loss of COL7 leads to upregulated TGF- β signalling, thus inducing fibrosis in the tumour-promoting dermal microenvironment of RDEB patients.⁵⁵

Although therapies to inhibit downstream events in SCC formation exist (e.g., TGF- β inhibitors; lipoxygenase [LOX] inhibitors), COL7 deficiency is upstream of the SCC cascade. Therefore, restoring COL7 function may prevent the downstream development of SCC. Restoring the function of COL7 may halt the SCC disease process, considering the role of COL7 in TGF- β activation and subsequently SCC development in DEB patients.

Figure 1.3: Tumorigenesis in EB due to blistered and chronically inflamed skin



AKT=protein kinase B; FAK= focal adhesion kinase; LOX=lipoxygenase; PI3K=phosphoinositide 3-kinase; TGF-β=transforming growth factor-β

Source: Adapted from Guerra *et al.* (2017)⁵⁴

Most patients with severe DEB will develop cutaneous SCC, which frequently progresses to metastatic disease and premature death. Even aggressive tumour resection is insufficient to stop the progression of SCC.¹⁶ Approximately 35%–44% of people with DEB who develop SCC undergo amputation to prevent spread of the disease. The median age at first amputation is 29 years.⁷ Loss of part of a limb can be devastating, especially where function is already compromised by scarring/contractures in other limbs.¹⁶ Mean survival time following amputation is 32 months (range 6–51 months) in people with severe DEB⁵⁶, with five-year survival approximately 20%.⁵⁷

SCC increases in incidence from adolescence and is frequently reported in patients aged over 20 years. In severe forms of DEB, the median age at diagnosis of the first occurrence of SCC is 24 to 29.5 years. Many individuals develop SCC at multiple sites.^{7,9,53} SCC tends to develop on the upper and lower extremities, and usually in areas of chronic ulcers, nonhealing wounds, and long-term cutaneous scars.^{7,10,52,53} SCC frequently progresses to metastatic disease, which is an important cause of death for people with DEB. The risk of death from metastases is 60% by age 65 in less severe forms of DEB and 87% by age 45 in more severe forms of DEB.^{9,10,52} Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Need for multiple surgeries

Complications from extensive scarring can include pseudosyndactyly, a joint deformity that involves fusion of the fingers and toes, requiring multiple surgeries beginning at a young age.⁷

People with severe forms of DEB may undergo surgery to release pseudosyndactyly in their first decade of life. In 62 patients (US and Canadian cohort), the median age at their first-hand surgery was 8.1 years (range, 3–25 years). The median number of hand surgeries performed was 3.0 (range, 1–22) in 151 patients in the US National EB Registry who underwent mitten repair of the hands.⁷

Most people with severe forms of DEB will develop at least one cutaneous SCC. Wide local excision is the treatment of choice for people with DEB who develop SCC. More radical surgery (i.e., amputation) may be needed for patients with tumours not amenable to wide local excision. Compared with wide local excision, there is no evidence that more aggressive approaches reduce the risk of recurrence. Nevertheless, amputation may be chosen in preference to excision for functional reasons, particularly if consideration is being given to use of a prosthesis. Between 21% and 42% of individuals with SCC associated with DEB undergo therapeutic amputation of the leg, arm, hand, or foot.^{7,16}

1.3.5.2 Burden on people with DEB

DEB is associated with a substantial humanistic burden.⁷ People with DEB experience intense pain and pruritus, and often require a carer for wound care, which often takes several hours per day.^{7,40,58} Consequently, people with DEB experience substantial impairments in their quality of life (QoL), with QoL being worse in more severe disease.^{6,22}

DEB has a profound humanistic burden due to recurrent and chronic wounds, acute and chronic pain, and intense pruritus.⁷ More than 64% of people with DEB report having at least 10% of their body covered in wounds. Approximately 60% of people with more severe forms of DEB report wounds covering at least 30% of their body.⁶

Wound pain and pruritus

Most people with DEB (69%) report frequent or chronic pain.⁵⁸ People with DEB and their carers (as proxies) report acute pain (4.4–6.4 based on a scale of 1 [no pain]–10 [most severe pain]), chronic pain (3.4–5.3), and pruritus (4.3–7.2) associated with wounds.⁶ Wound pain and pruritus tend to be worse for people with more severe forms of DEB.⁶ Painkiller use is widespread, including opioids in some cases.³⁰ In a study by DEBRA UK (DEBRA UK 2023 Insights Study), a patient organisation

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

supporting people living with EB, a survey was conducted of patients with EB, including 97 patients with DEB and their carers, 72% of patients with DEB reported using pain killers to manage their symptoms.³⁰ Notably, 19% of patients reported using strong opioids such as morphine or hydrocodone, and 16% reported using weaker opioids.

Wound care

Wound care is burdensome, taking several hours and in some cases more than 4 hours a day and often requiring assistance from one (61%) or two (17%) carers.⁷ Wound care is specific to the person with DEB, based on age, pain, biopsychological needs, wound locations, and wound characteristics.⁵⁹ Wound care includes the use of dressings, emollients and specialist clothing.³⁰ The burden associated with wound care increases significantly with disease severity and the extent of skin involvement.⁶ Wounds frequently become infected and can require dressing changes up to three times daily.^{7,22} Dressings need special attention to prevent further skin trauma during removal.^{6,8} Wound care is painful for people with DEB and causes significant emotional distress.²³

In the DEBRA UK study, patients and their carers reported that, on a typical day, they spent 1.5 hours on blister/wound care. Data from all patients with EB (i.e., not limited to patients with DEB) showed that the amount of time spent on wound care was correlated with disease severity. Patients with severe disease spent an average of 2.6 hours per day on wound care, while those with mild disease spent 0.5 hours. Similarly, carers of patients with severe EB spent 2.4 hours on wound care, while caretakers of patients with mild disease spent 0.9 hours.³⁰

Impact on HRQoL

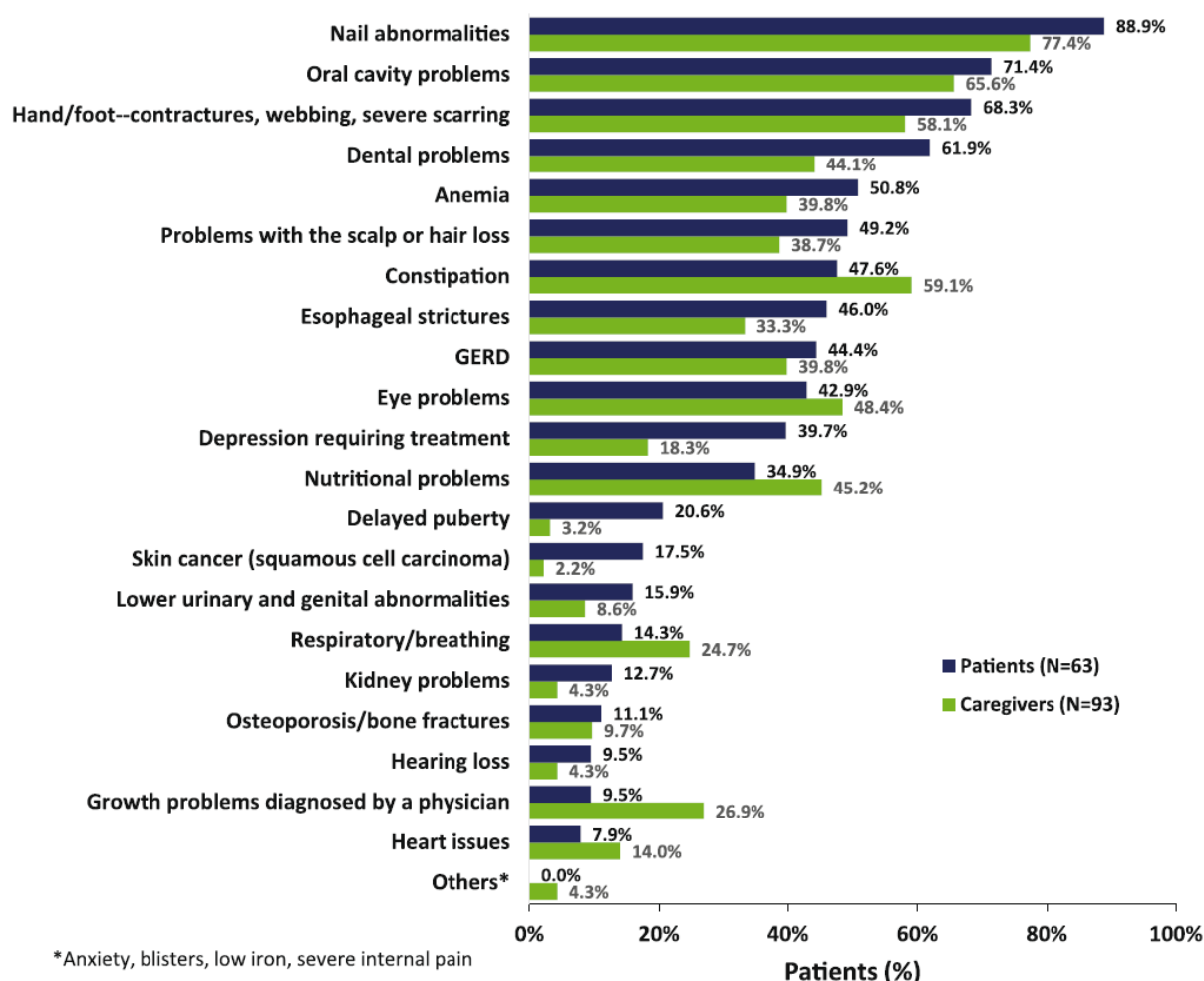
DEB is a devastating disease, and children and adults with DEB, particularly those with RDEB, experience a substantial impairment in HRQoL and have difficulties performing daily tasks, including bathing, moving around the home, eating, sleeping, and playing.⁶ Patients with DEB experience worse HRQoL than patients with any other dermatological condition,³⁹ and patients with RDEB have worse quality of life than patients with other forms of EB.⁷ QOLEB scores measured in individuals with more severe forms of DEB reflect a severe impact on HRQoL.²² Patients with EB experience psychosocial challenges, including learning to live with disfigurement and pain, coping with physical impairment, loneliness, and low self-esteem.⁶⁰

People with DEB experience a wide range of extracutaneous manifestations that interfere with daily functioning and require lifelong management (Figure 1.4).^{6,7} DEB is also associated with delayed puberty and growth disorders.⁶ Negative height velocity and failure to thrive has been reported among patients with DEB.⁷ A

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

retrospective study of 200 patients with EB found that more than 50% of children with RDEB showed wasting and/or stunting, and more than 80% of young adults with RDEB were underweight.⁴⁸

Figure 1.4: Patient-reported and carer-reported complications in people with EB



EB=epidermolysis bullosa; GERD=gastroesophageal reflux disease
Source: Bruckner *et al.* (2020)⁶

DEB interferes with all aspects of daily life, such as moving around the home, bathing, eating, sleeping, shopping, going to work or study, and participating in activities. The condition leaves people with DEB feeling frustrated (88.9%), embarrassed (74.6%), worried or anxious (69.8%), and depressed (66.6%).^{6,7} Children with EB also experience a lack of participation in activities and feeling different from others.³⁹

In the DEBRA study, most patients and their carers reported that DEB had a moderate or high impact on activities of daily life (Table 1.6).

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Table 1.6: Impact of DEB on daily activities of people with the condition, DEBRA study

Activity	Percent selecting high or moderate impact	
	Patients n=97	Carers n=38
Exercise	73%	45%
Everyday mobility and physical activity	73%	NR
Self-confidence	77%	37%
Hobbies	64%	53%
Enjoying life	66%	61%
Going to work/study	66%	50%
Mental health	63%	71%
Planning for the future	64%	74%
Aspirations for the future	69%	68%
Sleep	66%	53%
Being independent	59%	47%
Spending quality time with family/friends	47%	58%
Intimate relationships	66%	50%
Carrying out simple daily tasks (e.g., preparing food, getting dressed)	58%	NR
Personal hygiene (e.g., washing, brushing teeth)	59%	NR
Eating and drinking	64%	26%
Managing the finances	37%	50%
DEB=dystrophic epidermolysis bullosa Source: DEBRA UK (2023) ³⁰		

Wound care is time-consuming, with some people with RDEB reporting spending more than four hours on whole body wound care.⁶ Larger wounds are associated with worse skin disease severity and worse HRQoL, and lead to increased use of opioids.²²

1.3.5.3 Burden on carers of people with DEB

Carers, who are predominantly parents of children with DEB, experience emotional and psychological distress.^{6,7,19,20}

People with DEB rely on their carers for wound management and other support for living with consequences of DEB. Carers are most often parents to the person with DEB, are predominantly female, tend to be at a prime working age, and also in paid employment other than caregiving.⁶¹ Parents of children with EB report financial concerns as a result of reduced employment and earning capacity, which are more pronounced for mothers who are often the main carers.²⁰ Consequently, DEB leaves families and carers of people with DEB often experiencing chronic emotional and psychological distress.^{6,7,19,20}

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Wound care is time-consuming and burdensome, and often the assistance of one or more carers is required.⁶ Wound care is individualised to the person with DEB, and often performed by parents, carers, and specialised nurses who are most familiar with their condition.^{6,62} The burden associated with wound care increases significantly with disease severity and the extent of skin involvement.⁶ A study that 18% of carers of children and adults with RDEB reported that whole body wound care took longer than four hours.⁶

The entire family is at risk of experiencing a negative psychological impact as a result of DEB.⁶³ Parents and carers of people with DEB often experience chronic emotional and psychological distress due to exhaustion, sleep deprivation, frustration, high rates of guilt, sadness, fear, and isolation.^{6,19,20} The daily wound care routine places a substantial emotional impact on parents of children with EB, who report feeling powerlessness and sadness at seeing their child in pain and suffering.²⁰

The condition impacts family planning decisions, including whether to have more children, and contributes to divorce/separation.^{6,64} Siblings of children with EB also report a high emotional burden, including feeling sadness, helplessness, and fear, resentment and anger.¹⁹ School life and extracurricular activities of healthy siblings are impacted, since parents focus on the child with DEB.^{19,65} According to DEBRA UK, *“The impact on the family as a whole is devastating, especially the impact on siblings who are side-lined and possibly rolled into caring”*.⁴⁵

1.3.5.4 Economic burden

Economic burden associated with DEB is substantial, due to costs of wound care and high levels of healthcare utilisation.^{6,7,61,66} Both patients and carers report reduced employment as a result of DEB.^{6,67}

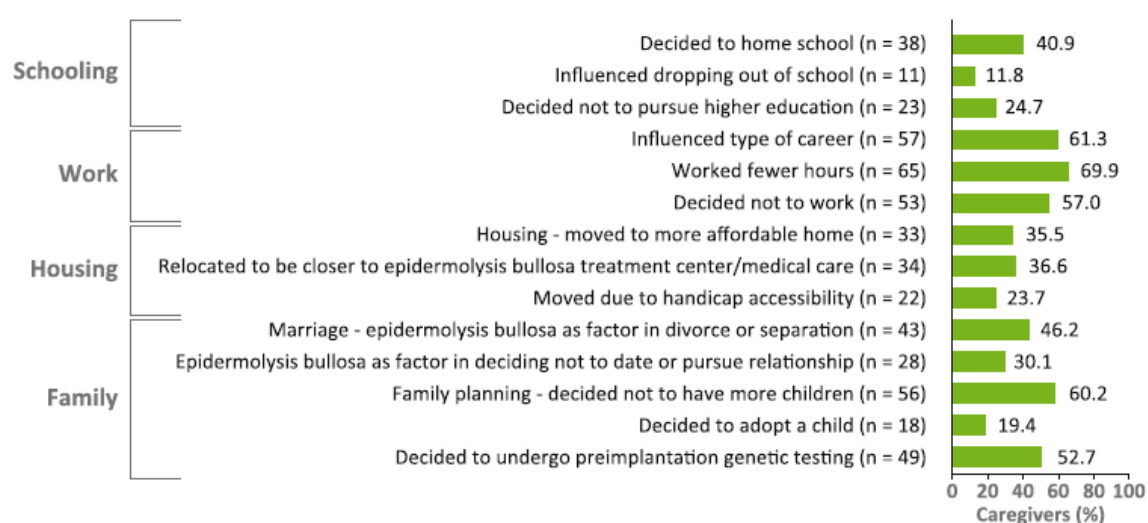
DEB has a substantial economic impact attributable to costs of wound care, medications, and hospitalisation, with worse disease severity linked to higher costs.^{6,7,61,66} The high-cost burden of DEB is attributed to the frequency and duration of wound dressing changes; use of antibiotics, analgesics, and antipruritics; dermatologist visits; visits to other specialists to manage serious complications of DEB; and healthcare utilisation (e.g., outpatient visits, emergency room visits, and inpatient stays).^{6,7,66} Notably, a study of EB patients from eight European countries showed that the average annual costs are higher for children than for adults with EB.⁵

People with DEB are compelled to make difficult life decisions to deal with the impact of their disease, or of their child’s disease. One study reported that carers dedicate

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

an average of 69 (range, 28–109) hours per week helping with activities of daily living. Carers tend to be parents to the person with DEB (58.2%), another relative (25.5%), female (83.6%), at a prime working age (mean age, 43.3 years), and also in paid employment other than caregiving (40.0%).⁶¹ DEB reduces carer's ability to work or perform other roles apart from caring for their child.^{6,67} A US-based study reported that approximately 70% of carers reduced their working hours, while 57% give up work entirely (Figure 1.5).⁶ Additionally, EB impacted carers' schooling, including deciding to homeschool (41%), dropping out of school (12%), or not pursuing higher education (25%).

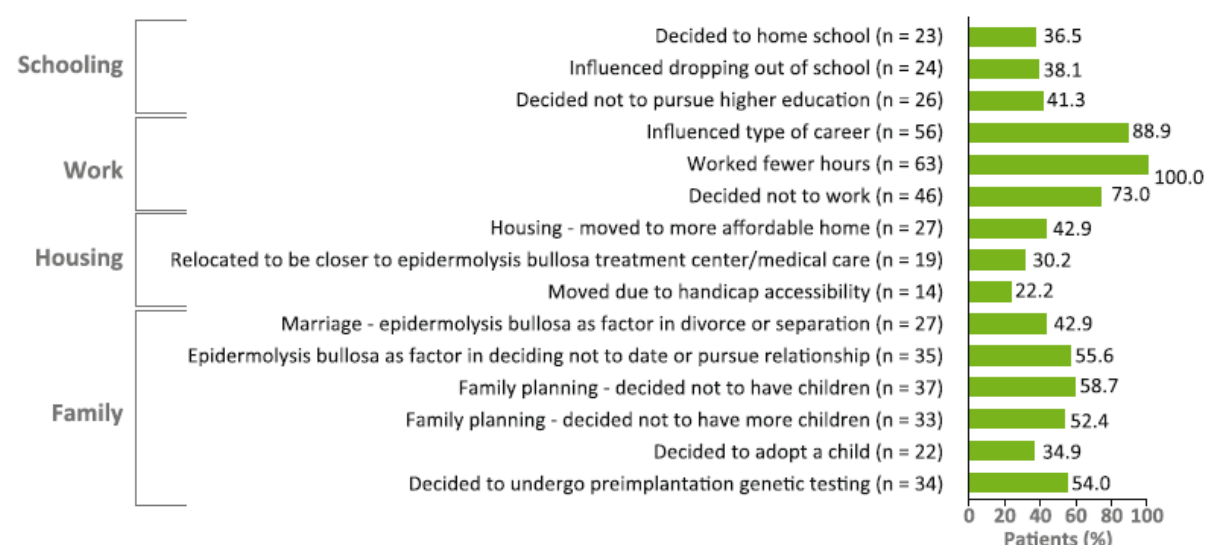
Figure 1.5: Impact of epidermolysis bullosa on life decisions of carers



Survey responses from 93 carers of people with epidermolysis bullosa.
Source: Bruckner *et al.* (2020)⁶

Adults with DEB report working fewer hours because of their condition, ~90% report that their disease influenced their career choice, and 73% decide not to work (Figure 1.6).⁶ DEB places a significant financial burden on many patients and their families, due to the need to purchase over-the-counter medications, dressing and wound supplies, and prescription medications.^{6,7}

Figure 1.6: Impact of epidermolysis bullosa on life decisions of people with the condition



Survey responses from 63 people with epidermolysis bullosa.
Source: Bruckner *et al.* (2020)⁶

In the DEBRA UK study, both patients and their carers reported spending a substantial amount of their time on disease-related activities (Table 1.7).³⁰ Nearly one quarter (23%) of patients with DEB reported that they were unable to work due to ill health.³⁰

Table 1.7: Mean daily time spent on activities of daily living among patients with DEB and their carers, DEBRA study

Activity	Patients with DEB n=53	Carers n=28
Resting/recovering	4.0hrs	2.4 hrs
Hobbies	1.6 hrs	1.9 hrs
Personal hygiene (bathing, washing, going to the toilet, eye care)	1.4 hrs	1.5 hrs
Blister/wound care including removing and applying dressings or bandages	1.5 hrs	1.5 hrs
Time spent checking on patients, including during the night	NA	0.9 hrs
Food preparation (e.g., if needing to puree food)	1.1 hrs	1.1 hrs
Getting dressed	0.5 hrs	0.6 hrs
DEB=dystrophic epidermolysis bullosa Source: DEBRA UK (2023) ³⁰		

1.3.6 Clinical pathway of care

DEB is inadequately addressed by current standard of care, which primarily involves the management of symptoms and secondary complications.^{6,21} BBE, which is the only treatment option available to patients with DEB, is not a targeted or corrective treatment and has shown efficacy limitations.⁶⁸

1.3.6.1 Overview

DEB is inadequately addressed by current standard of care, which is limited to the management of symptoms and secondary complications.^{6,21}

1.3.6.2 Current clinical pathway of care

Currently there are no approved curative or NICE-recommended targeted and corrective treatments for DEB; standard of care (SoC) consists only of best supportive care (BSC) strategies.^{6,7,21} BSC measures include dressings and regular bathing to reduce the risk of infection, antibiotics, analgesics and antipruritics, dental care, and enteral feeding (Figure 1.9).

In addition to supportive care, Filsuvez® (birch bark extract [BBE]) gel may be used as indicated for the “*Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.*”²⁸ The pivotal EASE trial was a phase III, double-blind, randomised, vehicle-controlled trial designed to assess the efficacy and safety of the topical gel BBE gel in treating target partial thickness wounds in EB.⁶⁸ The primary endpoint of the proportion of patients with first complete closure of target wound within 45 days was met in the group receiving BBE gel.⁶⁸ However, there was no future confirmation of whether the target wound remained closed. BBE gel for cutaneous application is the first EB-specific treatment to receive marketing approval in the UK²⁸ and EU²⁵ for the treatment of partial thickness wounds associated with DEB or junctional EB (JEB) in patients aged ≥6 months. BBE gel has been recommended for reimbursement by NICE (HST28) in September 2023.²⁴

The precise mechanism of action of the active ingredient, BBE, is unknown.^{25,28} The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) noted important limitations in efficacy data for BBE gel, but concluded the totality of evidence was supportive of a modest beneficial treatment effect. According to the CHMP, “*The efficacy was regarded as modest, no disease-modifying effect has been demonstrated, nor any effects on prevention of complications like infections, full-thickness ulceration and malignant transformation.*”²⁷

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

The high unmet need was an important factor in the decision of the CHMP, with clinical experts and patient representatives advising that any improvement in wound closure was of value to patients.²⁷ However, the US Food and Drug Administration (FDA) rejected the new drug application for BBE gel due to lack of efficacy data in February 2022.^{69,70} The application to the FDA was then resubmitted with additional clinical evidence from the EASE trial (up to Day 45), which was approved in December 2023.⁷¹

The NICE evaluation committee concluded that treatment with BBE is not disease-modifying or curative,²⁴ and that it often takes patients and their carers several weeks and months to find the right mix of existing treatments, which can lead to resistance to trying a new approach.

1.3.6.3 Unmet need

There is a substantial unmet need for innovative therapies for DEB that address the genetic cause of the disease.^{7,8,10,25,34} Given that DEB often presents at birth^{9,10} or within the first year of life and that complications of DEB accumulate over a person's lifetime,²² therapies that are available as early in the disease course as possible (i.e., starting at birth) are needed to potentially prevent the devastating sequelae of DEB.

As detailed in Section 1.3.5, DEB is a lifelong, severe, and debilitating condition that substantially impairs quality of life of patients and their carers, and has a profound impact on all family members.^{6,20} Intense pain and pruritus that result from blistering and impaired wound closure can severely impact patients' ability to perform activities of daily living and lead to potentially life-threatening secondary complications.¹⁰ Wound care, which can take several hours per day, is particularly burdensome for patients and their carers.⁷ Carers of patients with DEB, who are most often patients' parents, are at a prime working age, and are most commonly female, experience a substantial psychological and emotional toll and a reduced HRQoL.^{6,7,19,20}

There is currently no cure for DEB, only supportive care measures to manage symptoms.^{7,8,10,25,34} BBE is currently the only treatment for DEB that has received a NICE recommendation²⁴; however, it has demonstrated only a modest clinical efficacy. Additionally, BBE is not disease-corrective or curative and its mechanism of action is unknown. In the absence of a cure, the cornerstone of DEB management is routine wound care, which focuses on symptom relief encouraging healing, reducing the risk of new injury and minimising complications.^{8,29} More than half (55%) of people with severe forms of DEB require oesophageal dilation, approximately 37%

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

require gastrostomy tube placement, and approximately 22% have hand surgery, often within the first decade of life.¹²

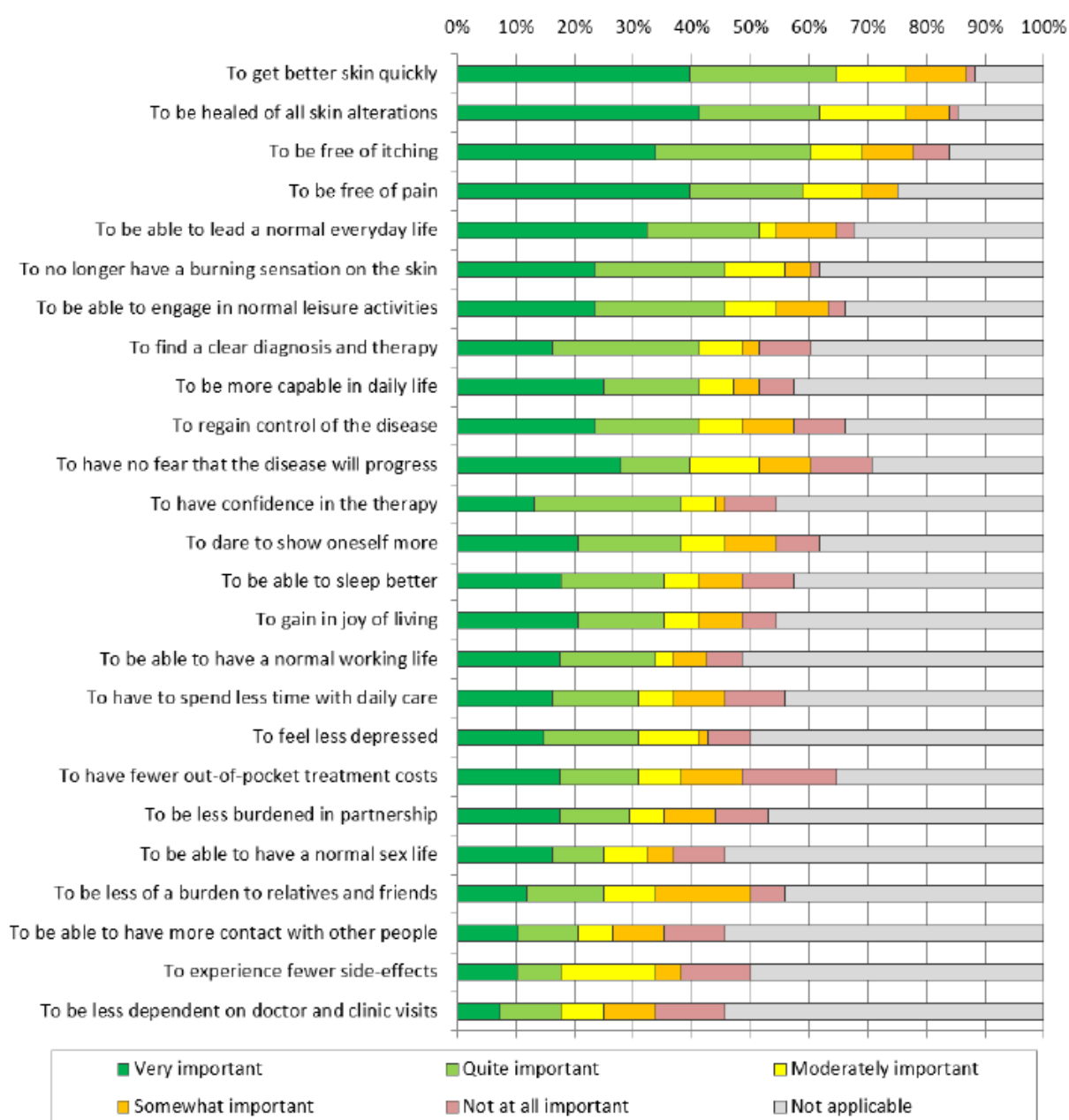
Most patients with severe DEB will develop cutaneous SCC, which frequently progresses to metastatic disease, and often necessitates amputation to prevent spread of the disease¹⁶ Loss of part of a limb can be devastating, especially where function is already compromised by scarring/contractures in other limbs.¹⁶ Additionally, SCC leads to premature death, with five-year survival approximately 20%.⁵⁷

There is an urgent need for a treatment approach that addresses the underlying cause of the disease and that delivers sustained wound healing that will reduce the number and severity of wounds^{6,31} and subsequently:

- Improve daily HRQoL through reduced pain and itch³¹;
- Reduce the burden of daily wound care;
- Reduce long-term secondary complications and the need for procedures (e.g., surgery to release pseudosyndactyly);
- Address mortality risks from severe infection and SCC;
- Address the genetic cause of the disease as early in the disease course as possible;
- Provide a sustainable and durable response.

People with DEB have identified the following needs (in decreasing order of importance): rapid improvement in skin condition, healing of all skin alterations, freedom from itching, freedom from pain, and to lead a normal everyday life (Figure 1.7).³¹

Figure 1.7: Importance of needs for people with DEB



DEB=dystrophic epidermolysis bullosa

Source: Schrader *et al.* (2021)³¹

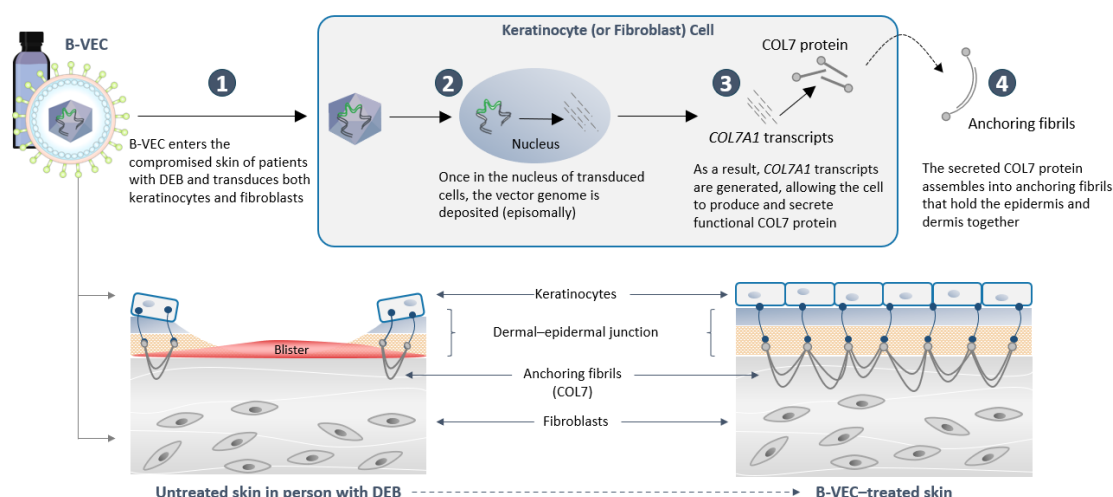
Given the important negative impact of DEB on many aspects of life,^{8,19,20,31} there is a high unmet need for a treatment approach that reduces the number and severity of wounds and breaks the cyclical nature of wounding, closure, and reblistering, to prevent the accumulation of debilitating and potentially life-threatening consequences of DEB.³¹

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

1.3.6.4 B-VEC

B-VEC is a replication-defective, herpes simplex virus 1 (HSV-1)–based gene therapy vector that has been genetically modified to express the COL7 protein. (Figure 1.8).^{32,33,39}

Figure 1.8: Mechanism of action of B-VEC



B-VEC=beremagene geperpavec; COL7=type VII collagen; DEB=dystrophic epidermolysis bullosa
Sources: Bardhan *et al.* (2020)³⁹; Gurevich *et al.* (2022)³³; Marinkovich *et al.* (2022)⁷²

B-VEC is based on an engineered, replication-defective HSV-1 vector platform, allowing delivery into the nucleus without host DNA integration.³² The HSV-1 vector has high payload capacity to accommodate the large size of the COL7A1 gene,⁷² tropism for the skin, and evades the immune system, enabling repeat dosing.³²

Upon cutaneous application to the wounds, B-VEC can transduce both keratinocytes and fibroblasts.¹ Following entry of B-VEC into the cells, the vector genome is deposited in the nucleus. Once in the nucleus, transcription of the encoded human COL7A1 is initiated. The resulting transcripts allow for production and secretion of COL7 by the cell in its mature form. These COL7 molecules arrange themselves into long, thin bundles that form anchoring fibrils. The anchoring fibrils hold the epidermis and dermis together and are essential for maintaining the integrity of the skin.¹

B-VEC clinical development programme has demonstrated that:

- B-VEC is a viable gene delivery vector that delivers two new copies of the COL7A1 gene that is missing in people with DEB^{32,33}
- Repeated topical application of B-VEC results in full-length COL7 protein expression and normalised anchoring fibril formation³³
- B-VEC restores the ultrastructure of the skin, based on baseline and post-treatment biopsies³³

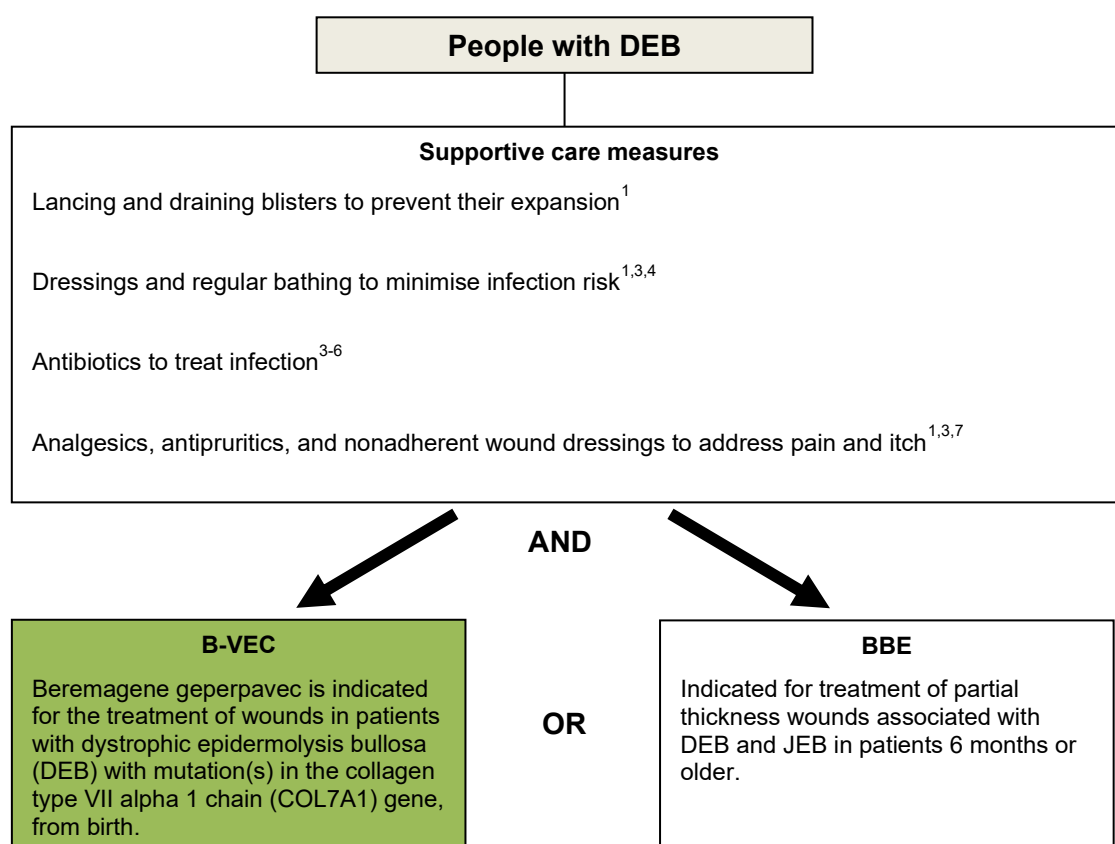
Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

- In the phase 3 study, 71% of B-VEC–treated wounds were closed at 3 months, and 67% at 6 months. In comparison, only 20% of placebo-treated wounds were closed at 3 months, and 22% at 6 months³²In the phase 3 study, durability of response (defined as 100% wound closure at both 3 months and 6 months) was reached in 50% of B-VEC–treated wounds compared with 7% of placebo-treated wounds³²

1.3.6.4.1 Place of B-VEC in therapy

B-VEC is expected to be used in addition to supportive care measures for the treatment of DEB in people from birth (Figure 1.9).

Figure 1.9: Anticipated clinical pathway of care for patients with DEB in the UK



BBE=birch bark extract; B-VEC=beremagene geperpavec; DEB=dystrophic epidermolysis bullosa; DDEB=dominant dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; JEB=junctional epidermolysis bullosa; RDEB=recessive dystrophic epidermolysis bullosa; SSRI=selective serotonin reuptake inhibitors.

In summary, B-VEC is a novel genetic therapy engineered to deliver functional *COL7A1* gene in a minimally invasive way to the skin to restore COL7 production to levels present in people without DEB. B-VEC is anticipated to be the first topical and redosable gene therapy, with marketing authorisation for the treatment of wounds in patients with DEB supported by data from two placebo-controlled trials.^{32,33}

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

1.4 Equality considerations

According to the Equality Act 2010, “A person has a disability for the purposes of the Act if he or she has a physical or mental impairment and the impairment has a substantial and long-term adverse effect on his or her ability to carry out normal day-to-day activities”.⁷³

A substantial proportion of people with DEB would meet the criteria for disability under the Equality Act 2010, given the frequency of progressive scarring leading to debilitating hand and foot deformities (pseudosyndactyly; Table 1.4) and ocular consequences (i.e., impaired vision and blindness; Table 1.5) of severe DEB. Furthermore, EB occurs in every racial and ethnic group throughout the world.⁷⁴ Together with the high cost of raising disabled children, families of minority ethnic communities often face negative attitudes towards disability that present barriers to accessing health and social care for their child, and financial support.^{75,76} In its review of the NICE evaluation for BBE [ID1505], DEBRA UK stated that, “*Equality for patients with EB impacts hardest on those that have least and who may be culturally disadvantaged*”.⁴⁵ Therefore, families who are socioeconomically disadvantaged, including those from minority ethnic communities, may be disadvantaged in their access to care as a consequence.

2 Clinical effectiveness

2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify clinical trials showing evidence on the efficacy, safety, and HRQoL modulation effect of B-VEC and other treatments used in the current treatment of wounds in DEB (DDEB and RDEB). The SLR was conducted following the NICE Methodology Process and Methods guide.⁷⁷ See the attached SLR report for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

2.2 List of relevant clinical effectiveness evidence

Table 2.1 provides a summary of the pivotal phase 3 GEM-3 study and phase 1/2 GEM-1 study that demonstrated the clinical effectiveness of B-VEC versus placebo.

Table 2.1: Clinical effectiveness evidence: GEM-3 and GEM-1

Study	GEM-3; B-VEC-03 (NCT04491604) Guide <i>et al.</i> 2022 ³²	GEM-1; KB103-001 (NCT03536143) Gurevich <i>et al.</i> (2022) ³³
Study design	Wound pairs were randomly assigned in a 1:1 ratio to receive once-weekly application of either B-VEC or placebo for 26 weeks until wound closure.	Wounds were randomly assigned in a 1:1 (phase 1 and 2c) or 2:1 (phase 2a and 2b) ratio to be treated with B-VEC or placebo.
Population	Patients aged ≥6 months with clinical diagnosis of DEB confirmed by genetic testing (including <i>COL7A1</i> mutation), and two cutaneous wounds similar in size, anatomical region, and appearance. N=31	Patients aged ≥18 years (phase 1), ≥5 years (phase 2a), or ≥2 years (phase 2b and 2c) with a clinical diagnosis of RDEB, with a genetic mutation in the <i>COL7A1</i> gene confirmed by genetic testing, immunofluorescence, and immunoelectron microscopy. Antibody negative to NC2. N=12 (9 distinct patients)
Intervention(s)	B-VEC (4×10^8 to 1.2×10^9 PFU depending on baseline wound size) mixed with excipient gel and applied topically once weekly	B-VEC mixed with excipient gel and applied topically as follows: • Phase 1: 1×10^8 PFU at Days 0, 2, 28, and 30 • Phase 2a: 6×10^8 PFU initially administered on Days 1, 2, 3, 4, and 5 • Phase 2b: 1×10^8 to 1.2×10^9 PFU per administration day dosed approximately every 2–3 days for 2 consecutive weeks and then at Days 30, 60, and 90 if wounds were open during study visits • Phase 2c: 8×10^8 to 1.57×10^9 PFU per wound per administration. Wounds underwent 2 cycles of treatment (Cycle 1 comprised 20 administrations over 25 days; Cycle 2 comprised 21 administrations over 24 days)
Comparator(s)	Saline mixed in excipient gel and applied topically once weekly	Saline mixed with excipient gel

Study	GEM-3; B-VEC-03 (NCT04491604) Guide <i>et al.</i> 2022 ³²	GEM-1; KB103-001 (NCT03536143) Gurevich <i>et al.</i> (2022) ³³
Indicate if study supports application for marketing authorisation	Yes	Yes
Indicate if study used in the economic model	Yes	Yes
Rationale if study not used in model	NA	NA
Reported outcomes specified in the decision problem	- Proportion of complete wound closure: - Proportion of primary wounds with complete wound closure at 6 months (Week 22+24 or Week 24+26) - Primary wounds with complete closure at 3 months (Week 8+10 or Week 10+12). - Pain: change from baseline to Week 22, 24, and 26 in pain severity during changes in wound dressing (assessed with VAS or FLACC-R) - HRQoL: change from baseline to Week 26 in EQ-5D-5L and Skindex-29	- Proportion of wounds with complete wound closure at Weeks 8, 10, or 12 - Time to wound closure - Duration of wound closure - Pain: patient-reported outcome for pain at BL and Days 3, 5, 15, 30, 60, and 90
All other reported outcomes	None	Disease severity: IGA score at BL and Days 3, 5, 15, 30, 60, and 90
BL=baseline; B-VEC=beremagene geperpavec; DEB=dystrophic epidermolysis bullosa; EQ-5D-5L=EuroQol 5-Dimension 5-Level questionnaire; FLACC-R=Face, Legs, Activity, Cry, and Consolability-Revised; HRQoL=health-related quality of life; IGA=investigator global assessment; NC=noncollagenous; PFU=plaque-forming unit; RDEB=recessive dystrophic epidermolysis bullosa; Skindex-29=29-Item Skindex instrument; VAS=visual analogue scale.		

Table 2.2 provides a summary of the phase 3 EASE study that demonstrated the clinical effectiveness of BBE versus control gel.

Table 2.2: Clinical effectiveness evidence: EASE

Study	EASE; BBE Kern <i>et al.</i> (2022) ⁶⁸
Study design	Double-blind, randomised, controlled, phase III, 90-day efficacy and safety study with a 24-month open-label, single-arm follow-up phase Participants were randomised 1:1 to receive either BBE or control gel.
Population	- Male and female patients with DEB, JEB, or KEB ≥ 4 years of age (reduced to > 21 days following an IDMC safety review in 2019) - EB target wound 10–50 cm² in size aged ≥ 21 days and < 9 months outside of the anogenital region (N=223)
Intervention(s)	BBE applied 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 covered with a standard of care non-adhesive wound dressing.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Study	EASE; BBE Kern <i>et al.</i> (2022) ⁶⁸
	The randomised treatment was to be applied during all dressing changes (at least every 4 days).
Comparator(s)	Control gel applied using the same schedule as the intervention
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	NA
Reported outcomes specified in the decision problem	Proportion of patients with first complete target wound closure within 45 days based on clinical assessment
All other reported outcomes	None

BBE=birch bark extract; EB=epidermolysis bullosa; DEB=dystrophic epidermolysis bullosa; IDMC=Independent Data Monitoring Committees; JEB=junctional epidermolysis bullosa; KEB= Kindler epidermolysis bullosa

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Summary of study design and methodology

The clinical development programme for B-VEC included:

- One phase 3 randomised control trial (RCT) (GEM-3) in patients aged ≥6 months with genetically confirmed DEB and two cutaneous wounds similar in size, appearance, and anatomical region³²
- One phase 1/2 RCT (GEM-1) in patients aged ≥6 years with molecularly confirmed RDEB and at least two skin areas with at least one wound in each area³³

The clinical development programme for BBE was also included:

- One phase 3 RCT (EASE) in patients with DEB, JEB, or Kindler epidermolysis bullosa (KEB) and a target partial-thickness wound lasting ≥ 21 days and < 9 months that was 10–50 cm².⁶⁸

Table 2.3: Summary of methodology for randomised controlled trials – GEM-3

Study name	B-VEC-03 (NCT04491604) GEM-3: Phase 3 Efficacy and Safety Study of Beremagene Geperpavec (B-VEC, Previously KB103) for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)
Objectives	To determine whether topical administration of B-VEC in addition to standard of care improved wound closure as compared to placebo in children, adolescents, and adults with DEB.
Location	Three study centres in the United States

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Study name	B-VEC-03 (NCT04491604) GEM-3: Phase 3 Efficacy and Safety Study of Beremagene Geperpavec (B-VEC, Previously KB103) for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)
Design	Multicentre, double-blind, placebo-controlled, randomised, intra-patient, efficacy, and safety study (i.e., each patient served as their own control)
Eligibility criteria	Inclusion criteria: • Age ≥6 months with clinical diagnosis of DEB • Confirmation of DEB diagnosis (either dominant [DDEB] or recessive [RDEB]) by genetic testing including COL7A1 • Two cutaneous wounds meeting the following criteria: – Location: similar in size, located in similar anatomical regions, and similar in appearance – Appearance: clean with adequate granulation tissue, excellent vascularisation, and did not appear infected • Use of reliable birth control throughout the duration of the study and for 3 months after the last dose of B-VEC, if of childbearing potential • Negative pregnancy test at Visit 1 (Week 1), if applicable • Willing to comply with study requirements; written informed consent from patient or legal representative Exclusion criteria: • Medical instability limiting ability to travel to the investigative centre • Diseases or conditions that could have interfered with the assessment of safety and efficacy of the study treatment and compliance of the subject with study visits/procedures, as determined by the investigator • Current evidence or a history of squamous cell carcinoma in the area that would undergo treatment • Actively receiving chemotherapy or immunotherapy at Visit 1 (Week 1) • Active drug or alcohol addiction as determined by the investigator • Hypersensitivity to local anaesthesia (lidocaine/prilocaine cream) • Participated in an interventional clinical trial within the past 3 months (not including B-VEC administration) • Receipt of a skin graft in the past 3 months • Pregnant or nursing
Method of randomisation	Using a pre-generated randomisation schedule, the matched primary wounds were randomised to receive either B-VEC or placebo gel. The randomisation schedule was generated using a block size of 6 for 7 sites with a maximum of 72 randomisations per site. The randomisations were not stratified. The randomisation schedule was generated by an independent statistician and validated by an independent statistical programmer.
Intervention(s) and comparator(s)	The wounds within each pair were randomly assigned in a 1:1 ratio to receive once-weekly application of either B-VEC or placebo for 26 weeks until wound closure. B-VEC (N=31): • Thawed cryopreserved drug product mixed with excipient gel (Methocel) • Topical dose ranging from 4×10^8 to 1.2×10^9 PFU depending on the baseline wound size Placebo (N=31): • Normal saline mixed with excipient gel, at a matched volume to B-VEC drug product Additional secondary wounds were selected for open-label B-VEC treatment.
Permitted and disallowed concomitant medication	• Topical administration of any medication (other than B-VEC and placebo) to a study target wound was prohibited throughout the study period up to Week 26 unless approved in advance by the medical monitor/sponsor. • Topical concomitant medications or treatments deemed necessary to provide adequate supportive care to nontarget wounds were permitted (and documented). Although prescription of tacrolimus, clobetasol, or becaplermin was permitted per protocol, none was applied during the study.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Study name	B-VEC-03 (NCT04491604) GEM-3: Phase 3 Efficacy and Safety Study of Beremagene Geperpavec (B-VEC, Previously KB103) for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)
	Women of childbearing potential using oral contraception must have consistently been taking their birth control for 3 months prior to Visit 1 (Week 1) and must have committed to continue using contraception throughout the study and for up to 3 months following the last dose of B-VEC.
Duration of follow-up, lost to follow-up information	Study period: August 2020 to April 2021 7-month follow-up (6-month double-blind period, 30-day safety follow-up) Treatment discontinuation: n=0 Study withdrawal: n=3 - One patient was lost to follow-up at Week 6 - One patient relocated at Week 12 - One patient withdrew at Week 24 because of travel constraints due to COVID-19
Primary outcomes (including scoring methods and timings of assessments)	Proportion of primary wounds with complete wound closure at 6 months (Week 22+24 or Week 24+26). - Only wounds that were healed for at least 2 consecutive weeks were counted as having had a response. - Complete wound closure was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin reepithelialisation without drainage, as determined by the investigator.
Other outcomes used in the economic model/specified in the scope	Key secondary endpoint: - Primary wounds with complete closure at 3 months (Week 8+10 or Week 10+12). Other secondary end points: - Change from baseline to Week 22, 24, and 26 in pain severity during changes in wound dressing. Assessed with the use of: - VAS (scores range from 0–10, with higher scores indicating greater pain) for patients aged ≥6 years - FLACC-R scale for patients aged <6 years. Exploratory endpoints: - Change from baseline to Week 26 in general HRQoL assessed using the EQ-5D-5L. - Change from baseline to Week 26 in skin-specific HRQoL assessed using the Skindex-29 questionnaire.
Preplanned subgroups	Subgroup analyses for the primary endpoint were prespecified on the basis of sex, age, and race.
B-VEC=beremagene geperpavec; DDEB=dominant dystrophic epidermolysis bullosa; DEB=dystrophic epidermolysis bullosa; COL7=type VII collagen; EQ-5D-5L=EuroQol 5-Dimension 5-Level questionnaire; FLACC-R=Face, Legs, Activity, Cry, and Consolability–Revised; HRQoL=health-related quality of life; HSV=herpes simplex virus; ITT=intent-to-treat; mITT=modified intent-to-treat; RDEB=recessive dystrophic epidermolysis bullosa; Skindex-29=29-Item Skindex instrument; VAS=visual analogue scale Source: Krystal Biotech Data on File (GEM-3 [B-VEC-03] CSR) ⁷⁸ ; Clinicaltrials.gov ⁷⁹	

Table 2.4: Summary of methodology for randomised controlled trials – GEM-1

Study name	KB103-001, NCT03536143 GEM-1: A Phase 1/2 Study of B-VEC, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)
Objectives	Phase 1: - To preliminarily assess the safety of topical B-VEC compared with placebo and to demonstrate evidence of molecular correction, that is, functional COL7 expression and anchoring fibrils, associated with B-VEC after treatment. - To preliminarily assess the effect of B-VEC on wound closure compared with placebo (wound surface area reduction, duration of wound closure). - To assess changes in laboratory values and the condition of the patients (HSV and COL7 antibodies, vital signs, physical examination).

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Study name	KB103-001, NCT03536143 GEM-1: A Phase 1/2 Study of B-VEC, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)
	Phase 2: • To further assess the of B-VEC on wound closure compared with placebo (wound surface area reduction, duration of wound closure, time to wound closure). • To demonstrate evidence of molecular correction (functional COL7 expression) associated with B-VEC after treatment.
Location	One study centre in the United States
Design	Interventional, single centre, open-label, randomised, inpatient, placebo-controlled study (i.e., each patient served as their own control)
Eligibility criteria	Inclusion criteria: • Age: – Phase 1: aged ≥18 years – Phase 2a: aged ≥5 years – Phase 2b: aged ≥2 years – Phase 2c: aged ≥2 years • Clinical diagnosis of RDEB confirmed by genetic testing, immunofluorescence, and immunoelectron microscopy • Confirmed RDEB COL7A1 mutations • LH24 antibody negative (NC2-negative and NC1-positive). (This criterion is applicable to the first 2 adults on the study (phase 1). Subsequent patients could be NC1-positive or NC1-negative) • Wounds meeting the wound size/surface area entry criteria: – Phase 1: 2 wounds up to 10 cm²; 1 randomised to B-VEC and 1 randomised to placebo – Phase 2a and 2b: At least 3 wounds up to 20 cm²; 2 wounds randomised to B-VEC and 1 randomised to placebo – Phase 2c: At least 2 wounds up to 50 cm²; at least 1 randomised to B-VEC and 1 randomised to placebo • Willing to comply with study requirements; written informed consent from patient or legal representative Exclusion criteria: • Medical instability limiting ability to travel to the investigative centre • Presence of medical illness (e.g., HIV, hepatitis B, or hepatitis C) expected to complicate participation and/or compromise the safety of the technique • Serum antibodies to COL7 (patients with negative results within 12 months of screening are eligible) • Active infection in the area that will undergo administration • Evidence of systemic infection • Known allergy to any of the constituents of the product • Current evidence or a history of squamous cell carcinoma in the area that will undergo treatment • Active drug or alcohol addiction • Hypersensitivity to local anaesthesia (lidocaine/prilocaine cream) • Receipt of chemical or biological study product for the specific treatment of RDEB in the past 3 months • Specific wounds that have previously been administered investigational gene or cell therapy • Use of systemic antibiotics within 7 days • Positive pregnancy test or breast-feeding • Clinically significant abnormalities as determined by the investigator
Method of randomisation	A complete randomised-block design, with each patient designated as a block to receive all conditions, was used to assign treatment. Investigator-assigned wound numbers were randomised using a pre-generated randomisation schedule. Randomisation schemes were generated via a customised program prior to the study, and randomisation assignments for the treatment sites of each study patient were provided in sealed envelopes. Once the wound pairs were identified and

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Study name	KB103-001, NCT03536143 GEM-1: A Phase 1/2 Study of B-VEC, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)
	labelled, the randomisation envelope was opened, and the assigned dose was then given.
Intervention(s) and comparator(s)	GEM-1 enrolled N=12 patients (9 distinct patients enrolled in the study; 3 enrolled in both phase 2a and 2b). Wounds were randomly assigned in a 1:1 (phase 1 and 2c) or 2:1 (phase 2a and 2b) ratio to be treated with B-VEC or placebo. B-VEC (N=12): - Thawed cryopreserved drug product mixed with excipient gel (Velesco Lot [phases 1, 2b, and 2c] or PluroGel® [phase 2a]) - Topical doses: - Phase 1 (n=2 adults): 1×10^8 PFU at Days 0, 2, 28, and 30; additional dose on Day 42 for patient 2 - Phase 2a (n=2 adults and n=2 paediatric patients): 6×10^8 PFU initially administered on Days 1, 2, 3, 4, and 5 - Patient 1 had additional administrations at Day 30, Day 44 (unscheduled), and Day 60 - Patient 3 had an additional administration on Day 30 - Patient 4 had an additional administration on Day 30 and Day 46 (unscheduled) - Phase 2b (n=3 adults and n=2 paediatric patients): 1×10^8 to 1.2×10^9 PFU per administration day dosed approximately every 2–3 days for 2 consecutive weeks and then at Days 30, 60, and 90 if wounds were open during study visits - Phase 2c (n=1 paediatric patient): 8×10^8 to 1.57×10^9 PFU per wound per administration. Wounds underwent 2 cycles of treatment: - Cycle 1 was 25 days and consisted of 20 administrations - Cycle 2 was 24 days and consisted of 21 administrations Placebo (N=12): - Isotonic saline mixed with excipient gel
Permitted and disallowed concomitant medication	- Patients were encouraged to restrict topical administration of any therapy to the wounds under study for a minimum of 48 hours following administration of the investigational product. - Throughout the study, any concomitant medications or treatments deemed necessary to provide adequate supportive care could be prescribed, including medication for the intradermal injections and biopsies to treat pain and/or anxiety (e.g., lidocaine, lorazepam). - Patients continued routine skin care throughout the study.
Duration of follow-up, lost to follow-up information	Study period: May 2018 to November 2019 Up to 2-month intervention (depending on phase) followed by long-term follow-up period consisting of annual telephone contacts (up to 5 years) with the patient and their primary care physician, which began after each patient completed the interventional portion of the study. Treatment discontinuation: n=4 3 patients were discontinued from phase 2a by the sponsor so they could roll over to phase 2b. These patients are considered to have completed the study. 1 patient completed their last dose on Day 61 and was discontinued by the sponsor due to not being able to participate further. This patient is considered to have completed the study. Study withdrawal: n=1 (due to inability to travel to study assessments)
Primary outcomes (including scoring methods and timings of assessments)	- Proportion of wounds with complete wound closure (was defined as at least 90% reduction in wound surface from baseline) at Weeks 8, 10, or 12. - Time to wound closure, defined as the time from the first treatment to complete wound closure (at least 90% reduction in wound surface from baseline).

Study name	KB103-001, NCT03536143 GEM-1: A Phase 1/2 Study of B-VEC, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)
	• Duration of wound closure, defined as the time from the complete closure (≥90% reduction in wound surface from baseline) to the first reopening of the same wound.
Other outcomes used in the economic model/specified in the scope	• Investigator global assessment score (wounds were compared against baseline at Days 3, 5, 15, 30, 60, and 90) • Patient-reported outcome for pain (wounds were compared against baseline at Days 3, 5, 15, 30, 60, and 90)
Pre-planned subgroups	• No subgroup analysis was planned or performed.
B-VEC=beremagene geperpavec; COL7=type VII collagen; DDEB=dominant dystrophic epidermolysis bullosa; DEB=dystrophic epidermolysis bullosa; HSV=herpes simplex virus; ITT=intent-to-treat; NC=noncollagenous; PFU=plaque-forming unit; RDEB=recessive dystrophic epidermolysis bullosa; Source: Gurevich <i>et al.</i> (2022) ³³ ; Krystal Biotech Data on File (GEM-1 [KB103-001] CSR) ⁸⁰ ; Clinicaltrials.gov ⁸¹	

Table 2.5: Summary of methodology for randomised controlled trials – EASE

Study name	EASE (previously BEB-13; NCT03068780, EudraCT2016-002066-32)
Objectives	The objective of the EASE DBP was to compare the efficacy, safety and tolerability of BBE with a control gel in patients with 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.
Eligibility criteria	• Male and female patients with DEB, JEB, or KEB • ≥ 4 years of age (reduced to > 21 days following an IDMC safety review in 2019) • EB target wound 10–50 cm² in size aged ≥ 21 days and < 9 months outside of the anogenital region
Method of randomisation	Participants were randomised 1:1 to receive either BBE gel or control gel. Randomisation was conducted according to blinded patient number, and the randomisation key was held solely by an independent statistician.
Intervention(s) and comparator(s)	BBE gel (n=109 randomised and received treatment) • 100g of BBE gel consists of 10g active pharmaceutical ingredient BBE 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. 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.
Permitted and disallowed concomitant medication	• Medications/ therapies were permitted during both the DBP and OLP of the trial, including liquid antiseptics at each dressing change, bathing, inhaled/

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Study name	EASE (previously BEB-13; NCT03068780, EudraCT2016-002066-32)
	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	The duration of the DB phase was 90 days. Of the 223 randomised participants, 199 (89.2%) completed the DBP (91.7%, BBE gel vs. 86.8%, control gel), and 24 (10.8%) discontinued (8.3%, BBE gel vs. 13.2%, control gel).
Primary outcomes (including scoring methods and timings of assessments)	Primary outcome: Proportion of patients with first complete target wound closure within 45 days based on INV assessment
Other outcomes used in the economic model/specified in the scope	Key secondary (confirmatory) efficacy endpoints: • 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)
Pre-planned subgroups	Participants were stratified according to their EB subtype and target wound size (cm²) into the following groups: • DEB 10 to < 20; • DEB 20 to < 30; • DEB 30 to 50; • JEB/ KEB 10 to < 20; • JEB/ KEB 20 to < 30; • JEB/ KEB 30 to 50.
AE=adverse event; BBE=birch bark extract; CFB=change from baseline; DB=double-blind; DDEB=dominant dystrophic epidermolysis bullosa; DEB=dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; EBDASI= Epidermolysis Bullosa Disease Activity and Scarring Index; INV=investigator; JEB=junctional epidermolysis bullosa; KEB=kindler epidermolysis bullosa; OLP=open label phase Source: Kern <i>et al.</i> (2023)⁶⁸; NICE (2023)²⁴	

2.3.2 GEM-3 study design and methodology

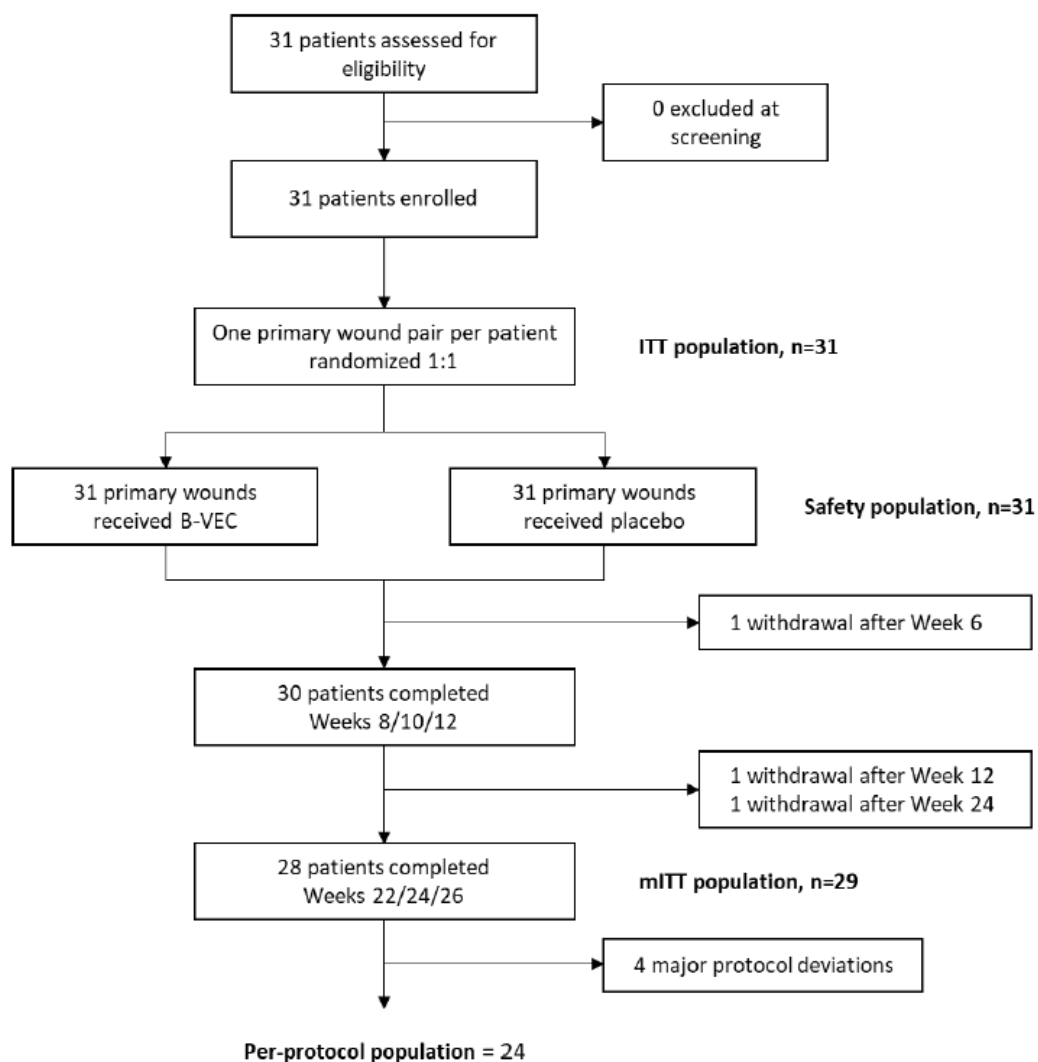
2.3.2.1 Objective

The objective of the phase 3 GEM-3 study was to determine whether topical administration of B-VEC in addition to standard of care improved wound closure as compared to placebo in children, adolescents, and adults with DEB.⁷⁸

2.3.2.2 Study design

The design of the phase 3 GEM-3 study is shown in Figure 2.1.

Figure 2.1: Overview of the phase 3 GEM-3 study design



B-VEC=B-VEC=beremagene geperpavec; ITT=intent-to-treat; mITT=modified intent-to-treat.
Source: Krystal Biotech (2022)⁷⁸

2.3.2.3 Patient selection criteria

The full eligibility criteria of the phase 3 GEM-3 study are listed in Table 2.3. Briefly, the study comprised patients aged ≥ 6 months with a clinical diagnosis of DEB confirmed by genetic testing, including *COL7A1* mutations. In addition, eligible patients had two cutaneous wounds similar in size, anatomical region, and appearance (i.e., clean with adequate granulation tissue, excellent vascularisation, and no appearance of infection).^{32,78}

Demographic and baseline characteristics of patients enrolled in GEM-3 are presented in Table 2.6. For each patient, the site investigator selected two wounds of similar size, anatomical region, and appearance (see Table 2.3). One wound was randomised to receive B-VEC, while the other received placebo. Therefore, each patient served as their own control.³²

Table 2.6: GEM-3: Demographic and baseline characteristics (ITT population)

Characteristic	Total patients (N=31)*
Age	
Median (range), years	16.1 (1–44)
≤ 12 years, n (%)	10 (32)
> 12 to ≤ 18 years, n (%)	9 (29)
> 18 years, n (%)	12 (39)
Sex, n (%)	
Female	11 (35)
Male	20 (65)
Race or ethnic group other than Hispanic or Latino, n (%) [†]	
White	20 (65)
Black	0
Asian	6 (19)
American Indian or Alaska Native	5 (16)
Native Hawaiian or other Pacific Islander	0
Hispanic or Latino ethnic group, n (%) [†]	16 (52)
Genotype	
Dominant dystrophic epidermolysis bullosa	1 (3)
Recessive dystrophic epidermolysis bullosa	30 (97)
Area of primary wound exposed to B-VEC	
Median (range), cm ²	10.6 (2.3–57.3)
< 20 cm ² , n (%)	23 (74)
20 to < 40 cm ² , n (%)	6 (19)
40 to 60 cm ² , n (%)	2 (6)
Area of primary wound exposed to placebo	
Median (range), cm ²	10.4 (2.3–51.5)
< 20 cm ² , n (%)	22 (71)
20 to < 40 cm ² , n (%)	8 (26)
40 to 60 cm ² , n (%)	1 (3)
*Percentages may not total 100% due to rounding. [†] Race and ethnic groups were reported by the patient, parent, or guardian. B-VEC=beremagene geperpavec; ITT=intention-to-treat Source: Guide <i>et al.</i> (2022) ³²	

2.3.2.4 Assessments

The secondary endpoint of pain severity during wound dressing changes was assessed using a visual analogue scale (VAS; scores ranging from 0–10, with higher scores indicating most severe pain) for patients aged ≥ 6 years, and using the Faces, Legs, Activity, Cry, Consolability Revised (FLACC-R) scale for patients aged < 6 years.³² The FLACC-R scale is used for young children who cannot accurately report their pain because they are too young or unable to understand what is being asked of them.⁷⁸

In GEM-3, children aged < 6 years were evaluated for each primary wound dressing change and received a score of 0, 1, or 2 in each category based on their behaviour during the dressing removal. A total score was to determine the overall pain and discomfort the subject was experiencing. The child's carer completed the scale at scheduled visits. It was important that the same carer completed the assessment at all visits, whenever feasible, to reduce inter-evaluator variability. FLACC-R was used throughout the study even if the age of the child changed. Both VAS and FLACC-R are generic instruments that can be used across different health conditions.⁷⁸

The exploratory endpoint of patient-reported HRQoL was measured using EuroQol 5-Dimension 5-Level questionnaire (EQ-5D-5L; generic HRQoL) and the 29-Item Skindex instrument (Skindex-29; HRQoL in dermatology) in patients aged ≥ 12 years at consent. Skindex-29 is a HRQoL measure composed of three domains (i.e., symptoms, functioning, and emotions) designed to be used across different skin conditions. Both EQ-5D-5L and Skindex-29 were administered at baseline and at Week 26.⁷⁸

2.3.2.5 Blinding

Trial participants (including their carers) and investigator as well as sub investigator conducting outcome-related assessments and procedures were blinded to the identity of treatment for the primary wounds. The unblinded staff, including the pharmacist or authorised designee, and the monitor remained separate from the primary study team and were not involved in any study conduct outside of their functions of managing the receipt, storage, preparation, dispensing, and reconciliation of all study products. No unblinding occurred during the study.⁷⁸

2.3.2.6 Endpoints

Primary and secondary endpoints for GEM-3 are summarised in Table 2.3 and briefly below:

Primary endpoint:

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

- Proportion of primary wounds with complete wound closure at 6 months (Week 22+24 or Week 24+26).

Key secondary endpoint:

- Primary wounds with complete closure at 3 months (Week 8+10 or Week 10+12).

Other secondary end points:

- Change from baseline to Week 22, 24, and 26 in pain severity during changes in wound dressing.
- VAS (scores range from 0–10, with higher scores indicating greater pain) for patients aged ≥6 years.
- FLACC-R scale for patients aged <6 years.
- Safety assessments included monitoring of adverse events (AEs) that emerged or worsened after the first application of B-VEC or placebo, physical examination, vital signs, and clinical laboratory tests. The severity of AEs was reported and graded by the investigator. Immunologic evaluation included testing for antibodies against HSV-1 and COL7.³²

2.3.3 GEM-1 study design and methodology

2.3.3.1 Objective

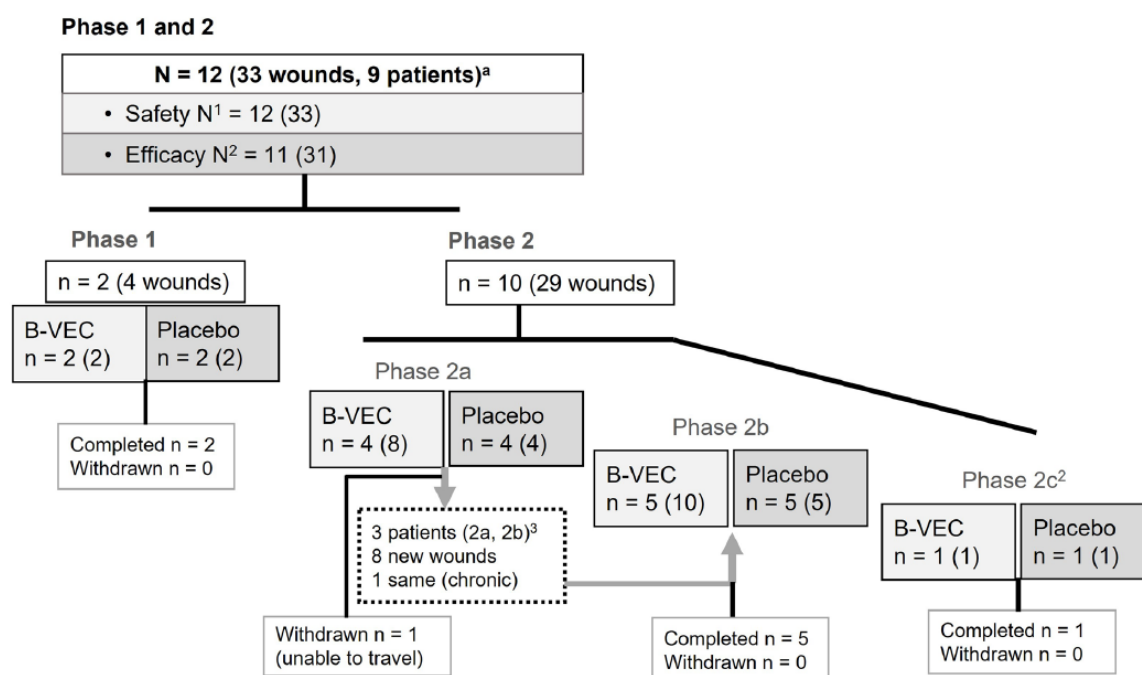
The objectives of the phase 1/2 GEM-1 are described in detail in Table 2.4. Briefly, the objectives of the study were to:^{33,80}

- Assess the safety of topical B-VEC compared with placebo and to demonstrate evidence of molecular correction (i.e., functional COL7 expression and anchoring fibrils) associated with B-VEC after treatment);
- Assess the effect of B-VEC on wound closure (i.e., wound surface area reduction, duration of wound closure, time to wound closure) compared with placebo.

2.3.3.2 Study design

The design of the phase 1/2 GEM-1 study is shown in Figure 2.2.

Figure 2.2: Overview of the phase 1 and phase 2 GEM-1 study design



^aThree patients were enrolled into both Phase 2a and Phase 2b. These patients' Phase 2b wounds were treatment-naïve except for a chronic (5-year) dorsal foot wound on Patient 3. A wash-out period of 3 months passed between treatments in phase 2a and 2b. Patients were enrolled in phase 2a as Pts 3, 5, and 6, and in phase 2b as Pts 11, 8, and 7, respectively.

¹Phase 1, 2a, 2b, 2c; all interventions all wounds.

²Phase 1, 2a, 2b; randomised wounds (Patient 12, 2c considered separately for efficacy).

³Patients were enrolled in phase 2a as Patients 3, 5, and 6 and in phase 2b as Pts 11, 8, and 7, respectively. B-VEC=B-VEC=beremagene geperpavec.

Source: Gurevich *et al.* (2022)³³

2.3.3.3 Patient selection criteria

GEM-1 comprised patients with a clinical diagnosis of RDEB, with a genetic mutation in the *COL7A1* gene confirmed by genetic testing, immunofluorescence, and immunoelectron microscopy.³³ The full eligibility criteria for each phase of the GEM-1 study are described in Table 2.7. Wounds were randomly assigned in a 1:1 (phase 1 and 2c) or 2:1 (phase 2a and 2b) ratio to be treated with B-VEC or placebo; therefore, each patient served as their own control.^{33,80}

Table 2.7: Summary of eligibility criteria and treatment randomisation for GEM-1

Phase	Age	Antibody status		Wound size	Treatment randomisation (number of wounds)	
		NC1	NC2		B-VEC	Placebo
1	≥18 years	Positive	Negative	2 wounds up to 10 cm ²	1	1
2a	≥5 years	Positive or negative	Negative	At least 3 wounds up to 20 cm ²	2	1
2b	≥2 years	Positive or negative	Negative	At least 3 wounds up to 20 cm ²	2	1
2c	≥2 years	Positive or negative	Negative	At least 2 wounds up to 50 cm ²	≥1	≥1
B-VEC=beremagene geperpavec; NC=noncollagenous Source: Gurevich <i>et al.</i> (2022) ³³ ; Krystal Biotech Data on File (GEM-1 [KB103-001] CSR) ⁸⁰						

Demographic and baseline characteristics for patients enrolled in GEM-1 are presented in Table 2.8.

Table 2.8: GEM-1: Demographic and baseline characteristics (safety and ITT populations)

Characteristic	Safety (N=12)	ITT (n=11)
Age		
Mean (SD), years	20.3 (8.05)	21.3 (7.72)
Median (range), years	19.5 (10–35)	21.0 (13–35)
Sex, n (%)		
Female	3 (25.0)	3 (27.3)
Male	9 (75.0)	8 (72.7)
Race or ethnic group, n (%)		
Not Hispanic or Latino	9 (75.0)	8 (72.7)
Hispanic or Latino	3 (25.0)	3 (27.3)
Female of childbearing potential, n (%)	3 (25.0)	3 (27.3)
B-VEC=beremagene geperpavec; ITT=intent-to-treat; SD=standard deviation Source: Krystal Biotech Data on File (GEM-1 [KB103-001] CSR) ⁸⁰		

2.3.3.4 Assessments

Wound images were taken using an iPhone camera system with the WoundMatrix application. WoundMatrix is a complete mobile wound management and telehealth solution for the secure investigator global assessment analysis (IGA) capture, measurement, and upload of images and data elements at the investigator–patient point of care.³³

Images could also be captured off-site by patients or their carers using the WoundMatrix application on their personal device. The patient had limited access to and no control regarding the measurement of the images. The patient ensured off-

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

site lighting was similar to on-site lighting, and they cleaned and dried the wounds before imaging.³³

2.3.3.5 Blinding

GEM-1 was an intra-patient, placebo-controlled, randomised open-label study, and treatment was not blinded.⁸⁰ Wound images were assessed by the unblinded principal investigator and by two independent blinded physician-dermatologists with bullous disease expertise.³³

2.3.3.6 Endpoints

Primary and secondary endpoints for GEM-1 are summarised in Table 2.4.

Safety assessments were conducted with a single systemic patient response as the independent outcome. AEs and concomitant medications were assessed at each visit. Blood and urine were assessed for B-VEC DNA using a validated quantitative polymerase chain reaction assay, and blood was assayed for COL7 and HSV-1 antibodies.³³

2.3.4 EASE study design and methodology

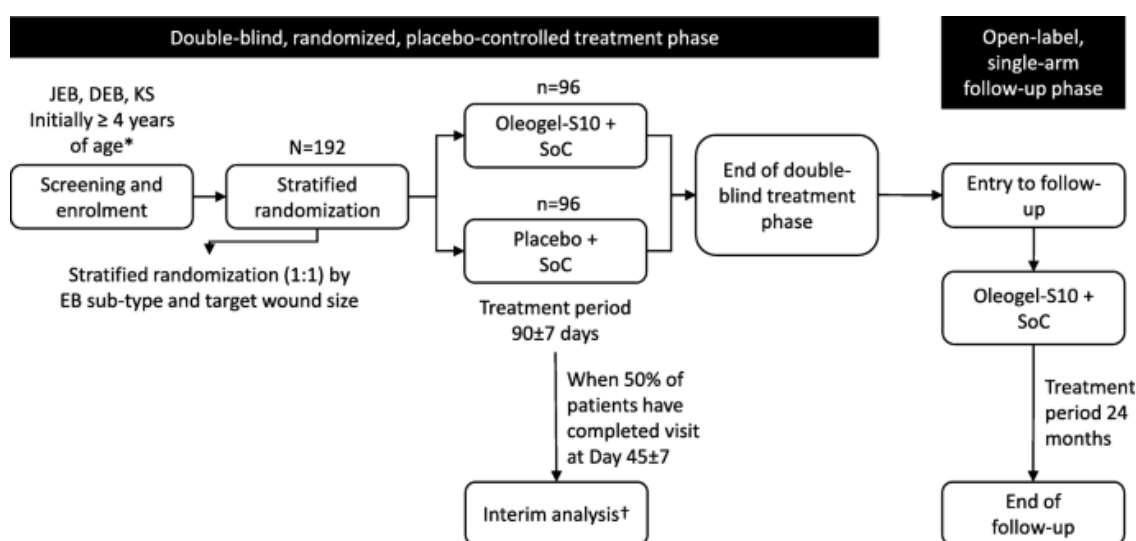
2.3.4.1 Objective

The objectives of the phase 3 EASE trial are described in detail in Table 2.5. Briefly, the objective of the study was to compare the efficacy, safety and tolerability of BBE with a control gel in patients with inherited EB (DEB, JEB and KEB).⁶⁸

2.3.4.2 Study design

The study design of EASE is shown in Figure 2.3

Figure 2.3: Study design of EASE (NCT03068780)



BBE=birch bark extract; DEB=dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; JEB=junctional epidermolysis bullosa; KS=Kindler syndrome; SoC=standard of care

Note: BBE is referred to as Oleogel-S10 in this figure

Source: Kern *et al.* (2019)⁸²

2.3.4.3 Patient selection criteria

Inclusion criteria for EASE are listed in Table 2.5. Briefly, patients with DEB, JEB or KEB and a target partial-thickness wound lasting ≥ 21 days and < 9 months that was 10–50 cm², were enrolled.⁶⁸ Patients with other subtypes of EB or EB target wound with clinical signs of local infection were excluded.⁶⁸

2.3.4.4 Assessments

For the assessment of wound closure and re-epithelialisation, the investigators photographed the EB target wound and all other wounds that match target wound criteria with the ARANZ Silhouette® system. A 3D model of the wound based on photographic data, derives measurements of the model, and records standardised notes. Patients were assessed during specific visit days, which included Days 0, 7 (± 2), 14 (± 5), 30 (± 7), 45 (± 7), 60 (± 7), 90 (± 7 ; end of double-blind period [DBP]). Once the wound was deemed closed, complete closure of the EB target wound was confirmed within at 1 week plus 2 days after first complete closure.

2.3.4.5 Blinding

Patients, carers, 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.²⁴

2.3.4.6 Endpoints

Primary and secondary endpoints for EASE are shown in Table 2.5.

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

Appendix B outlines the detailed flow of participants through the GEM-3 and GEM-1 clinical trials.

2.4.1 GEM-3 overview

The intent-to-treat (ITT) population of the GEM-3 study was defined as patients whose primary wounds were randomised regardless of whether they received randomised treatment or not.³² The modified ITT (mITT) population was defined as patients whose primary wounds were randomised and received B-VEC or placebo treatment with at least one postbaseline primary endpoint assessment. The per-protocol (PP) population was defined as all safety population patients (i.e., patients who were administered either B-VEC or placebo) who completed the study without any major protocol deviations.⁷⁸

Primary, key secondary efficacy analyses, and baseline summaries were based on the ITT population. If the results for the primary endpoint were significant, the two-sided 5% alpha level was to be passed to the key secondary endpoint.³²

2.4.1.1 GEM-3 sample size determination

Sample size determination was based on the exact McNemar test and incidences of response observed in the phase 1/2 trial at Week 8–12. At a power of 90% and a two-sided alpha level of 5%, it was determined 24 patients (24 primary wound pairs) would show a difference between trial groups if the true incidence of response was 75% for B-VEC and 25% for placebo and if responses for matched pair members were uncorrelated. A 20%–25% dropout rate was assumed with a target sample size of 30–32 patients.³²

2.4.1.2 GEM-3 study hypotheses

The primary endpoint was the proportion of DEB primary wound sites with complete wound closure from baseline in B-VEC-treated and placebo-treated intra-subject wound sites at Weeks 22 and 24 or Weeks 24 and 26, as determined by the

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

investigator, to evaluate durability of response and repeat dosing. Complete wound closure was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin re-epithelialisation without drainage. Only wounds that were healed for at least two consecutive weeks were counted as positive responses.⁷⁸

The null hypothesis of interest was the absence of a treatment effect on wound closure and the alternative hypothesis was the presence of a treatment effect on wound closure. In addition to testing the null hypothesis, the McNemar odds ratio and its 95% confidence interval (CI) were summarised to indicate the magnitude of the treatment effect with B-VEC treatment.⁷⁸

2.4.1.3 GEM-3 statistical analyses

Statistical analyses used to evaluate outcomes in GEM-3 are summarised in Table 2.9. Note that no interim analyses were planned or performed.⁷⁸

Table 2.9: Analysis of primary and secondary endpoints in GEM-3

Endpoint	Statistical method	Analysis population
Primary endpoint		
Proportion of primary wounds with complete wound closure at 6 months (Weeks 22+24 or Weeks 24+26)	Exact McNemar test (two-sided type I error rate of 0.05) A multiple imputation approach assuming MAR was used to impute missing endpoint data	ITT* Sensitivity analyses: PP, mITT, ITT with observed data (no imputation) ^{†,‡}
Secondary endpoints		
Proportion of primary wounds with complete closure at 3 months (Weeks 8+10 or Weeks 10+12).	Exact McNemar test (two-sided type I error rate of 0.05, if the primary endpoint was statistically significant) A multiple imputation approach assuming MAR was used to impute missing endpoint data	ITT* Sensitivity analyses: PP, mITT, ITT with observed data (no imputation) ^{†,‡}
Change from BL to Weeks 22, 24, and 26 in pain severity during changes in wound dressing:	ANCOVA with treatment as the fixed effect and baseline value as the covariate	ITT* Sensitivity analyses: PP, mITT ^{†,‡}
VAS (patients aged ≥6 years)		
FLACC-R (patients <6 years)		
Change from BL to Week 26 in generic HRQoL (EQ-5D-5L)	No statistical analysis or data imputation	ITT (observed data)*
Change from BL to Week 26 in skin-specific HRQoL (Skindex-29)	No statistical analysis or data imputation	ITT (observed data)*
*ITT population comprised patients whose primary wounds were randomised regardless of whether they received randomised treatment or not. [†]mITT population comprised patients whose primary wounds were randomised and received B-VEC or placebo treatment with at least one postbaseline primary endpoint assessment. [‡]PP population comprised all safety population patients (i.e., patients who were administered either B-VEC or placebo) who completed the study without any major protocol deviations. ANCOVA=analysis of covariance; BL=baseline; B-VEC=beremagene geperpavec; EQ-5D-5L=EuroQol 5-Dimension 5-Level questionnaire; FLACC-R=Face, Legs, Activity, Cry, and Consolability–Revised; HRQoL=health-related quality of life; ITT=intent-to-treat; mITT=modified intent-to-treat; MAR=missing at random; PP=per protocol; VAS=visual analogue scale Source: Guide <i>et al.</i> (2022)³²; Krystal Biotech Data on File (GEM-3 [B-VEC-03] CSR)⁷⁸		

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

2.4.2 GEM-1 overview

The ITT population of GEM-1 was defined as all patients who received investigational product and had at least one post-dose paired wound assessment. The PP population was defined as patients who received investigational product, had at least one post-dose paired wound assessment, and completed the protocol as planned. The safety population was defined as all patients who received investigational product.⁸⁰

Primary, key secondary efficacy analyses, and baseline summaries were based on the ITT population.⁸⁰ Post hoc statistical analysis was performed on the wound measurement data obtained from patients in the phase 1/2 clinical study. Data from randomised wounds were pooled for wound closure efficacy analysis of B-VEC compared with placebo.³³

2.4.2.1 GEM-1 sample size determination

A formal sample size calculation was not performed for this study. The sample size was based on consideration of an adequate number of participants for a rare disease in an exploratory phase 1/2 study to obtain sufficient information on the safety and effectiveness of B-VEC and to aid in designing a more robust confirmatory safety and efficacy study.⁸⁰

2.4.2.2 GEM-1 study hypotheses

The hypotheses for this study were that B-VEC-treated wounds would have:⁸⁰

- An AE profile similar to placebo-treated wounds
- A significantly greater proportion of wounds achieving complete wound closure, attributed to COL7 molecular correction, than placebo
- A significantly longer duration of wound closure than placebo
- A significantly shorter time to wound closure than placebo

2.4.2.3 GEM-1 statistical analyses

Statistical analyses used to evaluate outcomes in GEM-1 are summarised in Table 2.10. Note that no interim analyses were planned or performed.⁷⁸

Table 2.10: Analysis of primary and secondary endpoints in GEM-1

Primary endpoints	Statistical method	Analysis population
Proportion of wounds with complete wound closure, defined as $\geq 95\%$ reduction in wound surface from BL Stratified by timepoints (Weeks 8, 10, or 12)	CMH (stratified by timepoint) Breslow-Day (independence of weekly evaluations) Missing data were replaced by the last recorded observed value	ITT* Sensitivity analyses: PP†

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Primary endpoints	Statistical method	Analysis population
Time to wound closure, defined as the time from the first treatment to complete wound closure (at least 90% reduction in wound surface from BL)	ANOVA with treatment as the fixed effect Missing data were replaced by the last recorded observed value	ITT* Sensitivity analyses: PP†
Duration of wound closure, defined as the time from the complete closure (≥90% reduction in wound surface from BL) to the first reopening of the same wound	ANOVA with treatment as the fixed effect Missing data were replaced by the last recorded observed value	ITT* Sensitivity analyses: PP†
Secondary endpoints		
Investigator global assessment score (wounds were compared against BL at Days 3, 5, 15, 30, 60, and 90)	No statistical analysis or data imputation	ITT*
Patient-reported outcome for pain (wounds were compared against BL at Days 3, 5, 15, 30, 60, and 90)	No statistical analysis or data imputation	ITT*
*ITT population comprised patients who were administered investigational product and had at least one post dose paired wound assessment. †PP population comprised patients who were administered investigational product, had at least one post dose paired wound assessment, and completed the protocol as planned. ANOVA=analysis of variance; BL=baseline; B-VEC=beremagene geperpavec; CMH=Cochran-Mantel-Haenszel; EQ-5D-5L=EuroQol 5-Dimension 5-Level questionnaire; ITT=intent-to-treat; PP=per protocol Source: Gurevich <i>et al.</i> (2022)³³; Krystal Biotech Data on File (GEM-1 [KB103-001] CSR)^{80,83}		

2.4.3 EASE overview

2.4.3.1 Sample size determination

The sample size calculation for EASE was based on an assumed true control rate of 27% for the primary endpoint, derived from the estimated wound-closure rate in the control arm of the EASE trial. This estimation was informed by wound-closure rates observed in the ESSENCE trial of allantoin cream in EB. Using a two-sided, two-sample comparison of proportions at a significance level of $\alpha = 0.05$, a sample size of 91 patients per group (182 total) would provide 80% power to detect a 20-percentage-point improvement (resulting in a 47% rate in the BBE).⁸² To account for an anticipated 5% drop-out rate, a total of 192 patients (96 per arm) were planned for enrolment.⁸²

2.4.3.2 Statistical analysis

A summary of the statistical analyses undertaken in the EASE trial is shown in Table 2.11.

Table 2.11: Statistical analysis summary for the EASE trial

Endpoint	Statistical method	Analysis population
Primary endpoint		
Proportion of patients with first complete closure of the EB target wound within 45 ± 7 days based on clinical assessment	Compared using the Cochran-Mantel-Haenszel (CMH) test, stratified by EB sub-type and target wound size class. Cui, Hung, Wang approach using a weighted statistic for final statistical analysis. The overall level of significance for the primary endpoint analysis was 0.05 (2-sided).	FAS PPS* An individual with missing data will be defined as not having achieved complete closure.
Secondary endpoint		
Time to first wound closure until day 90 ± 7	Tested at the two-sided 5% significance level using the non-stratified log-rank test. Participants were censored at the date last known to have not achieved complete closure.	FAS
Incidence of wound infection between treatments	Compared using a CMH test considering the strata of EB sub-type and target wound size class	NR
Maximum severity of infection	Compared between treatments using a two-sided Wilcoxon Rank Sum test stratified by EB sub-type and target wound size class (van Elteren test)	NR
Change from baseline in “background pain,” “procedural pain,” and itching	Compared using a two-sided Wilcoxon Rank Sum test stratified by EB sub-type and target wound size class (van Elteren test)	NR

*Used for supportive analyses

EB=epidermolysis bullosa; FAS=full analysis set; ITT=intention to treat; NR=not reported; PPS=per protocol set

Source: Kern *et al.* (2019)⁸²; NICE (2023)²⁴

2.5 Critical appraisal of the relevant clinical effectiveness evidence

The complete quality assessment for each study is found in the SLR report⁸⁴ and Appendix B.

Results from the phase 3 GEM-3 and the phase 1/2 GEM-1 studies, and the EASE study, are presented in this submission to demonstrate the clinical efficacy of B-VEC and BBE for people with DEB. These data were published in peer-reviewed journals in the *New England Journal of Medicine* (GEM-3),³² *Nature Medicine* (GEM-1),³³ and The British Journal of Dermatology (EASE).⁶⁸ Table 2.12, Table 2.13, and

Table 2.14 present quality assessment results for GEM-3, GEM-1, and EASE, respectively. The quality of relevant clinical trials was appraised using a checklist adapted from the CRD Guidance for Undertaking Reviews in Health Care.⁸⁵

Table 2.12. Quality assessment results for GEM-3

Trial	GEM-3
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	NA – Intra-patient design
Were the groups similar at the outset of the study in terms of prognostic factors?	NA – Intra-patient design. Primary wounds were similar in size between those exposed to B-VEC and those exposed to placebo.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in dropouts between groups?	NA – Intra-patient design
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes
B-VEC=beremagene geperpavec; NA=not applicable	

Table 2.13. Quality assessment results for GEM-1

Trial	GEM-1
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	NA – Intra-patient design
Were the groups similar at the outset of the study in terms of prognostic factors?	NA – Intra-patient design, but there was variability in wound size observed across the small participant sample.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in dropouts between groups?	NA – Intra-patient design
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes
NA=not applicable	

Table 2.14 Quality assessment results for EASE

Trial	EASE
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in dropouts between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

2.6 Clinical efficacy results of the relevant studies

Repeated topical application of B-VEC results in full-length COL7 protein expression, normalised anchoring fibril formation, and durable and consistent wound closure.^{32,33}

Phase 3 GEM-3 study

- Phase 3 evidence demonstrated that B-VEC treatment led to complete closure of significantly more wounds than placebo at 3 months (71% vs. 20%; $p < 0.001$) and 6 months (67% vs. 22%; $p = 0.002$).³²
- B-VEC–treated wounds remained durably and consistently closed. Numerically more B-VEC–treated wounds than placebo-treated wounds had complete closure at both the 3-month and 6-month timepoints (50% vs. 7%).³²
- B-VEC treatment led to a consistent treatment response regardless of sex, age, and wound diameter.³²
- B-VEC treatment led to numerically greater improvements in pain, consistent with a wound closure response.³²

Phase 1/2 GEM-1 study

- Phase 1/2 evidence demonstrated that B-VEC treatment led to complete closure of significantly more wounds than placebo at 3 months ($p = 0.0026$, based on wound closure responder analysis).³³
- B-VEC–treated wounds remained durably and consistently closed. Median time to wound closure was shorter with B-VEC (13.5 vs. 22.5 days) and median duration of wound closure was longer with B-VEC (103.0 vs. 16.5 days) than placebo.³³
- The treatment effect of reduction in wound area was statistically significant ($p < 0.025$) at Weeks 8, 10, and 12.³³
- Analysis of microscopy data from GEM-1 indicated that B-VEC treatment restored COL7 NC1 and NC2 expression at the dermal–epidermal basement membrane consistent with the location of anchoring fibrils in normal skin.³³

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Phase 3 EASE study

- In the Phase 3 EASE study, the percentage of patients with first complete target wound closure within 45 days was significantly higher in the BBE (referred to as Oleogel-S10 in the primary publication) arm (41.3%) compared with the control gel arm (28.9%; $p=0.013$).⁶⁸ Differences in total wound burden measured by EBDASI skin activity and BSAP, and time to first target wound closure over the 90-day double-blind period for the Oleogel-S10 arm compared with control gel did not reach statistical significance.⁶⁸

2.6.1 GEM-3 clinical efficacy results

2.6.1.1 Complete wound closure at 6 months

In the phase 3 GEM-3 study, the primary endpoint of superiority of B-VEC over placebo in terms of the percentage of wounds with complete closure at 6 months was met. Of the 31 wound pairs in the ITT population, 67% of wounds treated with B-VEC and 22% of wounds treated with placebo were completely healed at 6 months, a statistically significant difference of 46 points (95% CI 24, 68; $p=0.002$; Table 2.15).³² The definition of complete wound closure used in GEM-3 required that wounds be completely healed (100% wound closure from the exact wound area selected at baseline, specified as skin reepithelialisation without drainage, as determined by the investigator) for at least two consecutive weeks, representing a high bar for patients who often have recurrent wounds that are prone to reopening quickly.^{32,86} Requiring closure at two time points distinguished the transient closure observed in wounds exposed to placebo from the more durable closure observed in wounds exposed to B-VEC.

Table 2.15: GEM-3: Primary and key secondary endpoint analyses (imputed data)

Endpoint	B-VEC (n=31)	Placebo (n=31)	Absolute difference, % (95% CI)	p value
Primary endpoint: complete wound closure at 6 months,* n (%)	20.9 (67)	6.7 (22)	46 (24–68)	0.002
Key secondary endpoint: complete wound closure at 3 months,† n (%)	21.9 (71)	6.1 (20)	51 (29–73)	<0.001
Complete wound closure was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin reepithelialisation without drainage, as determined by the investigator. The primary and key secondary endpoints were analysed in the ITT population. Multiple imputation methods were used to account for missing data. Fractional counts are due to the multiple imputation procedure (MAR) used for analysis. In the first stage of multiple imputation, imputations for missing data are generated based on statistical characteristics of the data and this procedure is repeated many times, resulting in data sets with replaced missing information. In the second stage, any analysis of the imputed data sets can be conducted within each of the imputed data sets as if there were no missing data. After the statistical analysis is run separately on each imputed data set, the estimates of interest from all the imputed datasets are combined into a single estimate using standard combining rules. Hypothesis testing was performed with the use of an exact McNemar test. *Primary wounds were assessed at Weeks 22+24 or Weeks 24+26.				

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

†Primary wounds were assessed at Weeks 8+10 or Weeks 10+12.
B-VEC=beremagene geperpavec; CI=confidence interval; ITT=intent-to-treat; MAR=missing at random
Source: Guide *et al.* (2022)³²

2.6.1.2 Complete wound closure at 3 months

Key secondary endpoint analysis found that B-VEC led to complete wound closure in significantly more wounds than placebo control at 3 months (71% vs. 20%; $p<0.001$); (Table 2.15).³²

2.6.1.3 Durable wound closure

Supplementary analysis assessed complete wound closure at various time points (Table 2.16). A durable response was defined as meeting the responder definition for complete wound closure both at 3 months (Weeks 8 and 10 or Weeks 10 and 12) and at 6 months (Weeks 22 and 24 or Weeks 24 and 26).³² Durability was also assessed by considering the proportion of wounds that met the definition of closure at both 3 months and 6 months (meeting both the primary and key secondary endpoints simultaneously). Using this rigorous definition, once-weekly treatment with B-VEC led to durable complete wound closure in 49.7% treated wounds compared with 7.1% placebo-treated wounds ($p=0.002$).³²

Table 2.16: GEM-3: Supplementary analyses for durability of wound closure (imputed data)

Endpoint	B-VEC (n=31)	Placebo (n=31)	Absolute difference, % (95% CI)
Durability of response,* n (%)	15.4 (49.7)	2.2 (7.1)	42.6 (22.6–62.6)
Complete wound closure, n (%)			
Weeks 8, 10, and 12	14.8 (47.7)	5.1 (16.5)	31.3 (10.6–51.9)
Weeks 22, 24, and 26	13.4 (43.2)	2.0 (6.5)	36.8 (19.8–53.7)
Complete wound closure was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin reepithelialisation without drainage, as determined by the investigator. Percentages are based on the number of participants in the ITT population; CIs are based on McNemar test. Fractional counts are due to the multiple imputation procedure (MAR) used for analysis. In the first stage of multiple imputation, imputations for missing data are generated based on statistical characteristics of the data and this procedure is repeated many times, resulting in data sets with replaced missing information. In the second stage, any analysis of the imputed data sets can be conducted within each of the imputed data sets as if there were no missing data. After the statistical analysis is run separately on each imputed data set, the estimates of interest from all the imputed datasets are combined into a single estimate using standard combining rules. *Defined as meeting the responder definition for complete wound closure both at 3 months (Weeks 8+10 or Weeks 10+12) and at 6 months (Weeks 22+24 or Weeks 24+26). B-VEC=beremagene geperpavec; CI=confidence interval; ITT=intent-to-treat; MAR=missing at random Source: Guide <i>et al.</i> (2022)³²			

2.6.1.4 Improvement in pain severity associated with wound dressing

In patients 6 years of age and older, pain severity was assessed as a secondary outcome. Secondary endpoint analyses found that once-weekly treatment with B-VEC led to numerically greater reduction in VAS pain scores versus placebo when assessed at 6 months (Table 2.17). Although the effect size was modest, the mean change in pain in GEM-3 was favourable and directionally consistent with wound closure.³²

Table 2.17: GEM-3: Secondary endpoint analysis for pain severity during wound dressing changes

Change from baseline pain severity during wound dressing changes	B-VEC (n=31)	Placebo (n=31)	Absolute difference, % (95% CI)*
Wounds evaluated at Week 22, n	24	24	-0.61 (-1.10 to -0.13)
Mean change on VAS	-0.88	-0.71	
Wounds evaluated at Week 24, n	25	25	-0.88 (-1.79 to 0.03)
Mean change on VAS	-0.64	-0.08	
Wounds evaluated at Week 26, n	24	24	-0.56 (-1.17 to 0.05)
Mean change on VAS	-0.63	-0.38	
Data shown are for pain severity (secondary end point) as assessed with the use of a VAS (scores range from 0 to 10, with higher scores indicating greater pain) among patients aged ≥6 years. *Least-squares mean differences were generated from an analysis of covariance linear model, with trial product and patient (paired) as the fixed effect and the baseline value as the covariate. The widths of the 95% CIs were not adjusted for multiple comparisons, and no definite conclusions can be drawn from these data. B-VEC=beremagene geperpavec; CI=confidence interval; VAS=visual analogue scale Source: Guide <i>et al.</i> (2022) ³²			

No conclusions on pain assessed by the FLACC-R scale (assessed on patients <6 years) could be made due to the small sample size (n=4).³²

2.6.1.5 Improvement in HRQoL associated with wound dressing

Change in general and skin-specific HRQoL was measured at baseline and at Week 26 using the EQ-5D and Skindex-29 questionnaires, respectively, in patients aged ≥12 years. Most patients improved by at least one health level or had no change in the EQ-5D-5L dimensions at 6 months as compared to baseline. Skindex-29 scores generally were the same at follow-up.³²

2.6.1.6 Treatment of large, secondary wounds

The potential of B-VEC to treat very large, chronic wounds was qualitatively explored in up to four unmatched secondary wounds per patient without exceeding the remaining weekly dose. Consistent treatment response in favour of B-VEC was observed for wound diameter, although this exploratory analysis was not powered to demonstrate statistical significance.³²

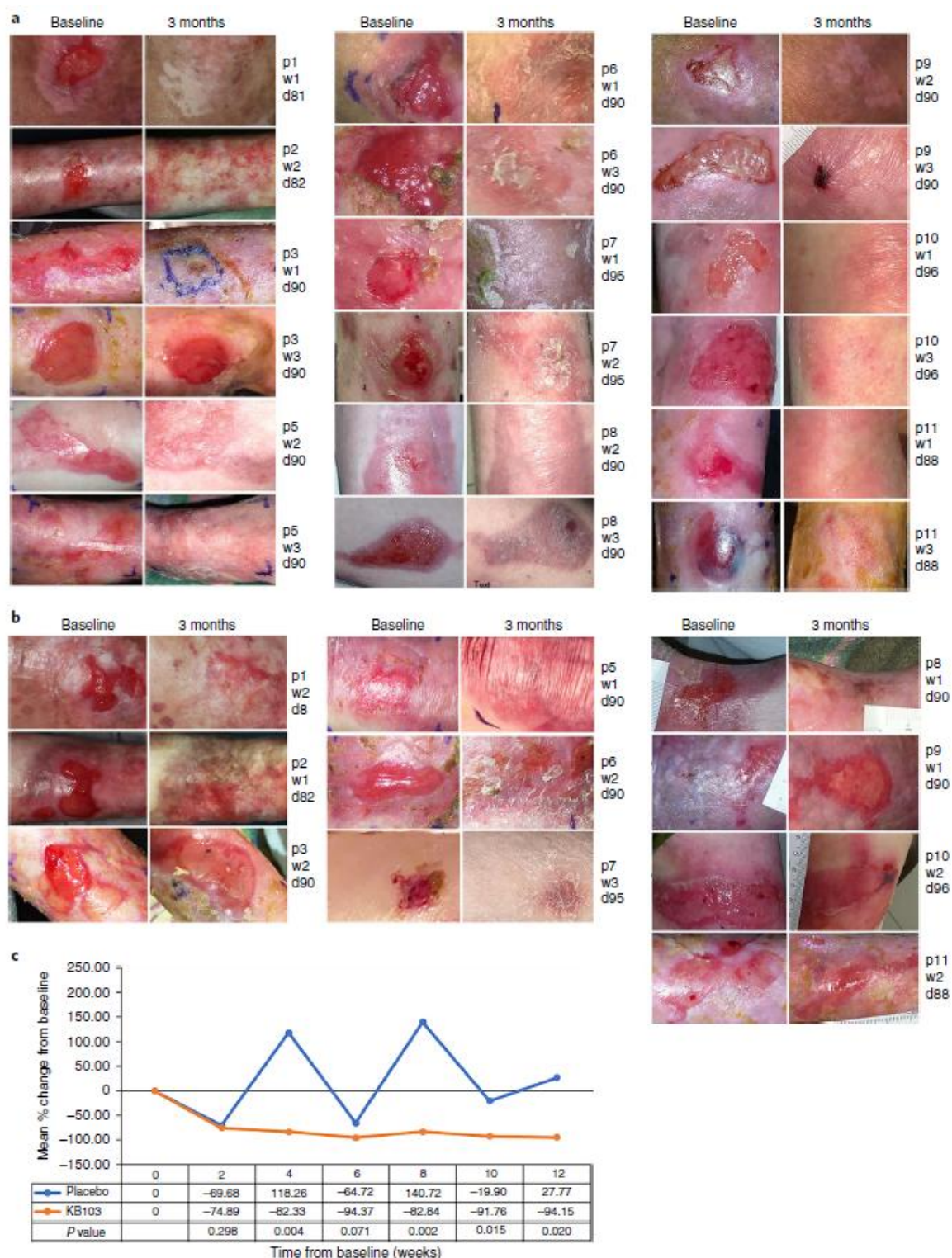
Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

2.6.2 GEM-1 clinical efficacy results

2.6.2.1 Complete wound closure at 3 months

In the phase 1/2 GEM-1 study, all except one wound treated with B-VEC had closed by 3 months (Figure 2.4). The exception was a chronic (5 year) dorsal foot wound that partially closed at 1 month, was not closed at 3 months, but completely closed upon retreatment, and remained healed throughout monitoring (8 months), highlighting the effectiveness of repeated application of B-VEC.³³

Figure 2.4: Wound closure in patients with RDEB following topical B-VEC or placebo



^{a,b}Photos of B-VEC–treated (a) or placebo-treated (b) wounds (w#) on the indicated patients (p#) at baseline, and approximately 3 months after treatment.

^cMean percent change from baseline in the area of all target wounds in patients 1–11.

KB103 (B-VEC)=beremagene geperpavec

Source : Gurevich *et al.* (2022)³³

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

B-VEC–treated wounds were statistically significantly different from placebo wounds ($p=0.0026$) based on complete wound closure responder analysis, which is indicative of improved wound closure with B-VEC (Table 2.18). Furthermore, the treatment effect of reduction in wound area was statistically significant ($p<0.025$) at Weeks 8, 10, and 12 (Figure 2.4c).³³

Table 2.18: GEM-1: Primary endpoint analysis for wound closure (observed data)

Endpoint	B-VEC	Placebo*	Difference, %
Complete wound closure, n (%) [†]			
Week 8 (n=21)	13/14 (93)	0/7 (0)	93
Week 10 (N=20)	11/14 (79)	2/6 (33)	46
Week 12 (n=19)	10/12 (83)	1/7 (14)	69
Complete wound closure, n (%) [†]			
Weeks 8+10 (N=21)	11/14 (79)	0/7 (0)	79
Weeks 10+12 (N=19)	9/12 (75)	0/7 (0)	75
Responder analysis: complete wound closure [‡] at Weeks 8+10 or Weeks 10+12 (3 months); (n=21)	11/14 (79)	0/7 (0)	79 $p=0.0026^{\ddagger}$
Results and analysis reported are based upon observed data without imputed values for missing data. *One patient was not imaged and was excluded from the responder analysis. [†] Complete closure defined as $\geq 90\%$ reduction in wound surface area from baseline. [‡] Significant at $p<0.025$. The phase 1 protocol collected wound closure data at weeks 6 and 12 (no Week 8 or Week 10 datapoints), therefore the phase 1 patients (patients 1 and 2) were excluded from the responder analysis. Patient 4 withdrew after initial dosing due to inability to travel. Included in the analysis are data from Week 8 for patients 3–10, Week 10 for patients 3–10 (missing datapoint for patient 10, placebo), and Week 12 for patients 3–10 (missing datapoints for patient 7, B-VEC). B-VEC=beremagene geperpavec Source : Gurevich <i>et al.</i> (2022) ³⁴			

2.6.2.2 Durability of response

In the phase 1/2 GEM-1 study, median time to wound closure was shorter with B-VEC (13.5 days) than placebo (22.5 days), as shown in Table 2.19. Furthermore, median duration of wound closure was longer with B-VEC than placebo (103.0 vs. 16.5 days).

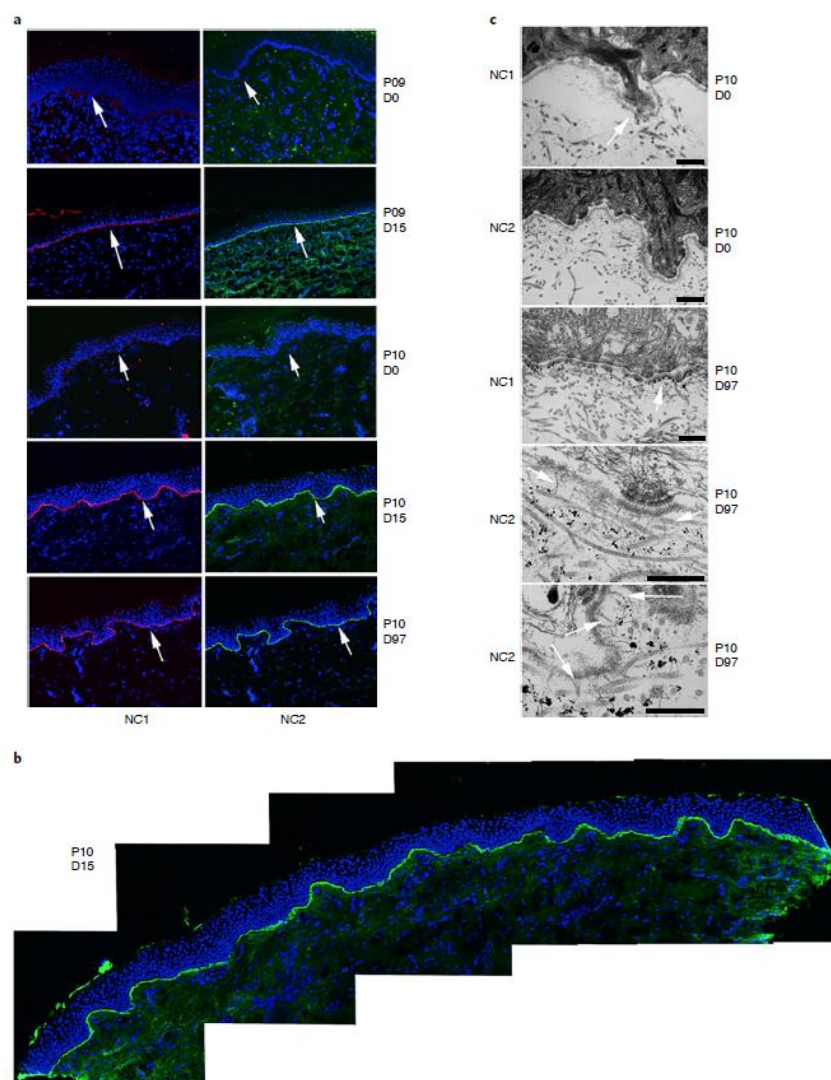
Table 2.19: GEM-1: Primary endpoint analysis for time to and durability of wound closure (observed data)

Endpoint	B-VEC	Placebo	p value*
Time to complete closure, 95% CI, days ^{†,‡}	13.5 (8–21)	22.5 (8–64)	0.0216
Duration of closure, median (95% CI), days [†]	103.0 (94–118)	16.5 (0–66)	0.0009
*p value based on log-rank test. [†]Complete closure defined as ≥95% reduction in wound surface area from baseline. [‡]Time to wound closure was defined as the time from the first treatment to complete wound closure (≥95% reduction in wound surface area from baseline) observed for 2 consecutive weeks. Results and analysis reported are based upon observed data without imputed values for missing data. B-VEC=beremagene geperpavec; CI, confidence interval Source: Gurevich <i>et al.</i> (2022)³³; Krystal Biotech Data on File (GEM-1 [KB103-001] CSR)⁸⁰			

2.6.2.3 Molecular correction of COL7

Analysis of microscopy data from GEM-1 indicated that B-VEC treatment restored COL7 NC1 and NC2 expression at the dermal–epidermal basement membrane consistent with the location of anchoring fibrils in normal skin (Figure 2.5).³³

Figure 2.5: Molecular correction of COL7 and anchoring fibrils after topical B-VEC therapy



^aRepresentative images showing indirect immunofluorescence analysis of COL7 NC1 and NC2 expression from biopsies obtained from patients 9 and 10 treated with topical B-VEC. Biopsies were analysed using dual label immunofluorescence for expression of the COL7 NC1 and NC2 domains using anti-NC1 antisera (red) and an anti-NC2 monoclonal antibody, LH24 (green), and counter-stained with nuclear stain (blue). The arrows indicate the dermal–epidermal junction.

^bExamination of COL7 NC2 expression across an entire tissue section of skin. Multiple sections of a skin biopsy taken from a healed wound area 15 days after B-VEC treatment were analysed using immunofluorescence and merged together to show the results across the entire tissue section.

^cRepresentative images showing immunoelectron microscopy analysis of COL7 NC1 and NC2 expression and anchoring fibrils following topical B-VEC treatment in patient 10. Images collected at the indicated times were analysed with immunoelectron microscopy using antibodies to the COL7 NC1 domain (NP185) and COL7 NC2 domain (LH24). Arrows in the upper and middle panel show positive immuno-gold staining for the NC1 domain in the lamina densa region. Arrows in the lower two panels show the presence of mature banded anchoring fibrils associated with immuno-gold staining for the NC2 domain approximately 300 nm from the lamina densa. Scale bars, 500 nm.

B-VEC=beremagene geperpavec; D=day; NC=noncollagenous; P=patient

Source: Gurevich *et al.* (2022)³³

2.6.2.4 Improvement in IGA and patient-reported pain scale

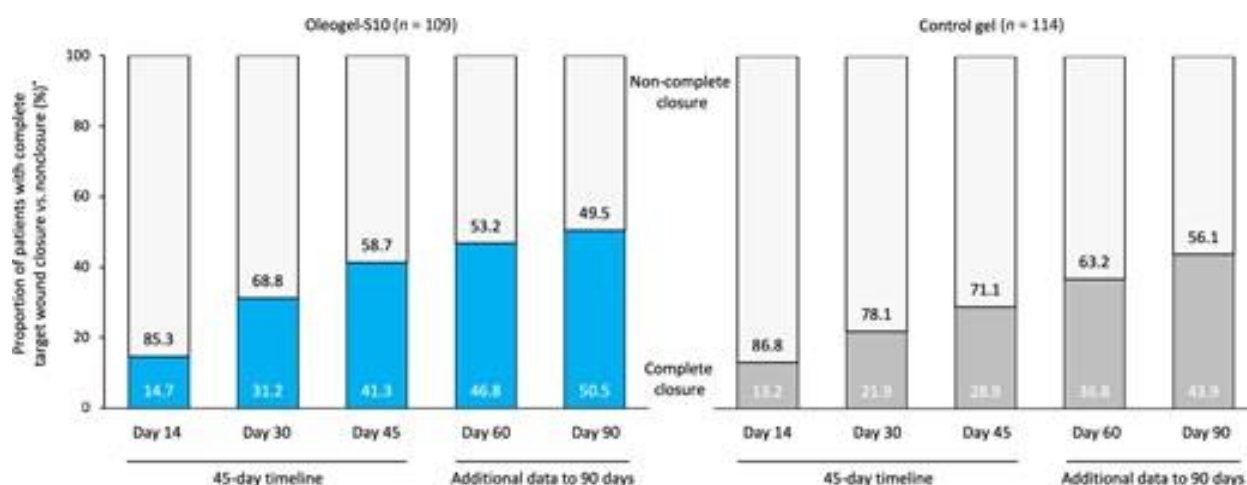
The secondary endpoints of IGA scores and patient-reported pain scale were evaluated at Days 3, 5, 15, 30, 60, and 90, and compared with baseline. B-VEC–treated patients had a numerically higher percentage of wound closure and a numerically lower mean pain score than placebo-treated patients over a 3-month period. No formal statistical comparisons were performed on IGA or patient-reported pain scores.⁸⁰

2.6.3 EASE: clinical efficacy results

2.6.3.1 Proportion of patients with first complete closure of EB target wound by Day 45

In the overall population (i.e., patients with DEB and JEB), complete closure of target wounds, defined as skin reepithelisation without drainage within 45±7 days of treatment, was achieved in 41.3% of wounds treated with BBE, compared to 28.9% of those treated with the control gel (RR 1.44, 95% CI 1.01–2.05; p0.013 [Figure 2.6]). This represents a 44% higher likelihood of wound closure with BBE versus control gel.⁶⁸

Figure 2.6: Proportion of patients with first complete closure of EB wound by visit



Note: In the BBE (Oleogel S10) group, 91 (83.5%) had RDEB, 6 (5.5%) had DDEB, and 11 (10.1%) had JEB. In the control group, 84 (73.7%) had RDEB, 14 (12.3%) had DDEB, and 15 (13.2%) had JEB. Two patients with EB simplex (EBS) were enrolled and were included in the analysis; a subsequent protocol amendment excluded EBS.

DDEB=dominant dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; RDEB=recessive dystrophic epidermolysis bullosa

Source: Kern *et al.* (2022)⁶⁸

Subgroup analysis by EB subtype showed that, in patients with RDEB, the likelihood of complete wound closure by Day 45 was significantly higher in the BBE group than

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

in the control group (odds ratio [OR] 2.52, 95% CI 1.27, 4.98). However, there were no differences between BBE and control gel in patients with DDEB (OR 1.25, 95% CI 0.15, 10.7).⁶⁸

2.6.3.2 Time to complete target wound closure

An analysis of time to first target wound closure up to day 90 was conducted over the key timepoints during the DBP; mean of 37.7 (standard deviation [SD] 21.7, 95% CI 50.0, NE) days and 44.5 days (SD 26.2, 95% CI 89.0, NE) in the BBE arm and control gel arm, respectively.⁶⁸ In the overall population, the difference in the time to first target wound closure in the two arms was not statistically significant (log-rank test, $P=0.302$).⁶⁸ Notably, no statistical difference was observed in any of the EB subtypes, including RDEB or DEB.

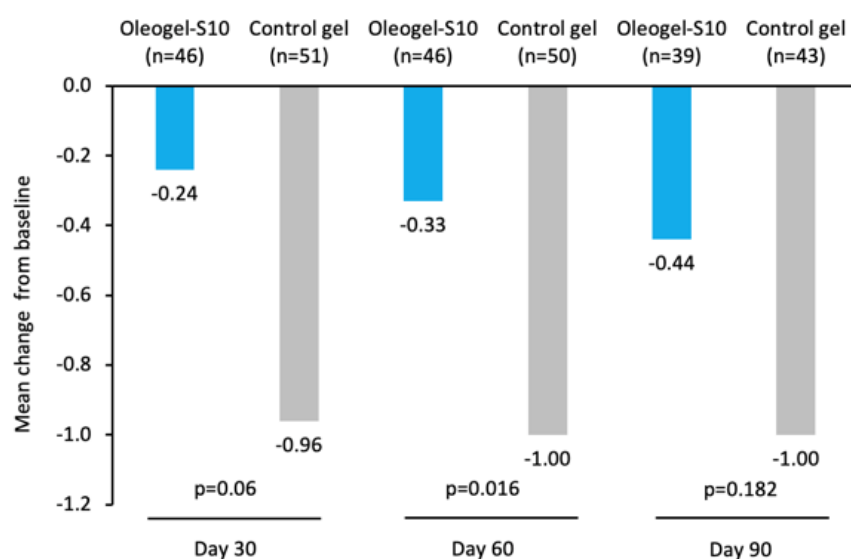
2.6.3.3 Total body wound burden

Differences in total wound burden (measured by EBDASI skin activity and BSAP) for the BBE arm compared with control gel did not reach statistical significance.⁶⁸

2.6.3.4 Procedural pain, itch

Among all patients aged 4-13 years, improvements in the Itch Man Scale (for patients aged 4–13 years) were observed with both treatments, although improvement was numerically higher with the control gel compared with BBE on Day 30 and Day 90, and significantly higher with the control gel on Day 60 (Figure 2.7). Data regarding itch was not provided separately for patients with DEB.

Figure 2.7: Evaluation of itch using the Itch Man Scale in patients ≥ 4 –13 years



Source: Kern *et al.* (2022)⁶⁸

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Data on procedural pain (pain during dressing changes), showed a significantly greater mean reduction in pain with BBE compared to the control gel on Day 14 (BBE -1.4, 95% CI -1.9 to 0.9; control gel -0.8, 95% CI -1.3 to -0.2; $p=0.02$). However, this difference was not statistically significant on Day 30, 45, 60, or 90. On Day 90, the reduction was -1.3 (95% CI -2.0 to -0.6) for BBE compared to -0.2 (95% CI -0.8 to 0.5) for the control gel ($p=0.051$).

2.6.3.5 Target wound infections

There were six patients with target wound infections: one patient (0.9%) in the BBE arm compared with five patients (4.4%) in the control gel arm.⁶⁸

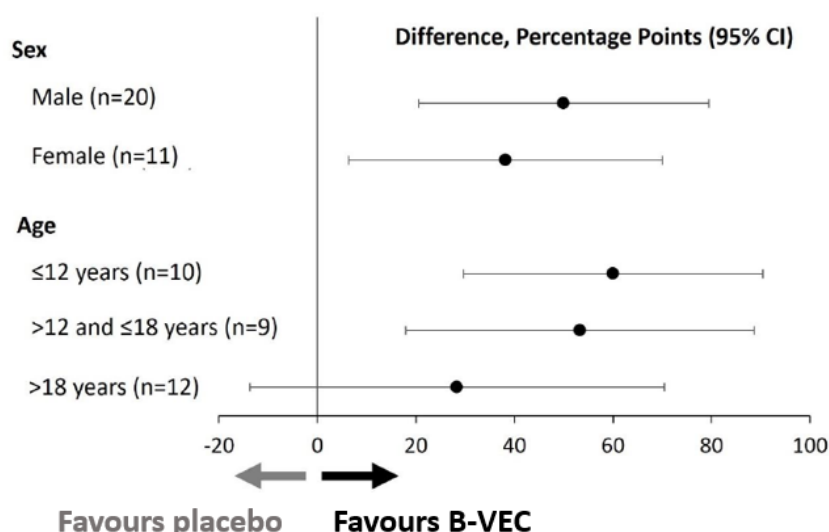
2.6.4 Subsequent treatments used in the relevant studies

There were no planned subsequent treatments administered in GEM-1, GEM-3, and EASE.

2.7 Subgroup analysis

There were no subgroup analyses undertaken in GEM-1. In GEM-3, subgroup analyses by sex and age were carried out for the primary efficacy endpoint (Figure 2.8). Although subgroups were not powered to demonstrate statistical significance, consistent treatment response favouring B-VEC was observed for both sexes (male; female) and all age groups (≤ 12 years; >12 and ≤ 18 years; >18 years).³²

Figure 2.8: Subgroup analyses for complete wound closure at 6 months in GEM-3

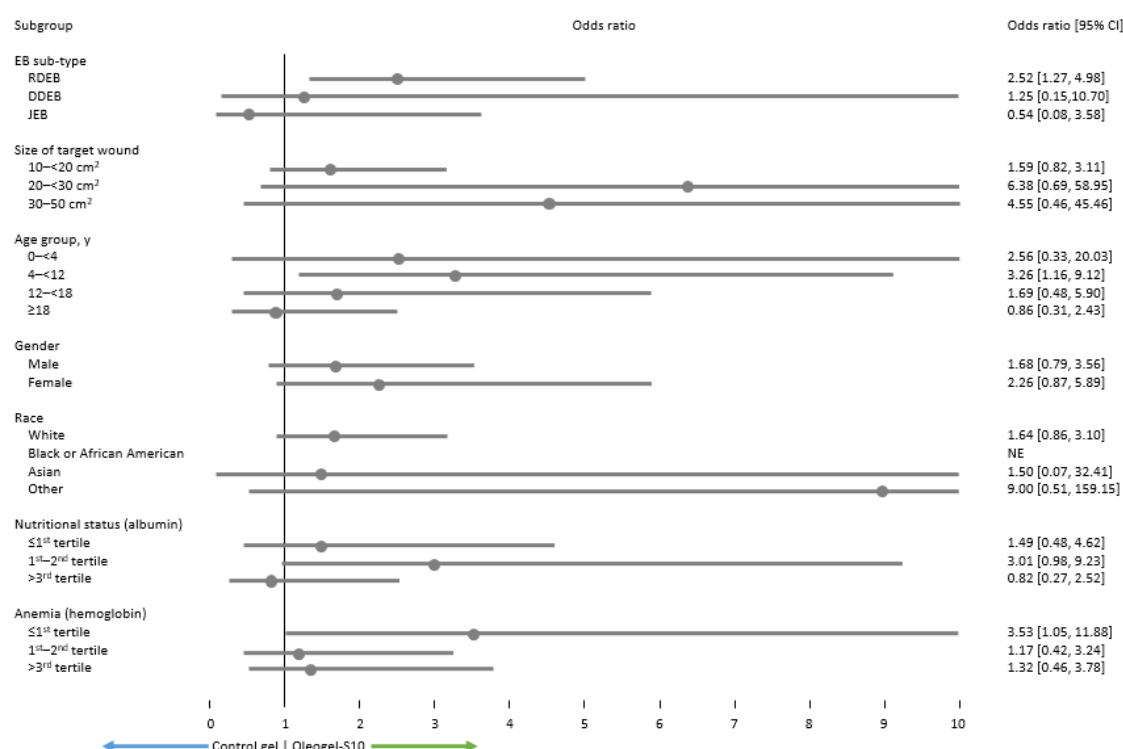


B-VEC=beremagene geperpavec; CI=confidence interval; ITT=intent-to-treat
Source: Guide *et al.* (2022)³²

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Figure 2.9 shows subgroup analyses from the EASE trial.

Figure 2.9: Subgroup analyses of the primary efficacy endpoint in EASE



CI=confidence interval; CMH=Cochran-Mantel-Haenszel; DDEB=dominant dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; EBS=epidermolysis bullosa simplex; eCRF=electronic case report form; EB=junctional epidermolysis bullosa; NE, not estimable (due to small number of patients available); RDEB, recessive dystrophic epidermolysis bullosa.

Currently, there is inadequate evidence to consider subgroup analysis for people with DDEB and people with RDEB in the relevant clinical trials. Although the EASE trial conducted subgroup analyses to compare the outcomes of people with DDEB and RDEB, the study was underpowered to determine a significant difference.⁶⁸ The planned post-authorisation safety study (PASS) will include the collection of the subtype of DEB based on genotype (RDEB or DDEB).

2.8 Meta-analysis

No meta-analyses were performed.

2.9 Indirect and mixed treatment comparisons

A feasibility assessment for an indirect treatment comparison (ITC) between BBE and B-VEC was conducted by Krystal Biotech. Four studies reporting on BBE or B-VEC, respectively, were identified: EASE (phase 3)⁶⁸ and BEB-10 (phase 2)⁸⁷, and GEM-1 (phase 1/2)³³ and GEM-3 (phase 3)³². The assessment identified several Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

sources of uncertainty, and therefore an ITC was not feasible. There are important differences between the pivotal studies assessing each intervention—study design, the study populations, outcome definitions, and treatment-effect modifiers and prognostic factors, which all have the potential to affect the robustness of an ITC.

Study design

In terms of study design, there were significant differences between the studies with regards to the treatment schedule. Further, the frequency of the application of placebo treatment differed between studies, meaning that it cannot be assumed that the effectiveness of placebo is consistent in each trial. Therefore, there is not a common comparator arm, analyses anchored on placebo could not be performed, and only (less reliable) unanchored analyses would be available for further consideration. Studies also differed in terms of permitted concomitant treatments, including differences in the use of concomitant topical medications (prohibited in GEM-3, discouraged in GEM-1, permitted in EASE, and not reported in BEB-10), with clinical opinion suggesting that concomitant treatment is a likely effect modifier. Another cause of uncertainty was that EASE used a parallel-group trial design, whereas the other three studies were intra-patient trials (i.e. two or more wounds within the same patient were treated with the intervention or comparator treatment). BEB-10 and GEM-1 were open-label studies, meaning patients and investigators knew which (part of the) wounds were treated with the active treatment or control gel (which can introduce bias). Lastly, there was wide variation in study duration from 14 days in BEB-10 to 26 weeks in GEM-3.

Patient population

The patient populations enrolled in the studies were also heterogeneous. The median age in EASE was 12 years, which was younger than GEM-3 (16 years), GEM-1 (21 years), and BEB-10 (20 years). Subgroup analyses in GEM-3 and EASE showed that patients aged <12 years had more favourable wound closure rates than older patients, therefore the age distribution of EASE is likely to bias treatment effects in favour of BBE compared with B-VEC.

At baseline, wounds in the B-VEC trials were smaller (median wound size of 10.6 cm² in GEM-3; 5.0 cm² in GEM-1) than in the BBE trial (median wound size of 15.6 cm² in EASE; mean wound size of 17.5-17.7 cm² in BEB-10). A subgroup analysis of wound closure rates from the EASE trial demonstrated patients with larger wounds had more favourable wound closure rates than patients with smaller wounds. This suggests that patients with larger wounds benefit more from receiving active treatment than those with smaller wounds, which would bias treatment effects in favour of BBE compared with B-VEC.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

EASE had a mixed population of patients with RDEB (n=175; 79%), DDEB (n=20; 9.0%), and JEB (n=26; 12%), while the other studies had no patients with JEB and no (GEM-1) or only one (GEM-3 and BEB-10) patients with DDEB. A subgroup analysis of wound closure rates from the EASE trial demonstrated that patients with RDEB had more favourable wound closure than patients with DDEB or JEB. Therefore, EB type appears to be an effect modifier that may bias an ITC in favour of B-VEC (more RDEB) if the ITT population from EASE were used in analyses.

Another potential source of heterogeneity arises from five (16.1%) GEM-3 patients who also undertook an earlier pilot study, therefore there is a high chance they were selected due to good results in the previous study and were subject to selection bias; this is acknowledged by the study authors.

Endpoint definition

Complete wound closure

Lastly, the definitions of endpoints differed across studies. All four studies reported data on complete wound closure at time of measurement; however, the results were reported at different timepoints. As the analysis aim was to compare the relative effectiveness of B-VEC versus BBE, timepoints were only evaluated if they were reported in at least one B-VEC trial and at least one BBE trial. This narrowed the evaluation to complete wound closure at 3 months (GEM studies) and 90 days (EASE).

Importantly, the definitions of complete wound closure differed between studies. EASE measured all wounds that had complete closure (definition not reported) at least once (without any confirmation of closure) by 90 days (even if the wound re-opened). Conversely, the GEM studies measured only wounds that were closed at 3 months (i.e., wounds that had closed and re-opened would not be counted as a success), with complete closure defined as at least 95% in GEM-1 and 100% in GEM-3.

Additionally, no confirmation of closure of wounds was required in EASE, while in the GEM trials closure of wounds had to be confirmed during two consecutive visits (only wounds closed in Weeks 8 and 10, or Weeks 10 and 12 were considered closed).

This would bias any ITC based on this outcome against B-VEC because a wound that closed early in the trial, but reopened by the 3 Month visit, would not be counted as closed in the GEM-3 trial, but would be counted as closed in the EASE trial. Similarly, a wound that was closed at the 3 Month visit had to remain closed 2 weeks later in GEM-3, which wasn't the case for EASE.

Time to wound closure

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Time to wound closure was reported in GEM-1, EASE, and BEB-10. While in GEM-1, the wound closure had to be observed in two consecutive weeks, this was not required in EASE or BEB-10, meaning that wounds that re-opened shortly after closing in EASE or BEB-10 would still be counted as a success. Therefore, results would be biased in favour of BBE.

Change in target wound size

Change in target wound size was reported in GEM-1, EASE, and BEB-10. The differences in endpoint definition are minor, pertaining to mixed use of mean and medians.

2.9.1 Uncertainties in the indirect and mixed treatment comparisons

As described in Section 2.9, an ITC was not possible. Therefore, this section is not applicable.

2.10 Adverse reactions

B-VEC is well tolerated and has not been associated with clinically significant immunologic reactions to the delivery vector.^{32,33,83}

2.10.1 GEM-3 safety findings

Table 2.20 summarises the safety findings from the phase 3 GEM-3 study. A total of 18 patients (58%) experienced at least one AE. Most events were mild; none led to treatment discontinuation or death. The most common AEs were (three events each) pruritus, chills, and SCC. Cases of SCC did not occur at sites of B-VEC or placebo administration. One AE (3%; mild erythema) was deemed possibly related to the study drug. Three patients (10%) experienced a total of five serious AEs, of which none were related to the study drug): cellulitis, anaemia (two events), diarrhoea, and positive blood culture. No clinically significant immunologic reactions were reported. Furthermore, treatment response to B-VEC was not associated with baseline HSV-1 serostatus or COL7 seroconversion. Repeated weekly treatment with B-VEC is well tolerated and has not been associated with clinically significant immunologic reactions to the delivery vector.³²

Table 2.20: GEM-3: Summary of AEs

Event	Safety population (N=31)
Total AEs, n*	45
Patients with ≥1 AE, n (%)†	18 (58)
Mild	15 (48)
Moderate	3 (10)
Severe	2 (6)
Serious‡	3 (10)

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Event	Safety population (N=31)
Related to B-VEC or placebo	1 (3)
Leading to discontinuation of B-VEC or placebo	0
AEs reported in ≥5% of patients, n (%) ^{†§}	
Skin and subcutaneous disorders	
Pruritus	3 (10)
Erythema	2 (6)
Rash	2 (6)
General disorders and site conditions: chills	3 (10)
Neoplasms: squamous-cell carcinoma of skin	3 (10)
Respiratory, thoracic, and mediastinal disorders	
Cough	2 (6)
Rhinorrhoea	2 (6)
*Data are for AEs that emerged or worsened after the first application of B-VEC or placebo. [†]At each level of summarisation, a patient was counted once if one or more events occurred. [‡]Five serious AEs occurred in three patients: one patient was hospitalised three times, once for diarrhoea (severe AE) and twice for severe anaemia (both severe AEs); one patient was hospitalised for treatment of cellulitis (severe AE); and one patient was hospitalised for a positive blood culture related to a haemodialysis catheter (moderate AE). [§]AEs were classified according to system organ class and preferred term in the Medical Dictionary for Regulatory Activities, version 24.1. AE=adverse event; B-VEC=beremagene geperpavec Source: Guide <i>et al.</i> (2022)³²	

2.10.2 GEM-1 safety findings

Twenty-one AEs were observed following 129 topical B-VEC doses that were administered during the phase 1/2 GEM-1 trial (Table 2.21). All events except one were considered mild; the exception was a moderate AE unlikely to be related to the study drug. Four mild events (fever, peculiar taste, rash, itch) were possibly related to the study drug. Two mild events (both application-site discharge) were probably related to the study drug. All AEs resolved without the need to reduce the B-VEC dosing or frequency.³³

No vector shedding was reported. HSV-1 antibodies, when present, were detected at variable levels before and after B-VEC treatment and did not affect efficacy or safety. Two patients had baseline COL7 antibodies (patients 2 and 5) and some COL7 titres increased after treatment; however, no tissue-bound skin immunoreactants were noted on immunofluorescence microscopy. The serum of patient 2 was subsequently found to be COL7 antibody-negative at approximately 28 months following B-VEC treatment. Patient 12 had no COL7 immunogenicity, despite having the greatest B-VEC exposure (8×10^8 PFU per dose every 1–2 days for two 25-day treatment cycles).³³

Table 2.21: GEM-1: Summary of AEs

Event	Safety population (N=12)
Total AEs, n	21
AEs experienced by patients, n	

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Event	Safety population (N=12)
Mild	20*
Moderate	1
Severe	0
Serious	0
Related to B-VEC or placebo	6†
Leading to discontinuation of B-VEC or placebo	0
*20 AEs were experienced by 9 patients †4 events were possibly and 2 probably related to study drug AE=adverse event; B-VEC=beremagene geperpavec Source: Gurevich <i>et al.</i> (2022) ⁸³	

2.10.3 GEM-3 OLE safety findings

A long-term extension (OLE) study (B-VEC OLE) was conducted to collect additional safety data in the context of longer duration of use.⁸³ The study provided extension of B-VEC treatment for participants who completed GEM-3 (rollover), and B-VEC treatment for newly enrolling (naïve) participants with DEB. The timing of the interval between end of treatment in the Phase 3 study and entry into this OLE study was not specified in the protocol.

Thirty-five patients (74.5%) experienced at least one treatment-emergent AE (TEAE) during the study (Table 2.22).⁸³

Table 2.22: GEM-3 OLE: Summary of AEs

Event	Rollover patients (N=24)		B-VEC naïve patients (N=23)		All patients (N=47)	
	n (%)	Events	n (%)	Events	n (%)	Events
Patients with ≥1 event						
TEAE	17 (70.8)	102	18 (78.3)	72	35 (74.5)	174
Drug-related TEAE	0	0	1 (4.3)	2	1 (2.1)	2
Severe TEAE	8 (33.3)	12	2 (8.7)	2	10 (21.3)	14
Serious TEAE	9 (37.5)	11	5 (21.7)	6	14 (29.8)	17
Drug-related serious TEAE	0	0	0	0	0	0
Serious TEAE leading to death	0	0	0	0	0	0
AE leading to premature discontinuation of study	0	0	0	0	0	0
Patients who died	0	0	0	0	0	0
AEs were coded using MedDRA, Version 25.0 AE=adverse event; B-VEC=beremagene geperpavec; TEAE=treatment-emergent adverse event. Source: Krystal Biotech Data on File (OLE [B-VEC-EX-02] CSR) ⁸³						

The TEAEs reported for at least 5% of patients are shown in Table 2.23. The most frequently reported TEAEs, reported for at least 10% of patients were COVID-19 (17 events in 15 patients, 31.9%), cough (11 events in 9 patients, 19.1%), pyrexia (9 events in 7 patients, 14.9%), skin infection (8 events in 6 patients, 12.8%), and vomiting (5 events in 5 patients, 10.6%). The types of TEAEs reported were similar

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

to those observed in the GEM-3 study,³² and consistent with those expected in the study population.⁶

Table 2.23: GEM-3 OLE: AEs reported for at least 5% of patients by system organ class and preferred term (safety population)

System organ class Preferred term	Rollover patients (N=24)		B-VEC naïve patients (N=23)		All patients (N=47)	
	n (%)	Events	n (%)	Events	n (%)	Events
Any TEAE	17 (70.8)	102	18 (78.3)	72	35 (74.5)	174
Infections and infestations						
COVID-19	9 (37.5)	9	6 (26.1)	8	15 (31.9)	17
Skin infection	4 (16.7)	4	2 (8.7)	4	6 (12.8)	8
Cellulitis	3 (12.5)	4	1 (4.3)	1	4 (8.5)	5
Rhinitis	3 (12.5)	3	1 (4.3)	1	4 (8.5)	4
Wound infection	2 (8.3)	2	1 (4.3)	2	3 (6.4)	4
Respiratory, thoracic, and mediastinal disorders						
Cough	6 (25.0)	8	3 (13.0)	3	9 (19.1)	11
Rhinorrhoea	2 (8.3)	2	2 (8.7)	2	4 (8.5)	4
General disorders and administration site conditions						
Pyrexia	5 (20.8)	7	2 (8.7)	2	7 (14.9)	9
Gastrointestinal disorders						
Vomiting	2 (8.3)	2	3 (13.0)	3	5 (10.6)	5
Diarrhoea	2 (8.3)	2	1 (4.3)	1	3 (6.4)	3
Metabolism and nutrition disorders						
Dehydration	2 (8.3)	2	1 (4.3)	1	3 (6.4)	3
AEs were coded using MedDRA, Version 25.0 AE=adverse event; B-VEC=beremagene geperpavec; TEAE=treatment-emergent adverse event. Source: Krystal Biotech Data on File (OLE [B-VEC-EX-02] CSR) ⁸³						

Of the 173 TEAEs with severity reported, 137 were mild, 22 were moderate, and 14 were severe. The 14 severe events occurred in 10 patients and included severe adverse events (SAEs) of cellulitis (2 patients), dehydration, pain (2 events for 1 patient), stridor, skin infection (2 patients), bacteraemia, pancreatitis, anaemia, and oesophageal stenosis, and TEAEs of Staphylococcal infection and squamous cell carcinoma. All of the severe TEAEs were reported as not related to study treatment and resolved.⁸³

Of the 173 TEAEs with relationship to study treatment reported, no events were considered by the investigator to be related to study treatment, 2 as possibly related (both events of wound haemorrhage), 10 as unlikely related, and 161 as not related.⁸³

Twenty-five (53.2%) participants reported 80 local TEAEs. Among all local TEAEs, information on the specific location was available for 48 of 80 (60%). Based on the information available, local TEAEs were categorised into 3 groups: TEAEs that occurred within the same target area as wounds that received IP, TEAEs that Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

occurred in a target area that was not treated with IP, and TEAEs where no information regarding location was received. Overall, the proportion of participants with local TEAEs was similar for treated target areas (17.0%) and non-treated target areas (21.3%). Infections and infestations were the most common local TEAEs (40.4%). Among infections, the proportion of participants with local TEAEs was similar for treated target areas (12.8%) and non-treated target areas (12.8%).⁸³

Nine (37.5%) rollover patients experienced 11 SAEs, which included cellulitis (2 patients), skin infection (2 patients), COVID-19 (1 patient), dehydration (1 patient), pain (1 patient), anaemia (1 patient), and bacteraemia and pancreatitis (1 patient). Five (21.7%) B-VEC naïve patients experienced 6 SAEs, which included skin infection (1 patient), oesophageal stenosis (1 patient), dehydration (1 patient), stridor (1 patient), and haematemesis and bronchial hyperreactivity (1 patient). All of the SAEs were considered not related to study treatment by the investigator.⁸³

No deaths occurred during the study, and no TEAEs lead to discontinuation.⁸³

2.10.4 EASE safety findings

At least one AE was experienced by 81.7% and 80.7% of patients receiving of the BBE and control gel, respectively (Table 2.24).

Serious AEs were reported in 6.4% of patients treated with BBE compared with 5.3% in those treated with control gel. There was one serious AE related to BBE that led to study withdrawal, a wound haemorrhage. Treatment-related AEs were observed in 24.8% and 22.8% in patients taking BBE and control gel, respectively.

Table 2.24: EASE: summary of AEs

AE category/system organ class preferred term	BBE (n = 109)	Control gel (n = 114)
Any AEs	89 (81.7)	92 (80.7)
Any serious AEs	7 (6.4)	6 (5.3)
Any severe AEs	13 (11.9)	6 (5.3)
Any AEs leading to study withdrawal	3 (2.8)	2 (1.8)
Any serious AEs leading to study withdrawal	2 (1.8)	0 (0.0)
Any serious related AEs leading to study withdrawal	1 (0.9)	0 (0.0)
Any serious AEs leading to death	0 (0.0)	0 (0.0)
AEs related to treatment	27 (24.8)	26 (22.8)
AE=adverse event. Source: Kern <i>et al.</i> (2023) ⁶⁸		

2.10.5 EASE OLP safety findings

An OLE study of EASE was conducted to collect additional safety data in the context of longer duration of use, in which all patients received BBE. AEs were reported in 77.1% of all patients during the OLP.⁸⁸

2.11 Ongoing studies

There are no ongoing studies evaluating B-VEC in the treatment of DEB.

2.12 Interpretation of clinical effectiveness and safety evidence

B-VEC is a novel, redosable genetic therapy engineered to deliver functional *COL7A1* gene in a minimally invasive way to the skin to restore COL7 production to levels present in people without DEB. Findings from clinical trials of B-VEC support the efficacy, tolerability, and safety of weekly repeat dosing with B-VEC.^{32,33,83}

Studies across a range of patient ages and wound sizes have shown that B-VEC is efficacious in restoring the structural stability of the skin for directly treated wounds. Repeated topical application of B-VEC in people with DEB results in full-length COL7 protein expression, normalised anchoring fibril formation, and complete, durable, and consistent wound closure, regardless of sex, age, and wound size. B-VEC is well tolerated and has not been associated with clinically significant immunologic reactions to the delivery vector.^{32,33}

In addition, B-VEC treatment leads to numerically greater improvements in pain compared with placebo treatment. Although the effect size is modest, the mean change in pain in GEM-3 is favourable and directionally consistent with wound closure.³² Although the intra-patient study design of GEM-3 aligns with FDA guidance for studying genetic skin conditions,⁸⁹ it is possible that this study design makes it challenging for patients to differentiate pain during dressing change for one wound (B-VEC treated) versus another (placebo treated). It is also possible that substantial improvements in pain are not detectable in patients with low baseline pain levels as there is less room for pain improvement. Baseline pain scores were ~2 to 3 out of 10 in GEM-3 compared with patient-reported scores of ≥ 4.5 out of 10 in a US survey.^{6,72}

The low baseline pain scores in GEM-3 may be a consequence of the need to meet the study inclusion criteria (i.e., finding patients with two cutaneous wounds similar in size, anatomical region, and appearance), rather than a reflection of the maximum pain experienced by patients with DEB during dressing changes.⁷⁸

Findings from the GEM-3 and OLE studies support the tolerability and safety of weekly repeat dosing with B-VEC.^{32,83} In both studies, the majority of TEAEs were

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

mild or moderate in severity, and were consistent with those expected in patients with DEB.

It is expected that B-VEC would be used to treat DDEB and RDEB patients. The majority of patients in GEM-3 had RDEB, however, in one patient with DDEB, complete wound closure at six months was achieved in the B-VEC-treated wound but not in the placebo-treated wound. Primary wounds were predominantly less than 40 cm², consistent with global survey data, although wound closure was noted even among large secondary wounds. The relatively small sample size limited the ability to conduct extensive subgroup analyses; however, the direction of treatment effect was consistently in favour of B-VEC across the pre-specified subgroups for age and gender.⁷⁸

The phase 3 GEM-3 trial evaluated wound closure, change in pain severity, and change in HRQoL,⁷⁸ which have been identified as priorities for treatment. Given that people with DEB have identified rapid improvement in skin condition, closure of skin alterations, freedom from itching and pain, and the ability to lead a normal daily life as the most important needs of treatment, treatment with B-VEC is expected to address key needs of patients with DEB. Further, considering that B-VEC is the only treatment that addresses the underlying mechanism of DEB by restoring functional protein COL7 in the cell,⁹⁰ its effect is expected to have superior durability over the current standard of care.

3 Cost-effectiveness

A *de novo* cost-effectiveness model (CEM) was developed to estimate the cost and healthcare resource use (HCRU), HRQoL, and survival impact of B-VEC for the treatment of DEB compared with BSC and BBE, for patients with DEB and their carers over a patient's lifetime with England as the base country. The model was designed to capture the benefit of B-VEC treatment on wound closure and durability of wound closure, and the prevalence of clinical manifestations associated with open wounds. The perspective taken was that of the NHS and Personal Social Services for costs and health effects.

Considering the current CEM aims to represent the actual HCRU and costs of DEB treatment in England, conservative estimates of the least expensive medications were made. Costs pertaining to drug use, concomitant medications, clinical manifestations, monitoring and bandage/dressing costs were incorporated. Patient HRQoL was gathered through a vignette study using the NICE-preferred EQ-5D-3L instrument, while carer HRQoL was gathered through the time trade-off (TTO) instrument in a validated approach also used in a previous NICE technology appraisal. Clinical inputs were mostly derived from the GEM trials and expert clinician input.

As discussed in Section 1.3.2., DEB results in the opening, closing, and re-opening of wounds. Complications from extensive scarring and fibrosis can lead to long-term complications and increased mortality for people with DEB.^{7,9,14-17} Considering that B-VEC has been specifically designed to address the underlying pathophysiology of DEB,^{32,33,39} patients initiating treatment with B-VEC are expected to have fewer recurrent and chronic wounds, less scarring and fibrosis, less potential to develop secondary long-term complications, and reduced risk for early mortality. The current CEM aims to capture the reduction of opened wounds as a result of B-VEC administration by defining the severity of the health states by BSA affected. The CEM follows simulated patients over a lifetime horizon due to the chronic and long-term nature of DEB.

3.1 Published cost-effectiveness studies

An SLR was conducted with the objective of identifying studies in published literature, pertaining to economic evaluations, cost and HCRU, and utility data in DEB. Table 3.1 provides a summary of the publications identified in this SLR that were relevant for this submission. Details of the searches and results of the SLR are provided in Appendix E.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

A total of four publications reporting three economic models were identified in the SLR. Two were deemed relevant for this submission as they are cost-effectiveness analyses for BBE; one as part of a reimbursement submission to Scottish Medicines Consortium (SMC)⁹¹ and one to NICE²⁴. In the submission to NICE, BBE resulted in an incremental cost-effectiveness ratio (ICER) of £95,980/quality adjusted life year (QALY) when compared with BSC. In the submission to SMC, BBE resulted in an ICER of £141,805/QALY.²⁴ The remaining two publications are discussed in Appendix E.

Table 3.1: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs	Costs	ICER (per QALY gained)
HST28 Highly Specialised Technology: Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa ID1505 ²⁴	2023	<i>De novo</i> CEM assessing impact of BBE gel for the treatment of partial-thickness wounds, relative to standard of care alone, for EB patients and their carers over a patient lifetime	People 6 months and older with partial-thickness wounds associated with DEB or JEB	BBE: 48.3 CCM: 46.0	BBE: £1,155,726 CCM: £939,290	£95,980
Birch bark extract (Filsuvez) ⁹¹	2024	<i>De novo</i> CEM assessing impact of BBE gel for the treatment of partial-thickness wounds, relative to standard of care alone, for EB patients and their carers over a patient lifetime	Patients 6 months and older with partial-thickness wounds associated with DEB or JEB	11.75	BBE: £1,188,219 CCM: £1,043,831	£141,805
BBE=birch bark extract; CCM=current clinical management; CEM=cost-effectiveness model; DEB=dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; JEB=junctional epidermolysis bullosa; QALYs=quality-adjusted life years; ICER=incremental cost-effectiveness ratio; UK=United Kingdom						

3.2 Economic analysis

The SLR commissioned by Krystal Biotech, which encompassed economic analyses, cost and HCRU, and utility data showed a scarcity of relevant economic analyses for EB treatments. Although two cost-effectiveness models were identified, they were both based on BBE. As explained in Section 2.9, there are important heterogeneities between the clinical trials of BBE and B-VEC, which makes it impossible to adapt those models for the current analysis. Therefore, a *de novo* Markov model was developed to assess the cost effectiveness of B-VEC compared with BBE, and BSC, as treatments for patients with DEB. This CEM incorporated expert opinion from physicians involved in the treatment of DEB in England for model inputs and assumptions.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

The pivotal GEM-1 trial was largely used for modelling the efficacy of B-VEC, as it tracks the size of B-VEC and placebo-treated wounds on a weekly basis for 24 weeks, while the GEM-3 trial only provides data on complete closure at 3 and 6 months. HRQoL data were derived from a vignette study, in which utilities were gathered through the NICE-preferred instrument, EQ-5D-3L. To calculate transitions between health states in the model—dependent on the proportion of BSA affected by recurrent and chronic wounds—data on the proportion of BSA open over time, reflecting wound closure and reopening, are required. Since these data are not directly available from the GEM clinical trials, individual patient simulations were conducted using data from GEM-1, GEM-3, and OLE studies, as well as relevant literature. Further details on the patient simulation in this model are presented in Section 3.2.2.1.

As an ITC for the change in wound size over time versus BBE was not feasible (see Section 2.9), it was not possible to include this product in the patient-level simulation. Instead, the comparison with BBE was introduced into the CEM by using an alternative methodology based on available data from NICE HST28 (see Section 3.3.1).²⁴

Consultants in Dermatology with expertise in DEB, were consulted for their opinions regarding modelling assumptions. Briefly, Krystal Biotech collaborated with York Health Economics Consortium (YHEC), a research company owned by the University of York to conduct a survey and validation workshop. Krystal Biotech identified assumptions requiring clinical validation following previous model discussions and calibration exercises. Overall, assumptions relating to 12 fields were selected.⁹² In the survey, the clinicians were presented with a series of assumptions and asked to indicate whether they agree or disagree that the assumptions are appropriate. Responses were recorded on a four-point Likert scale that ranged from 'strongly agree' to 'strongly disagree'. The survey was designed to take no longer than 15 minutes to complete to mitigate the response burden. Interactive HTML tooltips and hyperlinks were implemented to provide supplemental information about sources or definitions (e.g. health states). In total, two expert clinicians (Dr. Gabriela Petrof, and Dr. Anna Martinez) with experience in treating patients with DEB attended the meeting, and one additional expert clinician participated in the survey (Dr. Jemima Mellerio). A detailed report of the validation workshop is provided in Appendix J.

3.2.1 Patient population

The target population in this CEM comprised people with DEB who are: paediatric patients <6 years old; paediatric patients between 6-17 years old; or adult patients

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

(≥18 years old). These age subgroups were created because the differences between them were considered relevant, especially in terms of total BSA, which determines the absolute area with open wounds to be treated. These patient groups align with the populations in the pivotal B-VEC clinical trials, GEM-3 and GEM-1, and with the Summary of Product Characteristics (SmPC) for B-VEC, which states “Vyjuvek is indicated for the treatment of wounds in patients with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene, from birth.”¹

The phase 3 trial, GEM-3 (NCT04491604), enrolled 31 patients 6 months or older with genetically confirmed DEB. The phase 1/2 trial, GEM-1 (NCT03536143), enrolled 9 patients with RDEB.

Table 3.2 presents the baseline distribution of patients according to the age subgroups and DEB subtype based on GEM-3 data (Krystal Biotech, data on file), average age and the average BSA for each age subgroup.

Table 3.2: Baseline distribution and characteristics of patients in GEM-3 according to age subgroups

Age subgroups	Proportion of patients*	Average age, years*	RDEB			DDEB		
			Average weight (kg) [†]	Average height (cm) [†]	Average BSA (cm ²), calculated [‡]	Average weight (kg) [‡]	Average height (cm) [§]	Average BSA (cm ²), calculated [‡]
0 to <6 years	12.90%	2.25	11.06	88.07	5,129	12.95	90.74	5,607
6 to <18 years	48.39%	12.62	25.41	137.71	10,097	41.98	151.71	13,408
≥18 years	38.71%	27.99	38.81	164.68	13,764	63.63	172.21	17,541
BSA=body surface area; DDEB=dominant dystrophic epidermolysis bullosa; RDEB=recessive epidermolysis bullosa * based on GEM-3 data ⁷⁸ † based on Reimer <i>et al.</i> (2020) ⁴⁸ in the respective age and weighted by gender in GEM-3 data for each age group ‡ based on the Du Bois equation ⁹³ § based on WHO growth tables for the general population ⁹⁴								

In addition to age groups, the model also considered the proportion of patients with RDEB and DDEB, respectively. This is because, according to UK clinical expert elicitation (full details in Appendix J) and published data,⁴⁸ patients with RDEB are smaller and have a shorter life expectancy compared to the general population, while patients with DDEB have height, weight and life expectancy similar to those of the general population. Based on Bruckner *et al.*, it was considered that 57.6% (19 of the 33 included patients) have RDEB, and the remaining 42.4% (14 of the 33 included patients) have DDEB.⁶

The proportion of patients in each age group and average age are based on GEM-3 data.⁷⁸ Reimer *et al.* (2020) reported data on the weight and height of 200 German children with EB (157 with RDEB and 43 with JEB).⁴⁸ The height and weight of Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

RDEB patients was derived using the 50th percentile of RDEB data from this study, considering the mean age in each subgroup. The height and weight of DDEB patients was derived using the 50th percentile of general population growth curves in the UK considering the mean age in each subgroup. This approach was taken because clinical experts consulted by Krystal Biotech noted that the height and weight of DDEB patients is aligned with that of the general population. The weight and height data reported for the oldest age groups of Reimer *et al.* (22-27 years) and the general population statistics (18 years), for RDEB and DDEB respectively, were used for the adult cohort of the analysis.⁴⁸

BSA was calculated based on the Du Bois equation⁹³ (Equation 1 below).

$$BSA[m^2] = Weight [kg]^{0.425} \times Height [cm]^{0.725} \times 0.007184 \quad (Equation 1)$$

In terms of gender distribution, there is no evidence indicating a different predisposition to DEB between males and females. However, in line with the observed data from GEM-3, it was considered that 64.5% of patients (independent of age subgroup) are males.⁷⁸

3.2.2 Model structure

Key features of the economic model structure are shown in Table 3.3. A Markov model was developed using Microsoft ExcelTM to assess costs and effects, life-years (LYs), and QALYs of B-VEC and BSC in a simulated cohort of DEB patients. The Markov model looks at changes in affected BSA over time. The pivotal B-VEC trials, GEM-1 and GEM-3, had no information regarding the total BSA with open wounds or the total number of wounds per patient, instead the GEM trials only provide data at the level of the *target* wound.

The economic model for B-VEC follows a similar structure as a previous NICE technology appraisal (HST28),²⁴ where affected BSA is tracked over time. Considering that in GEM-1 and GEM-3, no direct outcomes could inform patient transitions between health states based on the total percentage of BSA with open wounds, the intermediate step of a patient-level simulation was used to generate transitions between health states (based on BSA). Details on this approach are presented in Section 3.2.2.1.

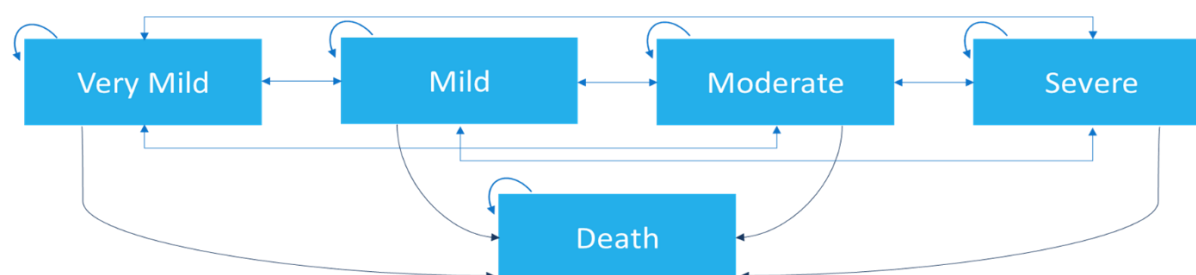
The model captures the benefit of B-VEC treatment in accelerating wound closure and durability of wound closure, and decreasing the prevalence of clinical manifestations associated with the presence of open wounds.

The cohort transitioned across five health states (Very Mild, Mild, Moderate, Severe, and Death). The model allows transitions from a health state for a non-neighbouring health state independently of whether the following health state represents an

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

improvement or a worsening, except when patients enter the Death health state, which they cannot leave (Figure 3.1).

Figure 3.1: Model design



Three age subgroups were created to reflect the differences between them in total BSA and therefore the absolute BSA covered by wounds to treat, patient distribution over the health states, disease progression and, consequently, HCRU.

All patients in the cohort enter the model according to the proportion of patients in each health state in each age subgroup as discussed in Section 3.2.2.3.

The efficacy of B-VEC and BSC was based on the transition probabilities obtained from a simulation tool, discussed in Section 3.2.2.1, using data from GEM-1 and GEM-3 trials.^{78,80} GEM-1 data were predominantly used to model B-VEC effectiveness because GEM-1 tracked the size of B-VEC and placebo-treated wounds on a weekly basis for 24 weeks, while GEM-3 only provided data on complete closure at 3 and 6 months. The following data points were used:

- Weekly percentage change in wound size
- Durability of closure
- Maximum BSA that can be treated weekly

The efficacy of BBE in the model was based on data reported in the NICE HST dossier for this product as described in Section 3.3.²⁴

In each Markov cycle, a patient can transition between any of the four alive health states (i.e., Very Mild, Mild, Moderate, and Severe) based on the transition probabilities obtained from the patient-level simulation for B-VEC and BSC or mapped from NICE HST28 in the case of BBE,²⁴ or the cohort may transition to death from any alive health state. No deaths were observed in the GEM-1 and GEM-3 trials, likely due to the short follow-up in both trials: 6 months (3 months of on-site visits followed by 3-month at-home imaging period) and 7 months (6-month dosing period followed by a 30-day safety follow up), respectively.⁹⁵ Nevertheless, in line with literature findings, the model includes mortality for patients according to health state (Section 3.3.5).

Table 3.3: Features of the economic analysis

	Previous appraisals	Current appraisal	
Factor	HST28	Chosen values/ sources	Justification
Time horizon	50 years	Lifetime (up to 100 years)	The lifetime horizon is the appropriate time scale for the CEA, given that DEB is a genetic disease that commonly presents in infancy or childhood and requires long-term specialist management across a patient's lifetime.
Cycle length	30 days	3 months	The cycle length is in accordance with the data time point for which the outcomes from GEM-1 and GEM-3 are available. This aligns with feedback from clinicians, who stated that they typically follow their patients every 3 months.
Model start age	16.7 years	Subgroup 0-6 years: mean 2.2 years Subgroup 6-18 years: mean 12.6 years Subgroup ≥ 18 years: mean 28.0 years	The average age in each subgroup is based on data from the pivotal trial for B-VEC, GEM-3.
Transition probabilities	EASE DBP	Simulated using data from GEM-1 and GEM-3 trials	There are no outcomes from the GEM clinical trials that could directly inform the transition of patients between health states based on the total percentage of their BSA that is open, therefore individual patients were simulated.
Source of resource use estimates	Literature/SEE estimates	HST28 committee papers, British National Formulary, SEE estimates	The current analysis was developed with the aim of including healthcare resources and costs that would closely represent the actual health care resource utilization and costs of DEB treatment in England and Wales.
Source of utilities	EASE (EQ-5D-3L and EQ-5D-Y)	Vignette study using EQ-5D-3L (UK general population)	The base case analysis assumed a health state vignette approach to define a base utility value based on the percentage of BSA covered by wounds and the pain and itching resulting from open wounds.
Mortality	Estimates based on Petrof <i>et al.</i> (2022) ¹¹	Estimates based on Petrof <i>et al.</i> (2022) ¹¹	Given the lack of trial evidence and natural history data from the existing literature, Kaplan-Meier curves from Petrof <i>et al.</i> (2022) ¹¹ were used to estimate mortality for each EB subtype.
Discontinuation	8.3% at 90 days, 1% per annum thereafter	1% per annum	In the GEM-1 and GEM-3 no discontinuations were observed; however, in a lifetime of B-VEC use, it is expected that some patients would discontinue. Discontinuation rate of 1% per annum aligns with the assumption in HST28. ²⁴
BSA=body surface area; B-VEC= Beremagene geperpavec; CEA=cost-effectiveness analysis; DBP=double-blind phase; DEB=dystrophic epidermolysis bullosa; EQ-5D-5L=EuroQol 5-Dimension 5-Level; EQ-5D-Y=EuroQol 5-Dimension Youth; SEE=structured expert elicitation			

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

3.2.2.1 Patient-level simulation

In GEM-1 and GEM-3, select wounds were randomised to receive B-VEC or placebo (two B-VEC and one placebo in GEM-1, and one B-VEC and one placebo in GEM-3), and each patient was treated with B-VEC for some wounds and with placebo for other wounds (i.e., patients served as their own control). Additionally, no information was available about the total BSA with open wounds or the total number of wounds per patient, instead the GEM trials only provide data at the (target) wound-level. This means that there are no outcomes from the GEM clinical trials that could directly inform the transition of patients between health states based on the total percentage of their BSA that is open.

To calculate transitions between health states in the model (which are dependent on the proportion of BSA covered in recurrent and chronic wounds), data are needed about the proportion of BSA open over time, with wounds closure and reopening. To address the issue of these data not being directly available from the GEM clinical trials, individual patients were simulated using data from GEM-1, GEM-3, and the OLE, and the broader literature. Data sources that were used in the patient-level simulation to estimate transitions between health states are listed in Table 3.4.

Table 3.4: Data sources used in the patient-level simulation to estimate transitions between health states

Model Input	Source
Baseline characteristics	GEM-3 ⁷⁸
Total BSA per age group	Reimer <i>et al.</i> (2020) ⁴⁸ (RDEB) General population ⁹⁶ (DDEB)
Rate of wound closure	GEM-1 ⁸⁰
Duration of wound closure in the BSC arm	GEM-1 ⁸⁰
Duration of wound closure in the B-VEC arm	GEM-3 and OLE
Number of wounds at risk of reopening	Eng <i>et al.</i> (2021) ²²
Size and increase in size of reopened wounds	GEM-1 ⁸⁰
Definition of chronic wounds	Eng <i>et al.</i> (2021) ²²
Proportion of weeks without treatment (compliance)	GEM-3 ⁷⁸
BSA=body surface area; BSC=best supportive care; OLE=open-label extension.	

The proportion of BSA open was tracked for up to 3 years to inform the calculation of transition probabilities and B-VEC vial consumption for the Markov model.

As an ITC for the change in wound size over time versus BBE was not feasible (see Section 2.9), it was not possible to include this product in the patient-level simulation. Instead, it was introduced into the CEM by using an alternative methodology based on available data from NICE HST28²⁴ (see Section 3.3.1).

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

3.2.2.1.1 Simulating baseline characteristics

The first step of the patient-level simulation was to simulate a cohort of 1,000 individual patients who were subsequently tracked while being hypothetically treated with B-VEC or placebo. The following characteristics at baseline were sampled:

1. Age group: A random number between 0 and 1 was used to sample the age group in which the simulated patient falls. If the random number was below 1/3, then the patients was in the 0-6 age group. If the random number was greater or equal to 1/3 and below 2/3, the patient was in the 6-18 years age group. For greater values, the patient was placed in the adult (18 years and older) age group. Thirds were used instead of the proportions in Table 3.2, to ensure that enough patients started the simulation in each age group, so that a rerun of the simulation is not required when a different age group distribution at baseline is selected. The proportions in the age groups presented in Table 3.2 are used in the Markov calculations.
2. Total BSA: A normal distribution was assumed around the average BSA for each age category. A random number between 0 and 1 was used to assign an exact BSA to the simulated patient considering the age group and the standard deviation of the mean BSA for the respective age group. For example, for an RDEB patient in the second age group (6-18 years old), the simulated BSA was drawn from a normal distribution with the respective mean BSA (10,097 cm²) and standard deviation (1,694 cm², given by the lower – 3rd percentile – and upper – 97th percentile – bounds of weight and height of patients considering the age in each age subgroup).
3. Health state: A random number between 0 and 1 was used to sample the health state to which the simulated patient was assigned at baseline. If the random number was below 1/3, then the patients was in the Mild health state, if the random number was greater or equal to 1/3 and below 2/3 then patient was in the Moderate health state; for greater values, the patient was in the Severe health state. Thirds were used to ensure that enough patients started the simulation in each health state, so that no rerun of the simulation is required when a different health state distribution at baseline is selected.
4. BSA with open chronic wounds: Within each health state, a uniform distribution of the BSA covered in chronic wounds was assumed. A random number between 0 and 1 defined the exact percentage of BSA covered in chronic wounds.
5. BSA with recurrent wounds: Within each health state, a uniform distribution was assumed with regards to the BSA covered in recurrent wounds. A random number between 0 and 1 defined the exact % of BSA covered in recurrent wounds.

Once the baseline patient characteristics for a patient were sampled, the next step was to track each patient in the hypothetical B-VEC and placebo arms.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

3.2.2.1.2 BSC arm

3.2.2.1.2.1 Wound Closure

Even though GEM-1 is a phase 1/2 study including only 9 patients (with a total of 20 wounds treated with B-VEC and 11 wounds treated with placebo), leading to a relevant uncertainty, it was considered the most useful source of data on which to base the wound evolution over time in the economic model. In the GEM-1 trial, all the wounds treated with placebo were recurrent (defined as wounds that healed within 12 weeks but subsequently reblistered in the same location).^{33,86} For recurrent wounds in the BSC arm, outcomes from the placebo arm of GEM-1 were used to define the wound dynamics of the existing open area. Using the average proportion of area closed per week and considering only the weeks where at least 50% of the wounds are still open (until week 6), it was found that 14.17% of the recurrent area that was open, closed spontaneously on a weekly basis.

In the absence of evidence on chronic wounds, and because chronic wounds, by definition, do not close, it was assumed that chronic wounds never close spontaneously in the BSC arm. Therefore, the area that is open chronically can only increase through recurrent wounds becoming chronic.

3.2.2.1.2.2 Wound Reopening

To calculate the probability of a wound reopening, the median duration of closure of the placebo-treated wounds was used (16.5 days in the GEM-1 trial). The weekly probability of a placebo-treated wound reopening was calculated assuming an exponential rate ($1 - \exp(-(\ln(2)/16.5) \times 7)$), resulting in 25.48%.

Subsequently, to estimate the weekly reopened wound area, Eng *et al.* (2021)²² was used to create assumptions of ranges of numbers of wounds that patients would have in each health state. The authors observed that the average number of wounds per patient was 11 recurrent wounds (SD 10, range 0-45) and 3 chronic wounds (SD 2, range 0-9). A normal distribution was assumed and the 25th and 75th percentiles were used to provide the lower-bound of the Moderate and Severe health states, respectively, while the average defined the lower-bound of the Moderate health state (Table 3.5).

Table 3.5: Number of wounds per health state at risk of reopening

Health state	Number of chronic wounds Range (average)	Number of recurrent wounds Range (average)
Very mild	0-4 (2)	0 (0)
Mild	5-10 (7.5)	1-2 (1.5)
Moderate	11-17 (14)	3-4 (3.5)
Severe	≥18 (31.5)	≥5 (7)

For example, a patient in the Mild health state has on average, 7.5 recurrent wounds and 1.5 chronic wounds. From this, it was calculated that every week, 2.29 wounds would reopen ($25.48\% \times \text{sum of } 7.5 \text{ and } 1.5$). This would mean that two wounds would reopen, with a 29% chance of a third wound reopening. A random number between 0 and 1 was used to define whether the third reopening occurred or not. If the random number was below 0.29 in the case of the example, then another wound would reopen.

For wounds that were previously treated with placebo, the size of the reopened wound was assumed to be on average [REDACTED] (standard error [SE] [REDACTED]) and growing to [REDACTED] cm² based on GEM-1 trial data. The size of the reopened wounds was based on the average size of the wounds in the week they reopened in GEM-1 for all wounds (i.e., pooled B-VEC and placebo-treated wounds). The pooled data was used because statistical analysis showed that there was no significant difference between the wound reopening size by treatment arm. The increase in wound size (to [REDACTED] cm²) was based on the average of the maximum size that placebo-treated reopened wounds reached relative to the initial size at the time of reopening. The increase in size was applied as a one-off because modelling the increase in size over time would add considerable complexity to the model, which is unnecessary as the transition probabilities for the Markov model are assessed at 3-month intervals. On the other hand, the observed time to reach the maximum size after reopening in GEM-1 was between 1 and 9 weeks.

3.2.2.1.2.3 Recurrent wounds becoming chronic

Wounds were considered chronic if they remained open for at least 8 weeks.²² Therefore, for the base case, it was assumed that $29.45\% ((1-14.17\%)^8)$ of the area of recurrent wounds that were open and treated with placebo were converted to chronic wounds per week.

Several evidence sources that evaluated duration of time for a wound to become chronic were evaluated. In Schwieger-Briel *et al.* (2017),⁸⁷ the authors “differentiated wounds that had appeared less than 6 weeks earlier and those with no tendency to heal for at least 6 weeks.” However, there was no justification provided for this value.⁸⁷ Further, Tang *et al.* (2021) was an SLR that noted a wound is chronic if it lasts 12 weeks or longer.⁷ Again, this seems to be an assumption as all of the citations in these papers were checked and the values of 6 or 12 weeks are not mentioned.⁷

Eng *et al.* (2021)²² was chosen as a basis of this assumption, as the authors provided the most detailed evidence on this topic. They categorised wounds at baseline as either chronic or recurrent, based on whether the wounds had been Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

open for more than 12 weeks. Interestingly, their findings revealed that all recurrent wounds healed within 8 weeks, while no wounds lasting beyond 8 weeks ever healed.²² This study was additionally referenced in a commentary by Solis *et al.* (2021)⁸⁶, which noted: “In a previous survey of 1,226 wounds in 85 patients with RDEB, 76% healed within 8 weeks, while 24% persisted for longer than 8 weeks. Respondents successfully classified these wounds into two groups.”

Given the available evidence, the latter (Eng *et al.* [2021])²² provided the most transparent evidence, which defined chronic wounds as wounds that had been open for 8 weeks or longer. Therefore, this value was assumed in the CEM.

3.2.2.1.3 B-VEC arm

3.2.2.1.3.1 Wound Closure

Outcomes from the B-VEC arm of GEM-1 were used to determine the wound dynamics of the existing open area. These were assumed to apply in the same manner to both chronic and recurrent open area, since B-VEC was used in recurrent and chronic wounds in the GEM-1 trial, presenting that both recurrent and chronic wounds can heal with B-VEC. This assumption was made as there were insufficient data from the trial to stratify wound type (i.e., recurrent and chronic).

As noted in Section 3.2.2.1.2.1, GEM-1 was the most useful source of data for tracking wound evolution over time. The weekly probability of wound closure in the B-VEC treatment arm was based on the average proportion of the wounds closed per week in the GEM-1 trial. Considering only the weeks when at least 50% of the wounds were still open (until week 6), it was assumed that on a weekly basis, treatment with B-VEC closed 42.54% of the wound area that was treated.

Importantly, as per the B-VEC SmPC, the maximum treatable area per week is 200 cm², so it may not be possible to apply B-VEC to all wounds at each treatment visit.¹ The remaining wounds that are not treated (considering the maximum treatment area allowed) were assumed to behave as they would in the BSC arm. It was also assumed that chronic wounds were treated with priority over recurrent wounds given that recurrent wounds can also heal spontaneously.

In GEM-3, a mean treatment compliance of 90% was reported in the per protocol population. Therefore, it was assumed in the base case, that patients treated with B-VEC would skip their treatment in 10% of the weeks (applied at random). During those weeks, all open wounds were subject to closing as per the probability applied for BSC, similar to non-treated wounds in the weeks where the patient does receive treatment.

3.2.2.1.3.2 Wound Reopening

To calculate the probability of a wound reopening in the B-VEC arm, the median duration of closure of the B-VEC-treated wounds was needed. For this, a combination of the GEM-3 and OLE data were used because it represents the longest period of observations using B-VEC. There were 8 patients who were treated with B-VEC in both GEM-3 and the OLE. For these patients the open or closed status of the wounds treated with B-VEC during each follow up visit in both studies was considered. As there were some missing data, and the number of days between the two studies varied between patients (median: 102 days), some assumptions were implemented in order to assess the median duration of closure:

- If the wound status (i.e., open or closed) during two consecutive visits (this includes the period between the last observation in GEM-3 and the first observation in OLE), then it was assumed it had remained that status in the period between these visits;
- If the wound status was different during two consecutive visits, then a pro rata probability of it being open or closed was applied in the months in between;
- Data were extrapolated to 25 months for all wounds, as this was the maximum duration of follow up;
- If a wound had closed and remained closed (under the assumptions 1 and 2) until the final visit, it was assumed to remain closed until Month 25;
- If a wound had had reopenings at any point in time, it was assumed that reopening occurred after 3 months, as this was the pattern typically observed. The period in between was imputed as per assumption 2;
- The months where the probability of the wound being closed was at least 50% (i.e., 'likely to be closed'), were counted for each period that a wound was closed;
- One wound could have multiple periods during which it was closed, with a period in between where it had reopened.

Based on this analysis, the median duration of wound closure was [REDACTED] which was translated to [REDACTED] for modelling purposes (pragmatically assuming each month has 30 days).⁹⁷ The weekly probability of a B-VEC-treated wound reopening was calculated based on its median duration of closure and assuming an exponential rate of closure ($1 - \exp(-(\ln(2)/[REDACTED]) * 7)$), resulting in [REDACTED].

To estimate the weekly wound area reopening, data from Eng *et al.* (2021)²² was used to determine the mean number of recurrent and chronic wounds per health state (see Section 3.2.2.1.2.2).

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

As described for the BSC arm, the baseline size of the reopened wounds previously treated with B-VEC was assumed to be on average [REDACTED], based on GEM-1 trial data (Krystal Biotech, data on file). For the B-VEC arm, no increase in size of reopened wounds was assumed since they are treated immediately once they reopen.

3.2.2.1.3.3 Recurrent wounds becoming chronic

Recurrent wounds that were not being treated (because the total BSA that was open exceeded 200 cm²) could heal spontaneously or become chronic, with the same rationale and probability as applied for BSC. Recurrent wounds treated with B-VEC are also at risk of becoming recurrent if they do not close, with a weekly probability of 1.19%, based on the weekly probability of closure for the area treated with B-VEC powered by the number of weeks a recurrent open wound takes to become chronic, that is, $(1 - 42.54\%)^8$.

3.2.2.1.4 Simulation over time

Over a period of three years, with weekly cycles, using the parameters discussed above, the percentage of BSA covered in chronic and recurrent wounds was tracked, and based on the total BSA open, patients were assigned to a health state each week. Additionally, the number of B-VEC vials consumed is tracked in the simulation. The period of three years was selected because it was observed in the patient-level simulation that after approximately 2–3 years, the per-cycle consumption of B-VEC vials had stabilised. The transitions between health states are tracked for only two years, as those stabilise earlier than the consumption of B-VEC.

The simulation was repeated until the outputs were stable, but for a maximum of 1,000 patients, and their outcomes were recorded. This record of simulated patients was then used to calculate transition probabilities and Markov model inputs on the consumption of B-VEC.

3.2.2.2 Model health states

The health states in this model were carefully structured to encompass all relevant costs and outcomes associated with DEB and its treatment pathway (Figure 3.1). Defining distinct health states is essential to accurately reflect variations in costs and outcomes, allowing for meaningful differentiation between states.⁹⁸

The economic model defined health states based on the BSA covered with open wounds. This approach was used because the larger the BSA with open wounds, the greater the clinical complications, symptoms, impairment, and, consequently, the disease severity.²² Severity of DEB could be assessed by the BSA affected by wounds, which is closely related to the type of wounds (i.e., recurrent vs chronic).

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Thus, the ideal health states should define patients according to these characterisations of disease severity.

In the literature, there is no available mapping that classifies disease severity with these characteristics; however, Bruckner *et al.* have developed detailed work on DEB patients' characterisation that was considered relevant for model health state definitions.⁶ This study collected outcomes reported by EB patients and carers. The sample comprised 63 patients and 93 carers with simplex, junctional, DDEB, and RDEB. The authors reported the number of patients with <10%, 10-30% and >30% of BSA covered by wounds (independently of whether they are recurrent or chronic), which was considered a fair approach to define the health states in the model (i.e., based on BSA covered by wounds). Data provided by Bruckner *et al.* (2021)⁶ were not directly considered for the health states definition, but they emphasised the relevance of considering BSA to define the health states. This aligns with the NICE technology appraisal for BBE, which defines health states by the percentage of BSA covered by wounds.²⁴

Additionally, using BSA covered in open wounds to define disease severity was considered appropriate because, as detailed in Section 1.3.3, there is no standardised measure of defining disease severity in DEB. Key available disease severity scales consider important aspects of the disease, including severity of wounds, impact on activity of daily living, pain, and itch. However, they cannot be mapped to outcomes from pivotal trials, GEM-3⁷⁸ and GEM-1⁸⁰.

EB burden-of-disease studies often classify patients by disease severity but mostly do so based on the patient's or their carer's own perception, which could not be considered an objective measurement. Due to the lack of a standardised approach and difficulty in mapping outcomes in GEM-3 and/or GEM-1, health state definitions based on existing DEB severity scales were not used.

The model considers five health states based on ranges of BSA covered by wounds that could be recurrent or chronic: Very Mild; Mild; Moderate; Severe; and Death. These health states are mutually exclusive and exhaustive: each patient represented in the model must be in one and only one of these health states at any given time. Milder health states are associated with lower prevalence of reversible and irreversible clinical manifestations, lower mortality, improved HRQoL of patients and carers, and lower costs.

One of the model components the expert clinicians were asked to speak on is the percentage of BSA covered in open recurrent and chronic wounds, which are the estimates considered in the health state definition. Table 3.6 summarizes the definitions of health states in the base case analysis considering the total BSA

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

covered in open recurrent and chronic wounds. In other words, depending on the ranges of BSA covered by open recurrent and chronic wounds, based on the opinions of the consultants, the health state can be defined by the total area open (with recurrent and chronic wounds) as it is presented in the last two columns of Table 3.6.

Table 3.6: Definitions of model health states according to UK clinical experts

Health state	Percentage of BSA area open			
	Recurrent wounds	Chronic wounds	Total of recurrent and chronic wounds*	
			Lower bound	Upper bound
Very mild	0% to < 2%	0% to < 0.1%	0.0%	2.1%
Mild	2% to < 4%	0.1% to < 1%	2.1%	5.0%
Moderate	4% to < 15%	1% to < 10%	5.0%	25.0%
Severe	≥15%	≥10%	25.0%	none except at baseline

*Represents the sum of columns for recurrent and chronic wounds.
BSA=body surface area; UK=United Kingdom.

For modelling purposes and to estimate a reasonable proportion of BSA covered by wounds in the Severe health state at baseline (*and only at this moment*), it was assumed that the Severe health state is capped to 40% of BSA covered by wounds. A range of studies have provided information on the proportion of BSA involvement in DEB. Most use categories of approximately <10%, 10% to 30%, and >30% BSA involvement to categorise DEB severity. However, there is a paucity of data in DEB concerning the maximum proportion of BSA affected by wounds. Maximum BSA may be limited by biological factors but can also be expected to be limited by competing risks, with higher BSA involvement associated with important adverse health outcomes, leading to mortality. Bruckner *et al.* (2020) reported that 42 of 84 individuals with DEB (50%) had wounds covering at least 30% BSA.⁶ An even greater proportion (60%) of individuals with the severest form of DEB had at least 30% BSA affected by wounds. Although individuals with DEB are susceptible to infection and sepsis,⁷ it is unknown what extent of epidermal detachment is associated with these outcomes in DEB. In a spectrum of rare, severe mucocutaneous reactions (Stevens-Johnson Syndrome/toxic epidermal necrolysis), the total BSA involvement that is associated with mortality is 49% based on a retrospective analysis of two university hospitals in Japan (spanning 2000 to 2020)⁹⁹ and 78% based a retrospective analysis of a single U.S. burn centre (spanning 1995 to 2000).¹⁰⁰ In individuals with burn injuries, the critical threshold for discriminating between those who will have adverse outcomes (including mortality) and those who will not have adverse outcomes is 40% BSA involvement in adults and 60% BSA involvement in children.¹⁰¹ It is apparent from these skin conditions, that the higher

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

the affected BSA, the greater the risk for adverse outcomes. Given that the extent of epidermal detachment associated with adverse outcomes in DEB is unknown, it is reasonable to apply a threshold of 40% to the proportion of BSA to be treated with each application of B-VEC. While this threshold of 40% does not surpass the critical threshold observed in individuals with burn injury¹⁰¹ or Stevens-Johnson Syndrome/toxic epidermal necrolysis,^{99,100} it captures the proportion of the body affected by DEB (i.e., >30% BSA⁶) that will need to be treated in most individuals.

The threshold of 40% is further supported by wound progression data gathered from structured expert elicitation used in a previous HTA submission to NICE for treating skin wounds associated with DEB and junctional epidermolysis bullosa.²⁴ Furthermore, clinical experts Dr. Anna Martinez and Dr. Gabriela Petrof, were consulted to develop health state definitions to be used in HTA submissions for B-VEC (See Section 3.2 for an overview of the clinician survey). The clinical experts considered 40% BSA involvement to be the upper limit for severe DEB in their estimates of percent BSA affected by recurrent and chronic wounds. After baseline, the Severe health state had no upper limit, meaning that it is theoretically possible to achieve 100% BSA covered by wounds.

3.2.2.3 Health state baseline distribution

Patients were stratified by DEB subtype (i.e., RDEB or DDEB), and further divided by age groups: 0-6 years; 6-18 years; ≥18 years. All patients in the cohort, independently of treatment arm, enter the model in the Mild, Moderate or Severe health states. Patients do not enter the model in the Very Mild health state, as these patients are not expected to seek treatment for their DEB; however, they can reach and maintain it through treatment with B-VEC.

As detailed in Section 3.2.1, data from Bruckner *et al.* (2020)⁶ refer to patients with DDEB and RDEB. Although GEM-1 and GEM-3 included only one patient with DDEB, it was considered more appropriate to include both DEB subtypes in the model to ensure that all patients are being represented. Therefore, the percentage of patients with RDEB and DDEB at the initial disposition was gathered from Bruckner *et al.* (2020).⁶ Table 3.7 summarises the distribution of the cohort in Bruckner *et al.* (2020) according to the percentage of BSA covered by wounds in the RDEB and DDEB population.⁶

Table 3.7: Distribution of the cohort at baseline across the health states according to Bruckner *et al.* (2020)

% BSA covered by wounds	RDEB population			DDEB population		
	PRO (n)	CRO (n)	Total (n)	PRO (n)	CRO (n)	Total (n)
<10%	2	4	6	5	7	13

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

% BSA covered by wounds	RDEB population			DDEB population		
	PRO (n)	CRO (n)	Total (n)	PRO (n)	CRO (n)	Total (n)
10-30%	6	9	15	4	5	9
>30%	11	21	32	5	5	10
Total	19	34	53	14	17	31

BSA=body surface area; CRO=carer-reported outcomes; DDEB=dominant dystrophic epidermolysis; PRO=patient-reported outcomes; RDEB=recessive dystrophic epidermolysis bullosa

Although the three ranges of BSA covered by open wounds proposed by Bruckner *et al.* (2020) (i.e. <10%, 10-30% and >30%), do not perfectly align with the estimates in Table 3.6, the ranges provided by UK clinical experts still fit into the ranges by Bruckner *et al.* (2020).⁶ Therefore, it can be assumed that:

- The range 0.0%-2.1% is used for the Very Mild population as suggested by UK clinical experts, considering the absence of this health state in Bruckner *et al.* (2020);
- The range <10% proposed by Bruckner *et al.* (2020) can be a proxy for the Mild health state (range suggested by UK clinical experts is 2.1%-5.0%);
- The range 10-30% proposed by Bruckner *et al.* (2020) can be a proxy for the Moderate health state (range suggested by UK clinical experts is 5.0%-25.0%);
- The range >30% proposed by Bruckner *et al.* (2020) can be a proxy for the Severe health state (range suggested by UK clinical experts is 25.0%-40.0%).

Thus, aggregating the patient and carer outcomes (Table 3.7), the proportion of patients in each health state could be recalculated and it is presented in Table 3.8.

Table 3.8: Distribution of the cohort at baseline across the health states according to the Bruckner population

Health state	Definition according to Bruckner <i>et al.</i>	Range suggested by experts	% of patients (RDEB)	% of patients (DDEB)
Very mild	—	0.0-2.1%	0%	0%
Mild	<10.0%	2.1-5.0%	11.1% (6/53)	35.4% (12/31)
Moderate	10.0-30.0%	5.0-25.0%	29.0% (15/53)	29.0% (9/31)
Severe	>30%	25.0-40.0%	59.8% (32/53)	32.6% (10/31)

DDEB=dominant dystrophic epidermolysis bullosa; RDEB=recessive dystrophic epidermolysis bullosa
Source: Bruckner *et al.* (2020)⁶

3.2.3 Intervention technology and comparators

To estimate the relative cost-effectiveness of B-VEC within the economic analysis, the intervention of interest, B-VEC in combination with BSC, is compared to BSC alone and BBE alone.

3.2.3.1 Intervention (B-VEC)

Each vial of B-VEC contains 1 mL extractable volume of suspension at a nominal concentration of 5×10^9 (5 billion) plaque forming units (PFU) per mL. B-VEC suspension is mixed into gel prior to administration. After mixing, the gel consists of 5.0×10^9 PFU in a total volume of 2.5 mL.¹

B-VEC should be administered topically once a week. It may not be possible to apply B-VEC to all wounds at each treatment visit, as the maximum treatable area per week is 200 cm² (as per SmPC of B-VEC).¹ Wounds should be treated weekly until they are closed, with priority given to wounds that were previously treated and have re-opened. Once a wound is treated, it should be covered by a sterile non-adhesive wound dressing.

For patients 3 years and older, the weekly dose is up to 4.0×10^9 PFU (4 billion) of B-VEC, (i.e., a total of four syringes of 0.5 mL each can be used for those patients). For patients under 3 years of age, the weekly dose is up to 2.5×10^9 PFU (2.5 billion) of B-VEC. B-VEC should be applied topically by a healthcare professional in small droplets, evenly spaced (1cm-by-1cm) within a wound. The treatment volume applied may vary as the wounds decrease or increase in size.¹

As the younger age subgroup in the current CEM has a mean age of 2.25 years at baseline (based on GEM-3), in the first three cycles, the recommended dose would be the lower one. However, to simplify the model and make a conservative assumption, the higher dose was considered for all patients. Therefore, a total of four syringes containing 0.5 mL each could treat a total of 200 cm² of open wounds. Thus, one syringe could treat 50 cm² of open wounds.

B-VEC should be administered in combination with concomitant medication, meaning that B-VEC is an add-on to BSC. The economic model assumed that treatment with B-VEC would start immediately when the wound opened.

3.2.3.2 Comparator (BSC)

The comparator in this analysis is BSC, assumed to be consistent with the control arm of the GEM-3 trial.³² In the CEM, BSC may include the use of concomitant medication, such as psychiatric medications, analgesics, anti-itch medications, laxatives, topical antibiotics, and medihoney. Further details on concomitant medication usage are presented in Section 3.5.2.3.

3.2.3.3 Comparator (BBE)

The second comparator in the analysis is BBE. In the UK, BBE gel is available in a tube size containing 23.4 g of BBE gel.²⁴ Each tube is for single use only meaning that the tube should be discarded after use.²⁸

BBE should be administered topically at least every 4 days, at a thickness of 1 mm to the surface of the wound and covered by a sterile non-adhesive wound dressing.²⁸

In line with what has been reported in NICE HST28,²⁴ a monthly consumption of 29.67 tubes was considered for all patients treated with BBE.

BBE is, similarly to B-VEC, considered an add-on to BSC, so it should be administered in combination with concomitant medication.

3.3 Clinical parameters and variables

BSA was chosen to model health states given the lack of standardised and objective measures of defining disease severity in DEB. The severity of the disease is directly linked to the extent of BSA covered with open wounds. In simple terms, the larger the area of open wounds, the more severe the clinical complications, symptoms, and overall disease burden become.²² Severity can be effectively assessed by measuring the BSA affected by wounds, as this strongly correlates with wound characteristics. Therefore, the most accurate way to define health states in this model is by using BSA as the key metric, given its clear relationship to disease severity.

3.3.1 Replication of birch bark extract model as described in HST28

An ITC feasibility assessment was conducted based on endpoints collected in the EASE, GEM-1 and GEM-3 trials. It was concluded that an ITC was not possible due to heterogeneity in trial design, trial populations, in outcome definition and measurement timepoint (see Section 2.9).

Nevertheless, transitions between BSA health states in the BBE arm of the CEA could be informed directly from the EASE study, which collected BSA-level data over the follow-up period. This made the comparison in terms of cost-effectiveness between B-VEC and BBE possible, despite not having comparative efficacy from an ITC.

The data reported from the EASE trial and the description of the CEA used to assess the cost effectiveness of BBE compared with BSC in England (NICE HST28) were used to obtain data required for the simulation of BBE in the current CEM of B-VEC in DEB. To ensure a correct interpretation and extraction of data from the BBE CEM in HST28, the cost-effectiveness modelling, as described in the company submission

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

for HST28 was reproduced. The steps taken to allow for inclusion of BBE in the current CEM are described below.

3.3.1.1 Replication of company submission model used in HST28

The company submission as reported for HST28 was used to rebuild the model used for the initially submitted base case. The model inputs as presented in Table 9, Table 10 and Table 11 of the submission were used. A few inputs had to be adjusted from the submitted model to match the base case results presented in the company submission, namely:

- Proportion of RDEB-severe patients. The transition probabilities, health state costs, and per-cycle risk of death for RDEB-severe patients were clearly described in the company submission. The proportion of patients with RDEB-severe was not provided in the initial submission but was later provided in response to clarification questions from the evidence assessment group (EAG), i.e. 2.43% of the overall population in the model. However, when applying 2.43% as proportion of RDEB-severe patients in the replicated model, the total costs in BSC arm did not match those reported in the company submission. Following a calibration approach, we estimated a proportion of RDEB-severe patients of 25.16%, which would have been used to obtain the total costs reported in Table 37 of the company submission. Therefore, for the replication of the BBE model, it was assumed that the population consisted of 25.16% RDEB-severe patients.
- Utility of informal carers. The utility value of the carers whose HRQoL is affected as well as the number of carers to whom this applies for each health state was clearly described in the company submission. However, the assumption applied around the HRQoL of the remaining (i.e., informal) carers was not fully clear. It was calibrated such that if the informal carers had a utility value of 0.936, the total QALYs in the replicated model would match those reported in the company submission. This is a credible assumption, given that value is very similar to the general population utility of a young person. Therefore, it was assumed that the utility value of informal carers was 0.936.
- BBE acquisition costs. The company submission dossier reported the cost per tube of BBE (£275.33), but not the number of tubes used per month. From the response to EAG clarification questions it was clear that the mean number of tubes per month during the DBP of the EASE trial was 29.67 and that the number of tubes used in the model was based on both the DBP and OLP. The

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

consumption of BBE in the OLP was reported to be lower than during the DBP; however, the exact number of tubes consumed during OLP was not reported. Thus, it was not possible to estimate the acquisition cost of BBE per model cycle based on tube consumption data. As an alternative approach, the monthly drug acquisition cost for BBE of £2,146.18 was back calculated. The total costs in the comparator arm already matched those reported in the BBE Company submission, and so it could be assumed that the total costs for monitoring and bandages in the BBE arm were also matching those in the Company Submission model. As it was assumed that the only costs in the model were those for monitoring and bandages, and BBE acquisition, the total costs for BBE Acquisition could be calculated by subtracting the monitoring and bandages cost from the total costs. Then this amount divided by the modelled time on treatment was assumed to be the BBE acquisition cost per cycle and was used to inform the cost in the replicated model directly.

With the combination of the calibrated values of parameters described above and the values of parameters reported in the submission dossier, it was possible to replicate the total costs and total QALYs in the BBE and BSC arms as reported in Table 37 of the Company submission (Table 3.9).²⁴ The ICER calculated from these values was slightly different from what was reported, but this must be due to rounding differences.

Table 3.9: BBE model inputs

Input type	Input	Value
General model features	Time horizon	Lifelong
	Cycle length	1 month
Mortality	Mortality (except for RDEB-severe)	General population
	Per-cycle mortality for RDEB-severe patients	0.0028
	Proportion of RDEB-severe	<i>See description above table</i>
Baseline health state distribution	Health states 1 to 6	16.7% in each health state
Transition probabilities	BBE	<i>See Table 19 in HST28²⁴</i>
	BSC	<i>See Table 20 in HST28²⁴</i>
Treatment discontinuation	At 90 days	8.3%
	From 90 days onwards, annually	1%
Patient utilities	Health state 1	0.56
	Health state 2	0.51
	Health state 3	0.46
	Health state 4	0.35
	Health state 5	0.23
	Health state 6	0.08
Carer utilities	Health state 1 and 2	0.85
	Health state 3 and 4	0.76
	Health state 5 and 6	0.64
Number of carers	Health state 1 and 2	0.5
	Health state 3 and 4	1
	Health state 5 and 6	1.78
Annual costs of monitoring and bandages	Health state 1	£10,614.08
	Health state 2	£17,919.02
	Health state 3	£33,190.40
	Health state 4	£52,297.28

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Input type	Input	Value
	Health state 5	£77,781.78
	Health state 6	£108,569.11
Drug acquisition costs	BBE	See description above table
BSC=best supportive care; RDEB=recessive dystrophic epidermolysis bullosa		

3.3.1.2 Mapping from six to four health states

As the current model for B-VEC has four health states representing disease severity, and the BBE model had 6 such health states, the next step was to map the BBE model health states to the Very Mild, Mild, Moderate and Severe health states as used in the current model. This was done through manual calibration of the mapping, until the exact ICER as reported in Table 37 of the BBE Company Submission was matched. This resulted in a mapping between the health states of the two models as presented in Table 3.10 and utilities, health state costs and transition probabilities as presented in Table 3.11, Table 3.12, and Table 3.13. Other model inputs and assumptions were kept the same.

Table 3.10: Conversion from health states used in the BBE NICE submission to B-VEC health states

		Current model health state			
		Very Mild	Mild	Moderate	Severe
BBE NICE dossier health state	Health state 1	5%	95%		
	Health state 2		100%		
	Health state 3		5%	95%	
	Health state 4			100%	
	Health state 5			100%	
	Health state 6				100%
NICE=National Institute for Health and Care Excellence					

Table 3.11: BBE model inputs (mapped to four health states)

Input type	Input	Value
Baseline health state distribution	Very Mild	0.8%
	Mild	33.4%
	Moderate	49.1%
	Severe	16.7%
Transition probabilities	BBE	See Table 3.12 and Table 3.13
	BSC	
Patient utilities	Very Mild	0.56
	Mild	0.53
	Moderate	0.34
	Severe	0.08
Carer utilities	Very Mild	0.85
	Mild	0.85
	Moderate	0.72
	Severe	0.64
Number of carers	Very Mild	0.5
	Mild	0.51
	Moderate	1.26
	Severe	1.78
Annual costs of monitoring and bandages	Very Mild	£10,614.08
	Mild	£14,864.88
	Moderate	£54,810.16
	Severe	£108,569.11

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Table 3.12: BBE transition probabilities from HST28, mapped to four health states

Day 0-30				
From/to	Very Mild	Mild	Moderate	Severe
Very Mild	0.050	0.950	0.000	0.000
Mild	0.026	0.958	0.016	0.000
Moderate	0.000	0.140	0.860	0.000
Severe	0.000	0.000	1.000	0.000
Day 30-60				
From/to	Very Mild	Mild	Moderate	Severe
Very Mild	0.047	0.953	0.000	0.000
Mild	0.022	0.949	0.029	0.000
Moderate	0.000	0.018	0.982	0.000
Severe	0.000	0.000	0.976	0.024
Day 60-90				
From/to	Very Mild	Mild	Moderate	Severe
Very Mild	0.049	0.951	0.000	0.000
Mild	0.023	0.951	0.025	0.000
Moderate	0.000	0.024	0.976	0.000
Severe	0.000	0.000	0.992	0.008
Day 90+				
From/to	Very Mild	Mild	Moderate	Severe
Very Mild	0.048	0.952	0.000	0.000
Mild	0.023	0.950	0.026	0.000
Moderate	0.000	0.040	0.960	0.000
Severe	0.000	0.000	0.982	0.018

Table 3.13: BSC transition probabilities from HST28, mapped to four health states

Day 0-30				
From/to	Very Mild	Mild	Moderate	Severe
Very Mild	0.050	0.950	0.000	0.000
Mild	0.024	0.959	0.016	0.000
Moderate	0.000	0.131	0.869	0.000
Severe	0.000	0.000	1.000	0.000
Day 30-60				
From/to	Very Mild	Mild	Moderate	Severe
Very Mild	0.008	0.992	0.000	0.000
Mild	0.004	0.572	0.424	0.000
Moderate	0.000	0.017	0.983	0.000
Severe	0.000	0.000	0.309	0.691
Day 60-90				
From/to	Very Mild	Mild	Moderate	Severe
Very Mild	0.049	0.951	0.000	0.000
Mild	0.023	0.942	0.035	0.000
Moderate	0.000	0.019	0.981	0.000
Severe	0.000	0.000	0.968	0.032
BSC=best supportive care				

3.3.1.1 Change from monthly cycles to cycles of three months

The current model for B-VEC has 3-month cycles rather than monthly ones as in the BBE model. Therefore, the final step was to adjust the monthly data to 3-month cycles. It was deemed unfeasible to adjust the transition matrices from monthly to 3-month cycles, and therefore the distribution of patients over the health states from Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

the monthly cycles using four health states were used to inform distribution of patients over the health states with larger intervals in time. This meant that the distribution of patients over the health states in Cycle 3 (3 months) in the BBE model described in Section 3.3.1 as used to inform the distribution over the health states in Cycle 1 (3 months) in the 3-month model. Similarly, Cycle 6 from the monthly model was used to inform Cycle 2 of the 3-month cycle model, etc.

This way the ICER as calculated from the model described in Section 3.3.1.2 could be replicated, using 3-month cycles instead of monthly cycles.

3.3.1.2 Integration of replicated model inputs and assumptions into current CEM

Once the BBE base case model could be replicated within the model structure used for the current B-VEC model (i.e., 4 health states and 3-month cycles), the findings of the three steps described above were integrated into the CEM for B-VEC. In addition, the settings and assumptions of this model were adjusted to reflect the inputs and assumptions used in the base case of the BBE company submission as much as possible. An overview of the settings and assumptions used to replicate the BBE model results within the current model for B-VEC are presented in Section 3.10.

Table 3.14: Comparison of current model base case settings to settings used to replicate BBE Company Submission model

Model setting/assumption	Current model base case	BBE validation scenario
Population	All age groups	Only children
Mean baseline age	2.25 years for children	6 years
Baseline distribution over health states	Bruckner <i>et al.</i> (2020) ⁶	Equal distribution over HS1-6, mapped to current model health states
Source of BSC transition probabilities	Patient-level simulation	NICE HST28 ²⁴
Freezing health state of BSC patients	3 months	3 months
Freezing health state of BBE patients	12 months	12 months
BBE cost per month*	(29.67) £275.33 = £8,169.04	£2,146.18
Utility source	Vignette study	EASE trial utilities
Impact on HRQoL of secondary carer	77% of primary carer	Same as primary carer
Mortality	Linked to patient health state in model	Linked to baseline population (25% RDEB-Severe)
Approach to calculating nurse dressing costs	EAG preferred approach	Original company submission approach
Clinical manifestations	Included	Excluded
Cost of bandage changes in Very Mild	50% of costs in Health State 1 of BBE model	Same as costs in Health State 1 of BBE model
Concomitant medication costs	Included	Excluded
*The costs differ between the current model base case and the BBE validation scenario as the data used to calculate BBE costs per month in HST28 are unavailable in the public domain (i.e., monthly tube consumption, PAS)., BBE=birch bark extract; BSC, best supportive care; HRQoL=health related quality of life; NICE=National Institute for Health and Care Excellence; PAS=Patient Access Scheme		

Using the inputs and settings as described above, the results of the current model were very similar to those presented in Table 37 of the BBE company submission, as is presented in Section 3.3.1. This confirmation was used as a basis for the comparison of B-VEC to BBE in the current CEM.

Table 3.15: Comparison of model results from reproducing BBE model within current CEM

	BBE vs BSC		
	Incremental Costs	Incremental QALYs	ICER
BBE company submission model	£216,436	2.3	£95,980
BBE validation scenario	£241,135	2.61	£92,364
BBE=birch bark extract; BSC=best supportive care; ICER=incremental cost-effectiveness ratio; QALY=quality adjusted life years			

3.3.2 Transition probabilities

Transition probabilities for B-VEC and BSC were calculated from the simulation as discussed in Section 3.2.2.1 and were calculated separately for the three age groups in the model. They reflect the probability of patients moving between the different health states, based on the proportion of their baseline BSA with open wounds. Transition probabilities were calculated for 8 cycles of 3 months each (2 years in total), after which the final set of transition probabilities is recycled.

Despite GEM-3 being the pivotal phase 3 trial for B-VEC, it only evaluated complete wound closure at 3 and 6 months. Therefore, data from GEM-1 were chosen to model transition probabilities because BSA is tracked on a weekly basis.

Transition probabilities presented here were based on the assumptions described in Section 3.2.2.1.

Transition probabilities for the B-VEC and BSC arms are presented in Table 3.16 and Table 3.17, respectively.

Table 3.16: B-VEC transition probabilities based on simulated data

Starting health state	Resulting health state											
	Very mild	Mild	Moderate	Severe	Very mild	Mild	Moderate	Severe	Very mild	Mild	Moderate	Severe
	0 to <6 years				6 to <18 years				≥18 years			
Month 0 to 3												
Very mild												
Mild												
Moderate												
Severe												
Month 3 to 6												
Very mild												
Mild												
Moderate												
Severe												
Month 6 to 9												
Very mild												
Mild												
Moderate												
Severe												
Month 9 to 12												
Very mild												
Mild												
Moderate												
Severe												
Month 12 to 15												
Very mild												
Mild												

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Starting health state	Resulting health state											
	Very mild	Mild	Moderate	Severe	Very mild	Mild	Moderate	Severe	Very mild	Mild	Moderate	Severe
	0 to <6 years				6 to <18 years				≥18 years			
Moderate	■	■	■	■	■	■	■	■	■	■	■	■
Severe	■	■	■	■	■	■	■	■	■	■	■	■
Month 15 to 18												
Very mild	■	■	■	■	■	■	■	■	■	■	■	■
Mild	■	■	■	■	■	■	■	■	■	■	■	■
Moderate	■	■	■	■	■	■	■	■	■	■	■	■
Severe	■	■	■	■	■	■	■	■	■	■	■	■
Month 18 to 21												
Very mild	■	■	■	■	■	■	■	■	■	■	■	■
Mild	■	■	■	■	■	■	■	■	■	■	■	■
Moderate	■	■	■	■	■	■	■	■	■	■	■	■
Severe	■	■	■	■	■	■	■	■	■	■	■	■
Month 21 to 24												
Very mild	■	■	■	■	■	■	■	■	■	■	■	■
Mild	■	■	■	■	■	■	■	■	■	■	■	■
Moderate	■	■	■	■	■	■	■	■	■	■	■	■
Severe	■	■	■	■	■	■	■	■	■	■	■	■

Table 3.17: BSC transition probabilities based on simulated data

Starting health state	Resulting health state											
	Very mild	Mild	Moderate	Severe	Very mild	Mild	Moderate	Severe	Very mild	Mild	Moderate	Severe
	0 to <6 years				6 to <18 years				≥18 years			
Month 0 to 3												
Very mild												
Mild												
Moderate												
Severe												
Month 3 to 6												
Very mild												
Mild												
Moderate												
Severe												
Month 6 to 9												
Very mild												
Mild												
Moderate												
Severe												
Month 9 to 12												
Very mild												
Mild												
Moderate												
Severe												
Month 12 to 15												
Very mild												
Mild												
Moderate												

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Starting health state	Resulting health state											
	Very mild	Mild	Moderate	Severe	Very mild	Mild	Moderate	Severe	Very mild	Mild	Moderate	Severe
	0 to <6 years				6 to <18 years				≥18 years			
Severe												
Month 15 to 18												
Very mild												
Mild												
Moderate												
Severe												
Month 18 to 21												
Very mild												
Mild												
Moderate												
Severe												
Month 21 to 24												
Very mild												
Mild												
Moderate												
Severe												

3.3.3 Natural History

As discussed in Section 1.3, in individuals with DEB, the cycle of persistent blistering, impaired wound closure, and reblistering is accompanied by fibrosis and extensive scarring. The fibrotic microenvironment in the skin is a leading trigger in the development of highly disabling disease consequences (e.g., contractures, debilitating hand and foot deformities) and potentially life-threatening complications (e.g., SCC).^{4,9-13}

Current standard of care, which is limited to the management of symptoms and secondary consequences, does not address the underlying cause of DEB, and does not halt disease progression.^{1,14} B-VEC has been specifically designed to address the underlying pathophysiology, restoring COL7 production to promote wound closure and break the cyclical nature of wounding, healing, and reblistering.¹⁵⁻¹⁷ This means that wounds are expected to close and remain closed, thus avoiding the downstream consequences of reblistering. Individuals with DEB who initiate B-VEC early in the disease course are expected to have fewer recurrent and chronic wounds, less fibrosis and scarring, less potential to develop highly disabling consequences, and reduced risk for early mortality.

There is a lack of published data relating to the impact of skin fibrosis and scarring on HRQoL. This may be a consequence of the higher disease burden of downstream complications of DEB, rather than a reflection that skin fibrosis and scarring do not impact HRQoL. The durable wound-closing property of B-VEC is expected to improve the HRQoL of individuals with DEB by reducing the negative disease-related impacts on physical and mental health, improving their ability to perform daily activities, and reducing the degree of pain they experience during wound care. Consequently, individuals with DEB who are treated with B-VEC are expected to require less time and assistance from carers for wound management.

3.3.4 Clinical manifestations

Patients with DEB develop clinical manifestations according to disease severity. The study conducted by Eng *et al.* provided the number of patients who developed clinical manifestations by self-reported skin disease severity (Table 3.18).²²

Table 3.18: Clinical manifestations of DDEB by disease severity

Clinical manifestation	Number of patients with clinical manifestation			
	Mild (n = 22)	Moderate (n = 40)	Severe (n = 21)	P value*
Anaemia	5/22	22/40	16/21	<0.01
Ankyloglossia	11/22	21/40	14/21	0.48
Complete or partial mitten deformity of foot	10/22	19/40	17/21	0.02

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Clinical manifestation	Number of patients with clinical manifestation			
	Mild (n = 22)	Moderate (n = 40)	Severe (n = 21)	P value*
Complete mitten deformity of hand	1/22	5/40	5/21	0.15
Dysphagia to solids	10/22	21/40	14/21	0.36
Oesophageal strictures	13/21	27/40	15/21	0.67
Eye problems	10/22	18/40	15/21	0.11
Failure to thrive	4/22	8/40	9/21	0.12
Gastrostomy tube use	5/22	10/40	12/21	0.02
Infections	8/22	29/40	16/21	<0.01
Itch	19/22	34/40	19/21	0.92
Osteoporosis	1/22	3/40	6/21	0.03
Renal problems	2/22	2/40	4/21	0.24
Squamous cell carcinoma	0/22	2/40	4/21	0.04
*P values determined by Wilcoxon's rank sum test Source: Eng <i>et al.</i> (2021) ²²				

The clinical manifestations considered in the model were the ones that B-VEC could improve or prevent —i.e., anaemia, complete or partial mitten deformity of foot, complete mitten deformity of hand, infections, osteoporosis, and SCC.

Patients can develop more than one clinical manifestation. The clinical manifestations considered in the model were divided into those that are reversible and those that are irreversible. This is because reversible clinical manifestations can resolve and appear again, while once the patients develop irreversible manifestations, they always have them. For model proposes, some assumptions were made. For the Mild, Moderate, and Severe health states in the model, it was assumed that the prevalence of clinical manifestations is the same as reported in Eng *et al.* (2021)²² for patients categorised as being in the Mild, Moderate and Severe health state in that publication (i.e. the model health states could be considered proxy, in terms of definition, for the same health states names in Eng *et al.*)²² The source did not report Very Mild as a disease category; however, based on UK clinician input, it was assumed that no irreversible clinical manifestations would occur in this health state. Infections and osteoporosis are, based on the UK clinical validation, assumed to happen at the same rate as in the Mild health state (Appendix J).

For the reversible clinical manifestations, the model assumed a per-cycle probability given directly by the prevalence reported in Eng *et al.* (2021) (Table 3.19).²² Probabilities were used for reversible events because it was assumed these events can be repeatable, meaning that the total sum of the probabilities over time can be >100%. On the other hand, rates are used if the event can only happen only once as the irreversible events are, thus the sum should add up to ≤100%.

Table 3.19: Per-cycle probability of developing reversible clinical manifestations by health state

Reversible clinical manifestations	Per-cycle probability (%)			
	Very mild	Mild	Moderate	Severe
Infections	36.4	36.4	72.5	76.2
Anaemia	22.7	22.7	55.0	76.2
Osteoporosis	0	4.5	7.5	28.6
Source: Eng <i>et al.</i> (2021) ²²				

For the irreversible clinical manifestations, the rate per cycle was calculated based on the equation:

$$rate = \frac{-[\ln(1 - probability)]}{time}$$

It was considered that events had occurred in a time horizon of 21 years, which is the mean age of patients in Eng *et al.* (2021).²² Table 3.20 presents the per-cycle rate of developing irreversible clinical manifestations in the model.

Table 3.20: Per-cycle rate of developing irreversible clinical manifestations by health state

Irreversible clinical manifestations	Per-cycle rate			
	Very mild	Mild	Moderate	Severe
Squamous cell carcinoma	0	0	0.0006	0.0025
Complete or partial mitten deformity of foot	0	0.007	0.0077	0.0197
Complete mitten deformity of hand	0	0.006	0.0016	0.0032

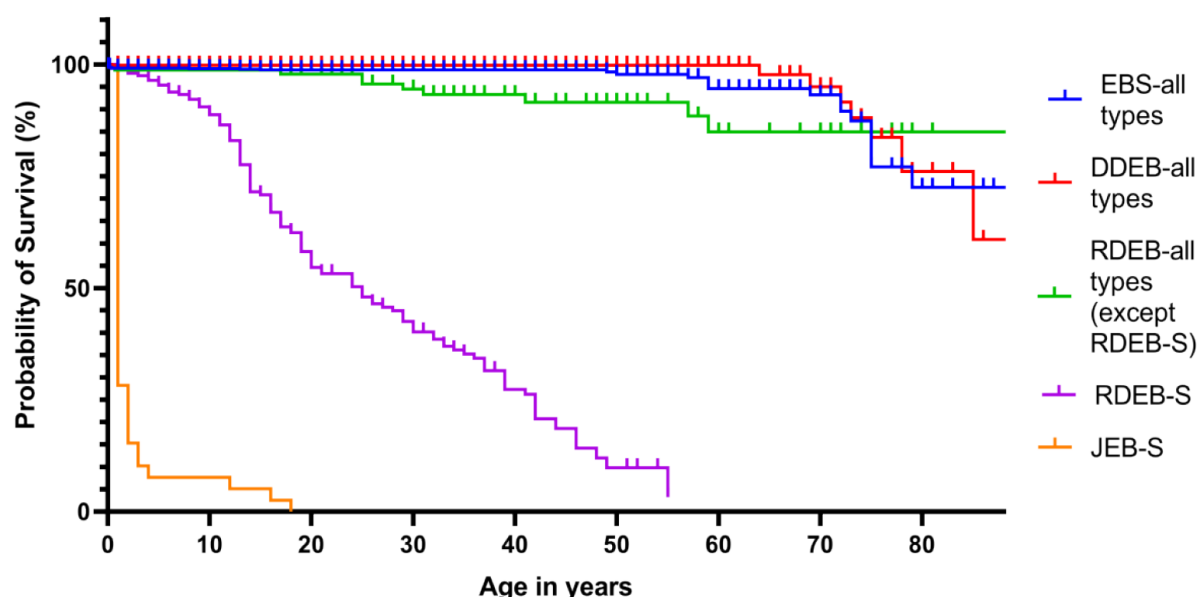
3.3.5 Mortality

In patients with DEB, mortality is related to disease severity and is dependent on the DEB subtype. In general, patients with DEB often survive to adulthood. However, more aggressive subtypes of DEB, such as Severe RDEB, are associated with a higher mortality, while mortality of DDEB could be considered similar to the general population mortality.^{11,56,102}

Petrof *et al.* developed an epidemiologic characterisation of patients with EB in the UK and Wales.¹¹ The demographic data were collected on an electronic database from January 2002 to April 2021. By March 2021, 2,594 individuals were registered. There were 234 deaths recorded since 2002, 77 with RDEB and 157 with other types of EB, including DDEB. DDEB and RDEB (all types except severe). Patients have a 98-100% probability of being alive at 18 years old. The Kaplan-Meier curves showing the survival probability by age, according to the EB subtype from Petrof *et al.* (2022), is presented in Figure 3.2.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Figure 3.2: Probability of survival among patients with EB according to age and EB type



DEB=dystrophic epidermolysis bullosa; DDEB=dominant dystrophic epidermolysis bullosa; EB/EBS=epidermolysis bullosa; JEB=junctional epidermolysis bullosa; RDEB=recessive dystrophic epidermolysis bullosa
Source: Petrof *et al.* (2022).¹¹

3.3.5.1 Mortality by health state

DDEB is a milder form of EB,¹³ and patients with DDEB have life expectancy that is similar to that of the general population.^{11,56,102} Based on the mortality as shown in Figure 3.2, the assumptions were made as shown in Table 3.21.

Table 3.21: Sources of mortality according to health state, DEB subtype, and model start age

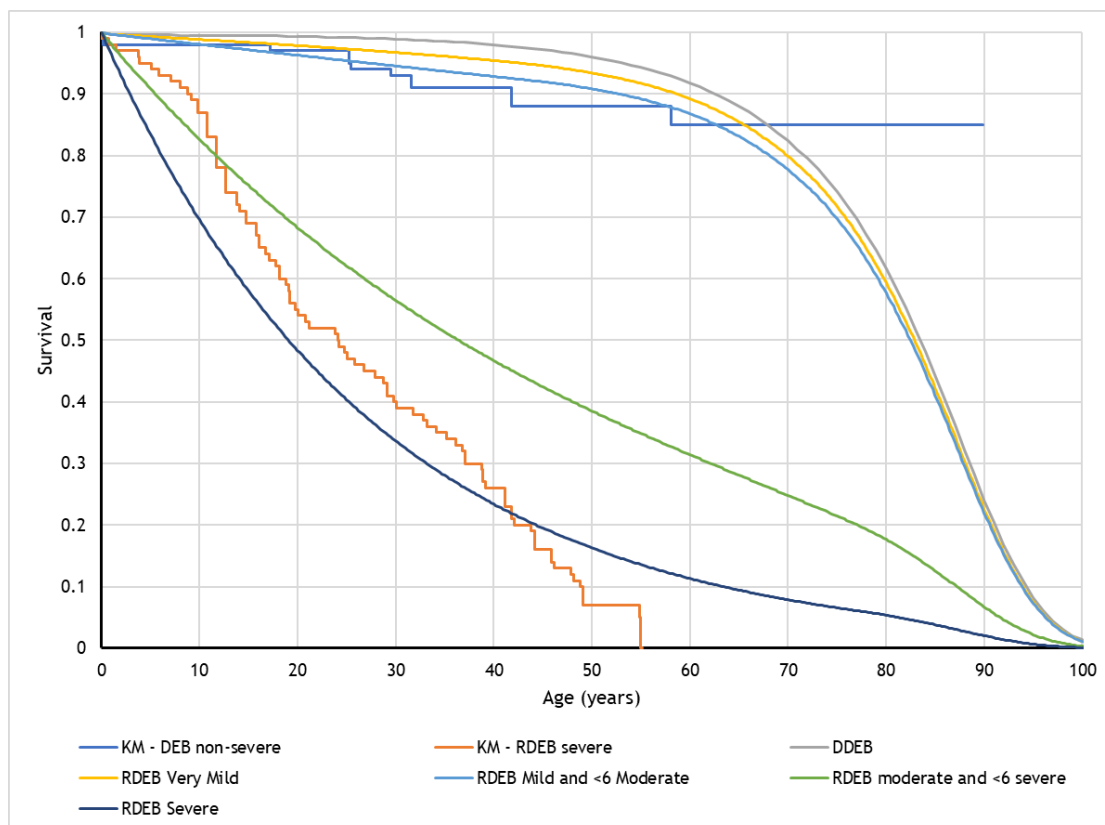
	DDEB	RDEB	
		Enter model at age <6	Enter model at age ≥6
Very Mild	General population	Average between general population ¹⁰³ and RDEB (except severe) ¹¹	Average between general population ¹⁰³ and RDEB (except severe) ¹¹
Mild	General population	RDEB (except severe) ¹¹	RDEB (except severe) ¹¹
Moderate	General population	RDEB (except severe) ¹¹	Average of RDEB (except severe) and RDEB severe ¹¹
Severe	General population	Average of RDEB (except severe) and RDEB severe ¹¹	RDEB severe ¹¹
DDEB=dominant dystrophic epidermolysis bullosa; RDEB=recessive dystrophic epidermolysis bullosa			

The direct use of Kaplan Meier curves was explored; however, the flat blocs would lead to an assumption that the probability of death would be null at these timepoints, which is not logical. Parametric survival adjustments remove this artefact because the survival function shows a proportion of patients dying in all cycles.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Figure 3.3 represents the mortality curves by health state and age adopted in the model based on the UK general population mortality¹⁰³ and Petrof *et al.* (2022).¹¹

Figure 3.3: Mortality by health state and age adopted in the model



Note: Mortality in the Very Mild health state was based on the mortality in the UK general population.¹⁰⁴ Mortality in the Mild, Moderate, and Severe health states was based on data from Petrof *et al.* (2022).¹¹

KM=Kaplan-Meier; DDEB=dominant dystrophic epidermolysis bullosa; RDEB=recessive dystrophic epidermolysis bullosa

3.3.6 B-VEC discontinuation

Treatment discontinuation represents unplanned interruption of treatment due to any reason. In the GEM-1 and GEM-3 trials, no discontinuations were observed; however, in a lifetime of B-VEC use it is expected that some patients would discontinue. Therefore, the base case assumes an annual B-VEC discontinuation rate of 1% of patients. A discontinuation rate of 9.68% in the first 6 months (4.96% per model cycle) and 1% annually thereafter was explored in a scenario analysis, in line with the observations in GEM-3 in terms of loss of follow-up due to any reason.

3.3.7 Birch bark extract discontinuation

In line with the BBE NICE submission,²⁴ a discontinuation of 8.3% at 90 days and 1% yearly thereafter was assumed.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

3.4 Measurement and valuation of health effects

This section describes HRQoL evidence that was used to inform the utility values incorporated into the CEM. The utility values implemented in the base case and scenario analyses of this CEM are described in Section 3.4.5.

3.4.1 Health-related quality-of-life data from clinical trials

3.4.1.1 GEM-3 trial

As discussed in Section 2.3, the GEM-3 trial was the pivotal trial for B-VEC in the treatment of DEB. In GEM-3, EQ-5D-5L, PR (Pain Relief), FLACC-R, and Skindex-29 were collected in patients being treated with B-VEC.⁷⁸

Both the EQ-5D-5L and Skindex-29 questionnaires were administered to participants who were 12 years of age or older at the time of consent. Questionnaires were provided to the participant after completing the visit and the participant then brought back the questionnaire at the next scheduled visit. There were 10 patients below 12 years old who therefore did not complete the EQ-5D-5L and Skindex-29 questionnaires.

Values collected from GEM-3 were not used to inform the base case in this model because the health state definitions in the CEM are based on the percentage of BSA covered by wounds, a measure that was not collected in GEM-3. Furthermore, few patients have multiple EQ-5D measurements that could be used to populate the model. From the 31 patients from the GEM-3 ITT population, 10 were younger than 12 years old, leaving only 21 patients available for the collection of EQ-5D data. All 21 patients had at least one EQ-5D assessment during the entire follow-up period. Of those 21, only 18 had at least two assessments, one in the first or second visit and the other in Week 24, 26 or 27. In other words, from the ITT population of 31, only 18 (58.1%) patients had EQ-5D data at or near baseline and around 26 weeks. Given the low sample size, and that utilities could not be assigned to health states, these data were not used to inform utility values in the base case but were used as a scenario analysis.

3.4.1.2 EASE trial

Data from the EASE trial were used to inform utility values as a scenario analysis. HRQoL data in the EASE OLP were collected using several tools, including the patient-completed section of iscorEB, the EBDASI, and the EQ-5D. A summary of the utility values observed in this study is shown in Table 3.22. Values ranged from 0.08 in the most severe health state to 0.56 in the mildest health state.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

HRQoL data were gathered using the EQ-5D-5L for adults in the OLP, while the youth version (EQ-5D-Y) was used for children aged 8–15 years. For patients younger than 4 years, responses were provided by a parent or carer proxy. Since the EQ-5D instruments were introduced as part of a protocol amendment, no HRQoL data were collected during the EASE DBP. This resulted in limited observations, as the data were gathered only during the OLP, with some missing responses where the EQ-5D was not completed.

Utility scores for adults were derived by mapping EQ-5D-5L domain scores collected in EASE to EQ-5D-3L values using the Van Hout *et al.* (2012)¹⁰⁵ mapping algorithm. For children and adolescents, where data were collected using the EQ-5D-Y, the adult EQ-5D-3L tariff was applied due to the absence of a validated value set specific to the youth version.

3.4.2 Mapping

Currently, no mapping algorithms are available to convert EB-specific instruments, such as the EBDASI, QoLEB, and iscorEB, to the EQ-5D for obtaining utility values.

3.4.3 Health-related quality-of-life studies

An SLR was undertaken to identify studies reporting utility values or studies that used a mapping approach to derive utility values, economic evidence, and HCRU, in DEB. The SLR methodology and overview of the results are outlined in Appendix F. Two studies that reported utility values for patients with DEB were identified and they are summarised below.

3.4.3.1 Hussain *et al.* (2024)

Hussain *et al.* (2024) was a poster presentation by DEBRA UK, which assessed the impact of EB on daily life, including the HRQoL, of patients and their carers/families as part of the 2023 Insights study. HRQoL of patients with EB was investigated using the EQ-5D-5L.¹⁰⁶ A total of 215 patients and 103 carers completed the study. Patients with DEB reported the mean EQ-5D-5L value of 0.141 (SD 0.404) “at its worst”, and 0.601 (SD 0.267) on a “typical day”.¹⁰⁶

3.4.3.2 Angelis *et al.* (2022)

Angelis *et al.* (2022) conducted a cross-sectional study, which recruited patients with EB across five European countries: France, Germany, Italy, Spain, and the UK. Patient and carer HRQoL values were recorded using EQ-5D-3L.⁶¹

Patients with DEB had substantially lower EQ-5D-3L utility scores compared to the overall EB population (mean 0.304, SD 0.449).⁶¹ Carers of patients with DEB had

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

slightly higher mean utility scores (0.713, SD 0.071) than those of carers in the broader EB population reported in the 2016 study. Patients with DEB in the UK had notably lower mean utility scores (0.304) compared to the average of patients with DEB across the five European countries (mean 0.456, SD 0.328).⁶¹

3.4.4 Adverse reactions

As detailed in Sections 2.10.1 and 2.10.2, B-VEC was well tolerated in both GEM-1 and GEM-3 trials. In GEM-1, there were no deaths, SAEs, or significant AEs. The only AEs determined by the investigator to be possibly or probably related to topical B-VEC or placebo administration were mild, and included rash, wound discharge, itching, and peculiar taste. Similarly, only mild AEs were associated with B-VEC administration/injection, including fever, swelling, redness, pain, and itching.⁸⁰ Similarly, in the GEM-3 trial, SAEs were rare overall, and no SAEs were considered to be treatment-related by the investigator.⁷⁸ SCC of the skin was reported in 3 participants; however, in all 3 participants, SCC occurred at sites that were not directly exposed to B-VEC.⁷⁸

Furthermore, in the GEM trials, patients served as their own control. Given the usage of B-VEC and placebo in the same patient, it is unknown which intervention is causing AEs.

Considering that most AEs in the GEM trials were of low severity, no SAEs were related to B-VEC, and that patients served as their own control, utility decrements or HCRU/costs associated with AEs have not been included in the CEM.

3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

3.4.5.1 Utilities

For the CEM, HRQoL data were required that assigned utility scores to each of the four alive health states. The following approaches are implemented in the model to provide several scenarios to be tested:

- Vignette study - General population sample (base case)
- Utility values used in the BBE NICE submission

Table 3.22 summarises the utility values according to each of the above approaches and the following subsections describe how the utilities were derived for each approach.

Table 3.22: HRQoL according to the different approaches

Health state	Vignette study - General population sample (base case)	BBE NICE submission
Very mild		
0 to <6 years	0.44	0.56
6 to <18 years	0.44	0.56
≥18 years	0.49	0.56
Mild		
0 to <6 years	0.02	0.53
6 to <18 years	0.02	0.53
≥18 years	0.22	0.53
Moderate		
0 to <6 years	-0.44	0.34
6 to <18 years	-0.44	0.34
≥18 years	-0.28	0.34
Severe		
0 to <6 years	-0.54	0.08
6 to <18 years	-0.54	0.08
≥18 years	-0.45	0.08

BBE=birch bark extract; NICE= National Institute for Health and Care Excellence

3.4.5.1.1 Vignette study (base case)

The results from the general population sample of the vignette study were used for the model base case. This source was used because for less prevalent health conditions, NICE deems it appropriate to use utilities derived from a general population sample should other sources not be available.¹⁰⁷ Furthermore, the general population sample size was larger than the patient population sample size, providing additional rationale to selecting the general population sample for generating utility values. The base case analysis assumed a health state vignette approach to define a base utility value based on the percentage of BSA covered by wounds and the pain and itching as a consequence of open wounds.

Two separate vignette studies were conducted, targeting a sample of the UK general population, and DEB patients and their carers, respectively. The general population sample was recruited via Qualtrics, while patients and carers were recruited via DEBRA UK, a patient advocacy group. The vignettes considered the following disease characteristics: number and size of wounds, global pain, itch, hours spent per day managing wounds and pain during wound management. Participants rated vignettes using the EQ-5D-3L for each health state in a random order according to two perspectives:

- The patient perspective, where participants were required to imagine experiencing the described conditions, and
- The carer perspective, where participants imagined their (hypothetical) child was experiencing the described conditions.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

All materials employed were validated by patients, patient representatives and clinicians through focus groups and survey ranking tasks to ensure content validity before commencing data collection.

The general population sample of the vignette study results were used for the model base case.

3.4.5.1.2 Utility values used in HST28

In the NICE BBE submission, the utility values adopted were based on EASE trial (Table 3.23).

Table 3.23: BBE NICE submission utility values

Health state	BBE NICE utility values
Health state 1	0.56
Health state 2	0.51
Health state 3	0.46
Health state 4	0.35
Health state 5	0.23
Health state 6	0.08

BBE=birch bark extract

In the scenario analysis, these values are adopted, using the mapping of HST28 health states onto the health states in the current model as presented in Table 3.10. Table 3.24 presents the utility values by B-VEC model health state based on the BBE NICE submission.

Table 3.24: Utility values by B-VEC model health state based on the BBE NICE submission

Health state	Utility values
Very mild	0.56
Mild	0.53
Moderate	0.34
Severe	0.08

BBE=birch bark extract

3.4.5.2 Carer utilities

Given that DEB is a debilitating disease, and that patients require substantial help with their daily routines, carer utilities were included in the analysis. The NICE appraisal HST28, included carer utilities based on data collected using the TTO method to elicit utility values. The TTO protocol and health states were validated by UK clinical and patient experts. Table 3.25 presents the carers' utility values by health state assumed in the base case, mapped to the current model health states as presented in Table 3.10.

Table 3.25: Base case carers' utility values

Health state	Utility values
Very mild	0.85
Mild	0.85
Moderate	0.72
Severe	0.64

Source: HST28²⁴

It was considered that patients in the worst health states would require more help than patients in milder states. Further, children would require more help than adults from carers, thus the model includes different numbers of carers by age subgroup or health state. The base case assumes that the number of carers needed is 0.5 for Very Mild, 0.51 for Mild, 1.26 for Moderate and 1.78 for Severe (based on HST28, 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, using the mapping to four health states presented in Table 3.10). It was considered that a second carer would have 77% of the HRQoL impact of the primary carer. This assumption is based on the NICE technology appraisal of BBE (HST28),²⁴ where the assumption was made based on a questionnaire hosted by DEBRA UK, exploring the HRQoL impact to second carers relative to the patients' main carer. The responses obtained suggest that the decrement corresponding to the second carer would be approximately 77% of that of the main carer. This supports the need of a second carer for patients with DEB and also how the HRQoL of a second carer is impacted.

3.5 Cost and healthcare resource use identification, measurement and valuation

The current analysis was developed with the aim of including HCRU and costs that would closely represent the actual HCRU and costs of DEB treatment in England and Wales. Where available, costs for previous years were inflated to 2024 values using the NHS Cost Inflation Index, published in the Manual for Unit Costs of Health and Social Care 2023.

The following costs are considered in the analysis:

- Drug costs of intervention and comparators (acquisition and administration)
- Concomitant medication costs
- Clinical manifestations costs
- Monitoring costs
- Bandage costs and dressing costs associated with nurses

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

The derivation of each cost for input into the model is described in the following subsections.

3.5.1 Cost and healthcare resource use identified in the SLR

As introduced in Section 3.4.3, an SLR was conducted to identify utilities, economic and HCRU evidence related to DEB. Ten records were identified reporting direct costs and HCRU, and one (Eng *et al.* [2021]) was used for the CEA. This study is explained below. Details of the SLR approach, and the identified evidence are available in Appendix G.

3.5.2 Intervention and comparators' costs and resource use

3.5.2.1 Eng *et al.* (2021)

Eng *et al.* (2021) conducted a cross-sectional study that surveyed patients with RDEB through the global EBCare Registry. The outcomes measured were disease severity, wound characteristics, pain, itch, extracutaneous symptoms, and medications, and HRQoL using QOLEB. Of the total of 85 RDEB patients who participated in the study, disease severity was self-reported as mild by 26%, moderate by 48%, and severe by 25%.²²

Patients in the severe group were significantly more likely to use opiates (52% vs. 14% in mild; $P = 0.02$), gabapentin (28% vs. 0%; $P = 0.02$), and Medihoney (29% vs. 0%; $P = 0.02$). They also required more pain medication, including opiates ($P = 0.02$), during dressing changes. There was a trend toward higher benzodiazepine use with increased severity, but no significant association with medications for itch, constipation, or topical antibiotics.

3.5.2.2 B-VEC

B-VEC administration costs include costs for preparation, including direct resources used for mixing and appropriate wear, home delivery, application, and disposal. The overall cost per administration for B-VEC in the model was █████ for the first administration and █████ for all subsequent administrations. The administration cost for B-VEC was determined based on a targeted literature review commissioned by Krystal Biotech.⁹² Administration cost included costs related to transport to pharmacy and storage, preparation, home delivery, application, and disposal.

A maximum dose of one vial of B-VEC is administered topically once weekly. The vial consumption depends on the BSA covered by wounds, which depends on the health state that patients are in and the time since entering the model. The maximum

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

recommended dose is one vial (four syringes) per administration, which represents a maximum treatment area of 200 cm².

Syringes of 1 mL should be filled with 0.5 mL of product. In the base case it was assumed that a total of four syringes can be filled with a B-VEC vial, each containing 0.5mL of B-VEC. As the total mixture has 2.5 mL, five syringes could be filled with a vial; however, it was assumed the last 0.5 mL could not be fully collected due to potential remaining pockets of air raising during the preparation phase. It was assumed that a single patient uses up to four syringes, which means that one vial could be efficiently used by a maximum of four patients if one syringe is enough to treat the open area that they have. It means that vial-level sharing, in other words vial optimisation, is possible, and the potential wastage is only on a syringe level.

Notably, the concept of vial optimisation is globally supported and recognised as a method of reducing wastage and optimising healthcare resources, and one that is underutilised in single technology appraisal (STA) submissions despite its abundant use in hospitals globally (approximately 83% of countries in Suzuki *et al.* [2019] used vial optimisation).^{108,109} The medication is mixed by a pharmacist, who then prepares the syringes.

As noted in the SmPC, under controlled and validated aseptic conditions B-VEC's chemical and physical in-use stability has been demonstrated for 168 hours (7 days) at 2-8°C.¹

Notably, if B-VEC is not mixed under aseptic conditions and if not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.¹ Further, it is expected that a 30-day stability period when B-VEC is mixed under aseptic conditions and then frozen, will be approved in the next version of the SmPC.

As it is not expected that vial optimisation will be fully possible, the base case model assumes that vial optimisation applies for 80% of the patients/vials.

Based on the patient-level simulation and the respective simulated area to treat over time for 3 years, the mean number of vials used per cycle could be calculated by age subgroup, year of treatment and health state.

In the scenario analysis, the following options were explored:

- Nine syringes can be filled per vial, which is a more optimistic assumption compared to the base case, where it is considered that four syringes can be filled with one vial;
- Vial sharing applies to 90% of vials/patients;
- Vial sharing applies to 70% of vials/patients.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Table 3.26: Number of B-VEC vials used per cycle by health state, by year and by age subgroup according to the patient-level simulation

Age subgroups	Year	Very mild	Mild	Moderate	Severe
0 to <6 years	1				
	2				
	3+				
6 to <18 years	1				
	2				
	3+				
≥18 years	1				
	2				
	3+				

The cost of each vial of B-VEC, including the expedient required for the mix, is £ 21,500. Table 3.27 presents the B-VEC cost per cycle (£) by health state, by year and by age subgroup.

Table 3.27: B-VEC cost per cycle (£) by health state, by year and by age subgroup

Age subgroup	Year	B-VEC cost per cycle (£)			
		Very mild	Mild	Moderate	Severe
0 to <6 years	1				
	2				
	3+				
6 to <18 years	1				
	2				
	3+				
≥18 years	1				
	2				
	3+				

3.5.2.3 Birch bark extract

The company submission for BBE reports the cost per tube of BBE (£275.33), but not the number of tubes used per month. From the response to EAG clarification questions it was clear that the mean number of tubes per month during the DBP of the EASE trial was 29.67, but that the number used in the model was based on both the DBP and the OLP. However, while it is reported that the average number of tubes in the OLP was lower than in the DBP, the exact number in this phase of the trial is marked confidential and is thus unknown. Because of this uncertainty, the average number of tubes of 29.67 per month was used in all health states. This results in 89 tubes per 3-month cycle, at a total cost of £24,507 per cycle on treatment with BBE.

3.5.3 Concomitant medication costs

B-VEC and BBE are administered as an add-on to BSC, which comprises of concomitant medication. Concomitant medications are the only drugs used in the

BSC arm and should be administered concomitantly in the B-VEC and BBE arms. Concomitant medication include:

- Psychiatric medications
- Selective serotonin reuptake inhibitors/tricyclic depressants (SSRI/TCA)
- Benzodiazepines
- Analgesics routinely
- Ibuprofen
- Gabapentin
- Opiates
- Anti-itch medications
- First generation antihistamines
- Second generation antihistamines
- Topical corticosteroids
- Laxatives
- Topical antibiotics
- Medihoney

Table 3.28 summarises the percentage of patients using each concomitant medication by health state. Concomitant medication costs are presented in Appendix I and are based on British National Formulary (BNF) for pack prices and recommended doses. Conservative estimates of the least expensive medications were used instead of a weighted average based on sales data.

Table 3.28: Percentage of patients using concomitant medication per health state

Concomitant medication	Percentage of patients using each concomitant medication (%)			
	Very mild	Mild	Moderate	Severe
Psychiatric medications				
SSRI/TCA	0	14	5	14
Benzodiazepines	0	0	5	14
Analgesics routinely				
Ibuprofen	0	50	63	57
Gabapentin	0	0	15	29
Opiates	0	14	23	52
Anti-itch medications				
First-generation antihistamines	0	23	18	43
Second-generation antihistamines	0	14	10	29
Topical corticosteroids	0	5	13	10
Laxatives	0	50	38	48
Topical antibiotics	0	77	65	48
Medihoney	0	0	20	29
SSRI=selective serotonin reuptake inhibitor; TCA= tricyclic antidepressants				
Source: Eng <i>et al.</i> (2021) ²²				

Details of the pack size and costs of the concomitant medications used in the model are given in Appendix I.

3.5.4 Clinical manifestation costs

The unit costs for the clinical manifestations, for which probabilities and rates are described in Section 0, are presented in Table 3.29. These costs are based on the National Schedule of NHS Costs 2023/24 applied to the proportion of patients in each health state that develop these clinical manifestations.

Table 3.29: Clinical manifestations costs

Resources	Cost per cycle (£)	Notes
Infections (non-sepsis and sepsis)	3,099	Codes WH07A, WH07B, WH07C, WH07D, WH07E, WH07F, and WH07G as proxy for infections non-sepsis and WJ06A, WJ06B, WJ06C, WJ06D, WJ06E, WJ06F, WJ06G, WJ06H, and WJ06J as proxy for infections sepsis. The total cost is a weighting between the unit cost of each code and the correspondent activity value. It was considered that 33% of the infections are non-sepsis (proxy from mild) and the sepsis (proxy from severe) are 67%.
Anaemia	1,602	Codes SA03G, SA03H, SA03I, SA03J, SA03K, SA03L. The total cost is a weighting between the unit cost of each code and the correspondent activity value.
SCC	2,130	Codes JD07A, JD07B, JD07C, JD07D, JD07E, JD07F, JD07G, JD07H, JD07J, JD07K, PJ35A, PJ35B, PJ35C, PJ35D, PJ66A, PJ66B, and PJ66C. The total cost is a weighting between the unit cost of each code and the correspondent activity value.
Complete or partial mitten deformity of foot	1,810	Codes HD23D, HD23E, HD23F, HD23G, HD23H, and HD23J. The total cost is a weighting between the unit cost of each code and the correspondent activity value.
Complete mitten deformity of hand	1,810	
Osteoporosis	3,347	Codes HD24D, HD24E, HD24F, HD24G, and HD24H. The total cost is a weighting between the unit cost of each code and the correspondent activity value.
Note: All the costs are based on National Schedule of NHS Costs 2023/24		

3.5.5 Health-state unit costs and resource use

3.5.5.1 Outpatient costs

The outpatient monitoring costs presented for the NICE BBE submission are also used for the B-VEC model. The number of outpatient visits per month has been estimated from a structured expert elicitation, conducted by the BBE submitting company. They indicate that with increasing disease severity, there would be an increased level of outpatient hospital visits. The BBE health states were mapped to the B-VEC health states as described in Section 3.3.1. The applied outpatient costs are summarised in Table 3.30. Administration costs for both B-VEC and BBE treatment arms are assumed to be included in the nurse time associated with dressing changes.

Table 3.30: Outpatient costs by health state (per cycle)

Health state	Per cycle outpatient costs
Very mild	£122.75
Mild	£132.91
Moderate	£231.90
Severe	£363.86

3.5.5.2 Bandage costs and dressing costs associated with nurses

Bandage costs and dressing costs associated with nurses are included in the model using the NICE BBE committee paper estimates and applied to the model's health states. These costs are summarised in Table 3.31.

The wound dressing costs were derived from Pillay *et al.* for patients with RDEB (n=53) to be £45,884 per patient.¹¹⁰ Estimated ratios of dressings per visit by health state severity was collected from the structured expert elicitation conducted for the BBE submission. The ratio was applied to the Pillay bandage costs to get estimated costs by health state. The BBE health states were mapped to the B-VEC health states as described in Section 3.3.1.

The dressing costs associated with nurses (or formal care) was estimated by the same structured expert elicitation as referred to above. The costs associated with formal care were estimated from Jones *et al.* at £58.00 per hour with a band 6 hospital-based nurse.¹¹¹ It is assumed that the formal care costs would also account for the administration costs of B-VEC and BBE. The BBE health states were mapped to the B-VEC health states as described in Section 3.3.1.

Table 3.31. Dressing and formal care costs by health state

Health state	Dressing costs (per cycle)	Formal care costs (per cycle)
Very mild	£1,349.56	£36.41
Mild	£3,816.34	£62.94
Moderate	£13,979.97	£1,750.48
Severe	£27,377.64	£5,243.75

3.5.6 Adverse reaction unit costs and resource use

Given the mild nature of AEs observed in the pivotal GEM-1 and GEM-3 trials, and the absence of SAEs linked to B-VEC, utility decrements and resource use or costs associated with AEs have not been factored into the CEM. Further details on AEs are provided in Section 2.10.

3.5.7 Miscellaneous unit costs and resource use

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

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

3.6 Severity

NICE's 2022 update introduced a decision modifier for medicines treating severe diseases, reflecting society's higher value on such treatments.¹¹² The decision modifier adjusts the willingness to pay (WTP) threshold for single technology appraisals (£30,000/QALY) based on a therapy's future health gains.

For assessing the severity of the condition in technology appraisals, the associated absolute and proportional QALY shortfall should be calculated. The absolute QALY shortfall is calculated using the following formula:

$$\text{Absolute QALY shortfall} = \text{QALYs without the disease} - \text{QALYs with the disease}$$

A greater absolute QALY shortfall indicates higher disease severity but is biased against older individuals due to life expectancy limits. Proportional QALY shortfall adjusts for this by considering the relative difference between future healthy life years (LYs) with and without the disease, with both measures discounted at 3.5% per NICE guidelines. The proportional shortfall is given by the following formula:

$$\text{Proportional QALY shortfall} = \frac{\text{Absolute QALY shortfall}}{\text{QALYs with the disease}}$$

Table 3.32 presents the absolute and proportional QALY shortfall threshold values for disease severity and the respective inferred WTP threshold.

Table 3.32: Absolute and proportional QALY shortfall threshold values for disease severity and the respective inferred willingness to pay threshold

QALY weight	Inferred willingness to pay threshold	Proportional QALY shortfall	Absolute QALY shortfall
1	Up to £30,000/QALY	Less than 0.85	Less than 12
x1.2	Up to £36,000/QALY	0.85 to 0.95	12 to 18
x1.7	Up to £51,000/QALY	At least 0.95	At least 18
QALY=quality-adjusted life-years			

Table 3.33 presents the absolute and proportional QALY shortfall in the current analysis (excluding carer QALYs) and the respective inferred WTP threshold. The high health gain offered by B-VEC suggest the WTP threshold can meet the £51,000/QALY.

Table 3.33: Absolute and proportional QALY shortfall threshold values for disease severity and the respective inferred willingness to pay threshold

Measures	Outcome
QALYs without the disease (discounted)	23.15
QALYs with the disease (discounted)	-5.23
Absolute shortfall	28.38
Proportional shortfall	1.226
QALY weight	1.7
Inferred WTP threshold	Up to £51,000/QALY
QALY=quality-adjusted life-years; WTP=willingness to pay	

3.7 Uncertainty

DEB is a rare disease, making clinical trial recruitment of a large number of study participants difficult. As such, the GEM clinical trials were not powered to assess differences in DEB subtypes. The EASE trial attempted to compare RDEB and DDEB populations; however, the results were not statistically significant given the small sample size in each group.

3.8 Managed access proposal

Not applicable.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

Table 3.34: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Population age	All ages to reflect the population in the GEM-3 trial	No alternative population ages were considered relevant	3.2.1
Time horizon	Lifetime (100 years)	No alternative time horizons were considered given the lifetime nature of DEB	3.2.2
Cycle length	3 months	No alternative cycle lengths were explored as this timeframe corresponds with data from GEM1 and GEM-3	3.2.2
Annual discount rate (Costs and QALYs)	3.5%	An alternative discount rate of 1.5% for costs and outcomes was explored	3.2.2
Health state distribution	Based on Bruckner et al (2021) RDEB population and DDEB populations, and expert opinion	NA	3.2.2.3
Baseline BSA	RDEB patients: Reimer <i>et al.</i> ⁴⁸ . DDEB patients: general population	NA	3.2.2

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Time to wound reopening with B-VEC	█ days as per the GEM-3 and OLE	NA	3.2.2.1.3.2
Vial optimisation	4 syringes per vial (max 4 per patient)	Alternative scenarios using 9 syringes per two vials and intra-patient vial sharing were explored	3.5.2.2
Proportion of patients to consider vial optimisation for	80%	Alternative scenarios using 90% and 70% of patients participating in vial optimisation	3.5.2.2
Number of weeks until wounds become chronic	8 weeks as per Eng <i>et al.</i> (2021) ²²	NA	3.2.2.1.3.3
B-VEC discontinuation	1% per year	9.68% per year in the first year, then 1% per year onwards for B-VEC	3.3.6
Utility values	Utilities as per vignette study using EQ-5D-3L (UK general population)	Utility values used in HST28	3.4.5.1
Carer disutilities	Included using TTO study. The number of carers varied by severity of patient from 0.5 in Mild health state to 1.78 in the Severe health state (based on HST precedence).	NA	3.4.5.2
Costs of clinical manifestations	Included based on National Schedule of NHS Costs 2023/24 ¹¹³	NA	0
Mortality	Very mild: average between the general population and RDEB-non-severe curve from Petrof <i>et al.</i> (2022). ^{11,103} Mild: RDEB-non-severe and severe curves from Petrof <i>et al.</i> (2022). ¹¹ Moderate: Enter model at age <6: RDEB-non-severe ¹¹ Enter model at age ≥6: average between RDEB-non-severe curve from Petrof <i>et al.</i> (2022). ¹¹ Severe: Enter model at age <6: Average of RDEB (except severe) and RDEB severe ¹¹ Enter model at age ≥6: RDEB-severe curve from Petrof <i>et al.</i> (2022) ¹¹ DDEB patients (all severities): general population ¹⁰⁴	NA	3.3.5
Costs	Costs of clinical complications derived from the National Schedule of NHS; SEE-derived resource estimates for bandage and outpatient costs, ²⁴ administration costs assumption, and BNF-derived estimates for concomitant therapy	NA	3.5
BNF=British National Formulary; BSA=body surface area; CI=confidence interval; DEB=dystrophic epidermolysis bullosa; OLE=open-label extension; QALY=quality-adjusted life-years; RDEB=recessive dystrophic epidermolysis bullosa; SCC=squamous Cell Carcinoma; TTO=time trade-off; UK=United Kingdom			

3.9.2 Assumptions

The assumptions made in the cost-effectiveness model, along with their justifications, are summarized in Table 3.35.

Table 3.35: Assumptions and justifications for model inputs

Assumption	Justification
Severe health state is capped to 40% of BSA (only at baseline)	- Bruckner <i>et al.</i> (2020) reported that 50% of patients with DEB had wounds covering at least 30% BSA.⁶ - Wound progression data gathered from SEE in HST28 support the threshold of 40%.²⁴ - Expert clinicians interviewed by Krystal Biotech, Dr. Martinez and Dr. Petrof, considered 40% BSA involvement to be the upper limit for Severe DEB (only at baseline) in their estimates of percent BSA affected by recurrent and chronic wounds.
The number of wounds per health state implemented in the model, are consistent with the ranges of the number of wounds that patients would have in each health state recorded in Eng <i>et al.</i> (2021). ²²	The authors observed in their sample that on average, the number of wounds per patient was 11 recurrent wounds (SD = 10, range = 0-45) and 3 chronic wounds (SD = 2, range = 0-9). A normal distribution was assumed and the 25th and 75th percentiles were used to provide the lower-bound of the Moderate and Severe health states respectively, while the average defined the lower-bound of the Moderate health state.
Wounds are considered chronic if they remain open for at least 8 weeks.	Several evidence sources that evaluated duration of time for a wound to become chronic were evaluated. Eng <i>et al.</i> reported the most detailed information on this topic, their findings revealed that all recurrent wounds healed within 8 weeks, while no wounds lasting beyond 8 weeks ever healed. ²²
The higher dose of B-VEC was considered for all patients despite the younger subgroup (0-6 years) potentially requiring a lower dose.	As the younger age subgroup has a mean age of 2.25 years at baseline, in the first three cycles, the recommended dose would be the lower one. However, to simplify the model and make a conservative assumption, the higher dose was considered for all patients.
80% of patients will participate in vial optimisation, and that it is feasible to share a vial between a maximum of 4 patients.	Theoretically, a total of five syringes can be filled with a single vial; however, to leave a buffer it was assumed that the last 0.5 mL could not be fully collected due to potential remaining pockets of air raising during the preparation phase, and so four syringes can be filled with one vial. Therefore, one syringe can be used by a maximum of four patients given that a nurse can bring the syringes to multiple patients on the same day, prepared syringes kept in the patient's own fridge will stay good for 7 days (when mixed under aseptic conditions). As it is not expected that vial optimization will be fully possible, the base case model assumes vial optimization applies for 80% of the patients/vials. The concept and utility of vial optimisation has also been discussed and approved of by multiple studies. ^{109,108}
B-VEC discontinuation is 0.25% per cycle, or 1% per annum.	This assumption was made in line with observations in the GEM-1 and GEM-3 trials, where no discontinuations were observed. However, in a lifetime of B-VEC use, it is expected that some patients would discontinue treatment. Due to that, the base case assumes that annually, 1% of patients discontinue treatment.
For the Very Mild health state, it was assumed that no irreversible clinical manifestations occurred. For	Probabilities are used for reversible events because it was assumed that these events can be repeatable,

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Assumption	Justification
the Mild, Moderate, and Severe health states in the model, it was assumed that the prevalence of clinical manifestations is the same as reported in Eng <i>et al.</i> (2021) ²² for patients categorised as mild, moderate and severe, respectively. For reversible clinical manifestations, the model assumes a per-cycle probability aligning directly with the prevalence reported in Eng <i>et al.</i> (2021). ²²	meaning that the total sum of the probabilities over time can be >100%. On the other hand, rates should be used if something can happen only once as the irreversible events are, thus the sum should add up to ≤100%. Infections and anaemia in the Very Mild health state, based on the UK clinical validation, were assumed to happen at the same rate as in the Mild health state. For the irreversible clinical manifestations, the rate per cycle was calculated based on the equation outlined in Section 3.3.3. It was considered that events had occurred in a time horizon of 21 years, which is the mean age of patients in Eng <i>et al.</i> (2021). ²²
The second carer of the patient experiences 77% of the HRQoL impact than the primary carer experiences.	Considering the lack of evidence from the GEM trials, the EASE trial, and general literature estimating the number of carers required per patient, this assumption was made based on a previous NICE technology appraisal in EB that received positive feedback from the ERG. ²⁴ A questionnaire hosted by DEBRA UK exploring the HRQoL impact to second carer relative to the patients' main carer suggested that the decrement corresponding to second carer would be approximately 77% of that of the main carer. The ERG considered this approach of modelling carer disutility appropriate. ¹¹⁴
DDEB mortality was assumed to match the mortality of the general population. Overall mortality rates across RDEB health states are consistent with those observed in Petrof <i>et al.</i> (2020)	This assumption was tested in a previous positively received EB NICE technology appraisal, ²⁴ where experts agreed that the mortality rate of DDEB and RDEB non-severe patients would be similar with that of the general population.
BSA=body surface area; DEB=dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; ERG=evidence review group; HRQoL=health-related quality of life; NICE=National Institute for Health and Care Excellence; OLE=open-label extension; QALY=quality-adjusted life-years; RDEB=recessive dystrophic epidermolysis bullosa; SEE=structured expert elicitation; SCC=squamous cell carcinoma; TTO=time trade-off; UK=United Kingdom	

3.10 Base-case incremental cost-effectiveness analysis results

3.10.1 Cost-effectiveness results

Table 3.36 presents summary results of the base-case CEM for B-VEC vs BSC and B-VEC vs BBE from the NHS and Personal Social Services perspective in England. Over the lifetime time horizon, there was a substantial gain in discounted QALYs for patients who received B-VEC compared with those who received BSC (26.23) and those who received BBE (16.48).

From the NHS perspective, the discounted total lifetime cost in the B-VEC arm was ████████, which was ████████ less than in the BSC arm and ████████ less than in the BBE arm.

Table 3.36. Base-case results

	Life-Years	Discounted Life-Years	QALY	Discounted QALY	Cost (£)	Discounted Cost (£)
B-VEC	62.29	25.31	128.29	51.76		
BSC	52.27	22.49	61.87	25.53		
BBE	62.26	25.44	88.25	35.28		
Comparisons						
B-VEC vs BSC	10.02	2.81	66.41	26.23		
B-VEC vs BBE	0.03	-0.14	40.04	16.48		

BBE=birch bark extract; BSC=best supportive care; QALY: quality-adjusted life-year

Considering the incremental QALY gains (26.23 QALYs and 16.48 QALYs for the comparison versus BSC and BBE, respectively) and the cost savings of [REDACTED] and [REDACTED] for the comparison versus BSC and BBE, respectively, the model shows that B-VEC is dominant versus both BSC and BBE. Because the ICER is negative and not informative, the net monetary benefit (NMB) is a more valuable measure to report. A NMB of [REDACTED] was observed for the comparison versus BSC, and a NMB of [REDACTED] was observed versus BBE (Table 3.37).

Table 3.37: Results of base case incremental cost-effectiveness analysis

Comparison	Inc. cost (£)	Inc. QALY	ICER (£/QALY)	NMB ((ΔQALYs*WTP - Δcost)), WTP = £ 51,000 (£)
B-VEC vs BSC	[REDACTED]	26.23	dominant	[REDACTED]
B-VEC vs BBE	[REDACTED]	16.48	dominant	[REDACTED]

BBE=birch bark extract; BSC=best supportive care; ICER=incremental cost-effectiveness ratio; NMB=net monetary benefit; WTP=willingness-to-pay

Cost breakdowns can be found in Appendix H.

3.11 Sensitivity analyses

3.11.1 Probabilistic sensitivity analysis

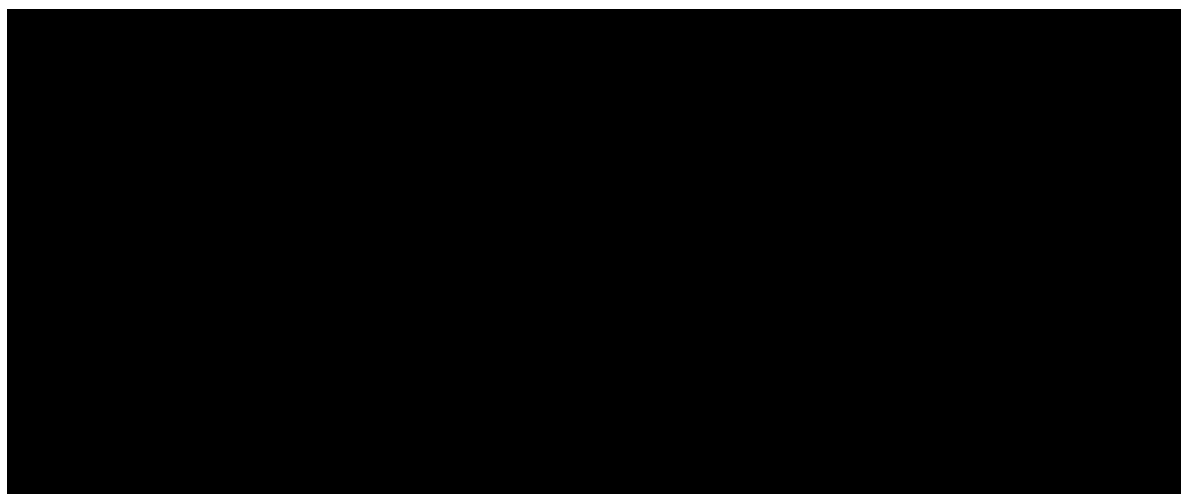
A probabilistic sensitivity analysis (PSA) was performed to assess the robustness of the model to parameter uncertainty. In the PSA, 1,000 simulations were performed, in which model parameters were varied simultaneously by sampling at random from hypothetical distributions. Population characteristics were not included in the PSA since they represent first order uncertainty.

Dirichlet distribution was used for groups of parameters for which the sum of variables should be equal to one, like the distribution of patients across the age subgroup or the distribution of patients across the health states. Normal distribution was used for parameters where the uncertainty is around the average. For proportions, beta was assumed to be the most appropriate distribution. Gamma distribution was adopted to represent the uncertainty around the costs.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

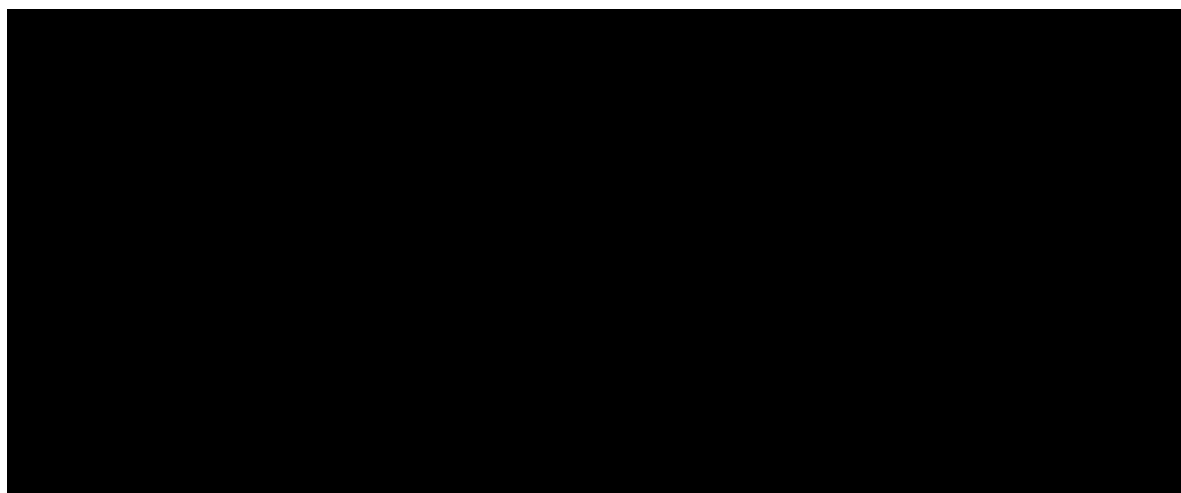
In the PSA, almost all iterations in the comparison to BSC are located in the South-East quadrant of the cost-effectiveness plane (i.e., negative incremental costs and positive incremental QALYs). Figure 3.4 and Figure 3.5 present the cost/effectiveness plane for the comparison to BSC and to BBE, respectively. The base case results were similar to the mean point in the cost/effectiveness plane (Table 3.38 and Table 3.39), confirming the overall robustness of the model results. Figure 3.6 and Figure 3.7 show the cost-effectiveness acceptability curve for the comparison to BSC and BBE, respectively.

Figure 3.4: Distribution of results of PSA simulations in the cost-effectiveness plane for the comparison to BSC



BSC=best supportive care; CE=Cost-effectiveness; PSA=Probabilistic sensitivity analysis; QALY=Quality-adjusted life year

Figure 3.5: Distribution of results of PSA simulations in the cost-effectiveness plane for the comparison to BBE



CE=cost effectiveness; QALY=quality adjusted life years

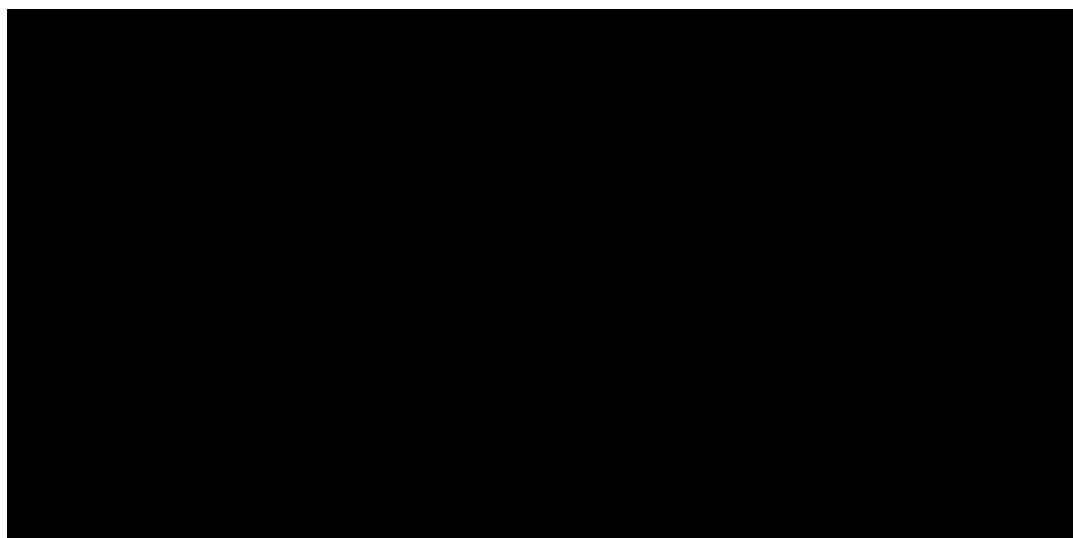
Table 3.38: Comparison of the base case and PSA results – comparison to BSC

Comparison	Costs (£)			QALYs			ICER	NMB (£)
	B-VEC	BSC	Incr	B-VEC	BSC	Incr		
Base case	██████	██████	██████	51.76	25.53	26.23	Dominant	██████
PSA mean	██████	██████	██████	51.56	25.64	26.02	Dominant	██████
PSA 95%CI lower	██████	██████	██████	48.09	21.74	20.79	Dominant	██████
PSA 95%CI upper	██████	██████	██████	55.33	29.60	31.06	Dominant	██████
BSC=best supportive care; ICER=incremental cost-effectiveness ratio; Inc=incremental; NMB=net monetary benefit; QALY=quality adjusted life years								

Table 3.39: Comparison of the base case and PSA results – comparison to BBE

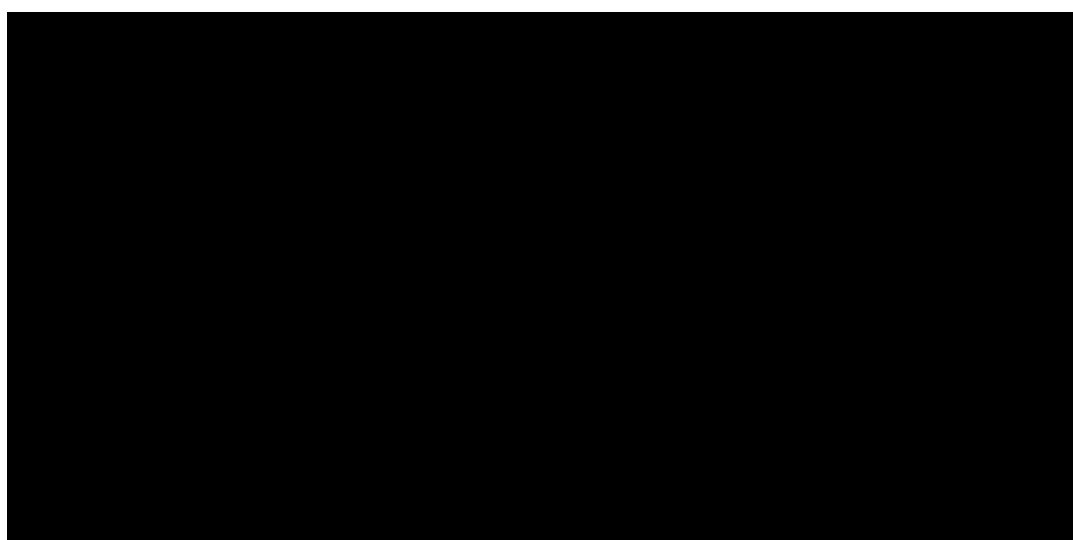
Comparison	Costs (£)			QALYs			ICER	NMB (£)
	B-VEC	BBE	Incr	B-VEC	BBE	Incr		
Base case	██████	██████	██████	51.76	35.28	16.48	Dominant	██████
PSA mean	██████	██████	██████	51.65	35.37	16.29	Dominant	██████
PSA 95%CI lower	██████	██████	██████	48.09	31.14	10.73	Dominant	██████
PSA 95%CI upper	██████	██████	██████	55.33	39.93	21.79	Dominant	██████
BBE=birch bark extract; BSC=best supportive care; CI=confidence interval; ICER=incremental cost-effectiveness ratio; NMB=net monetary benefit; PSA= probabilistic sensitivity analysis; QALYs=quality-adjusted life years								

Figure 3.6: Cost-effectiveness acceptability curve for the comparison to BSC



BSC=best supportive care; QALY=quality-adjusted life year; WTP=willingness-to-pay

Figure 3.7: Cost-effectiveness acceptability curve for the comparison to BBE



QALY=quality-adjusted life year; WTP=willingness-to-pay

3.11.2 Deterministic sensitivity analysis

To evaluate the sensitivity of model results to variation in input parameters, a series of one-way sensitivity analyses were performed, in which key model parameters were varied one at a time around their base-case values. The 95% confidence limits were used as the high and low values when reported in the data reference. If not reported, the 95% confidence interval was approximated by setting high and low values at the base-case value $\pm 1.96 \times \text{SE}$. When the SE was not reported, 10% of the base-case value was used as a proxy.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

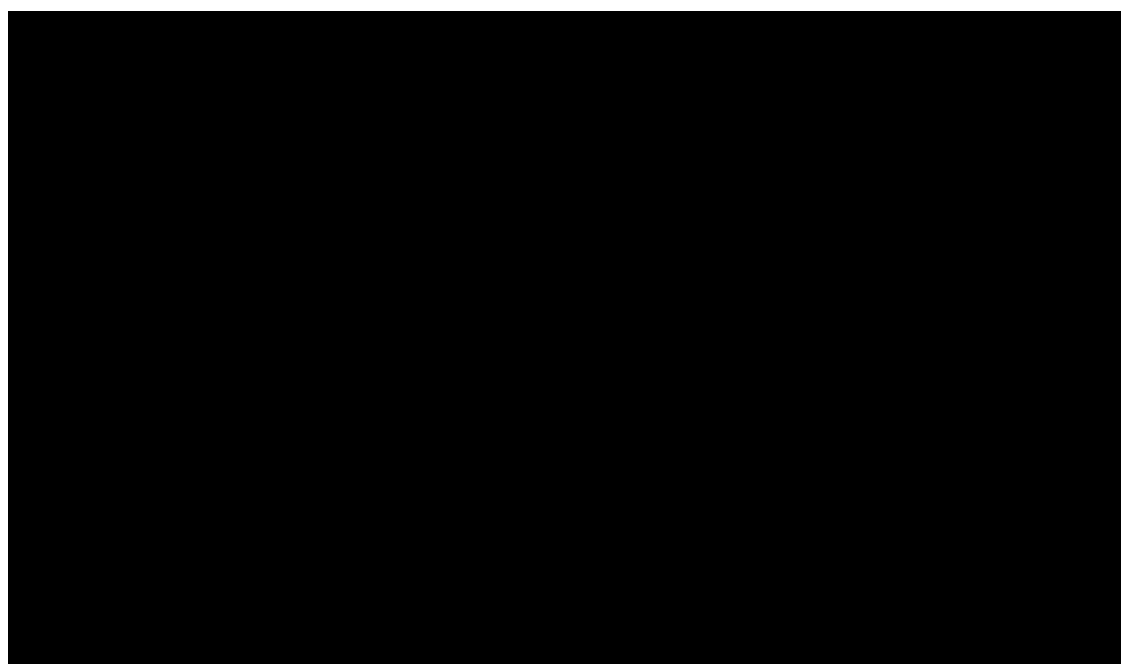
Table 3.40 and Figure 3.8 show the top 10 most influential model parameters in the comparison to BSC. In the one-way sensitivity analysis, the variables with the greatest influence on NMB was the discount rate for outcomes and costs. In the comparison to BSC, the next most influential parameters were the bandage cost per cycle in the severe health state, and the proportion of patients in the adolescents group. In the comparison to BBE, the third and fourth most influential parameters were the proportion of RDEB patients and the proportion of patients in the adolescent age group (Table 3.40 and Figure 3.9).

Table 3.40: Percentage change in base case results of comparison to BSC following lower and upper variation in the 10 most influential model parameters

Parameters	Percentage change vs base case	
	Lower value	Upper value
Discount rate outcomes		
Discount rate costs		
Bandage cost per cycle by health state (£) - Severe		
Distribution of patients by age group - [6-18]		
Distribution of patients by disease subtype - RDEB		
Distribution of patients by disease subtype - DDEB		
Distribution of patients by age group - ≥18		
Health states distribution by age groups - RDEB population [6-18] - Severe		
Impact of DEB on HRQoL of carer - Patients ≥18 years old - Very Mild		
Bandage cost per cycle by health state (£) - Moderate		

DEB=dystrophic epidermolysis bullosa; HRQoL=health-related quality of life

Figure 3.8: Results of the one-way sensitivity analysis for the comparison to BSC

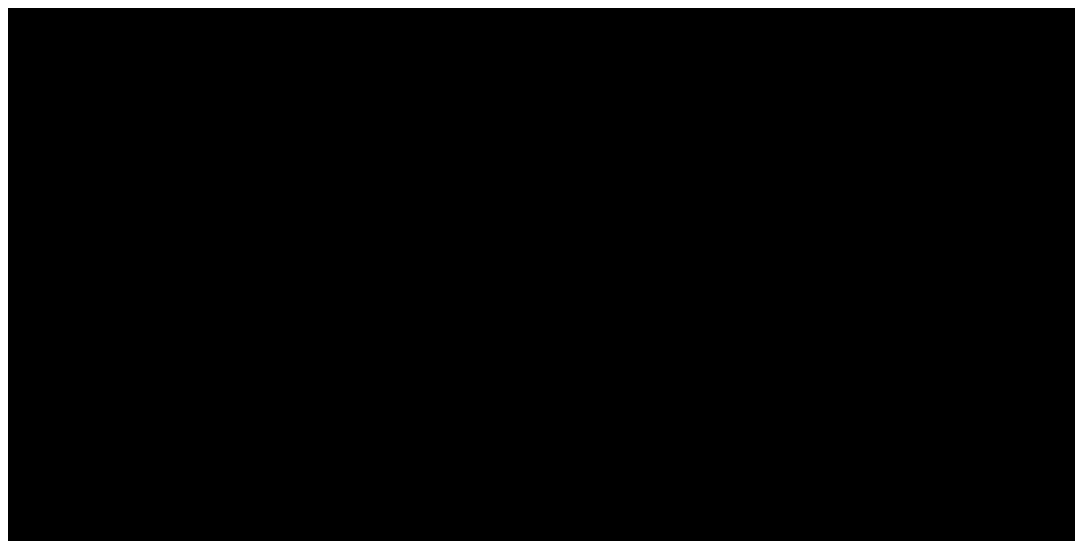


BSC=best supportive care; DDEB=dominant dystrophic epidermolysis bullosa; NMB=net monetary benefit; QoL=quality of life; RDEB=recessive dystrophic epidermolysis bullosa; WTP=willingness to pay

Table 3.41: Percentage change in base case results of the comparison to BBE following lower and upper variation in the 10 most influential model parameters

Parameters	Percentage change vs base case	
	Lower value	Upper value
Discount rate costs		
Discount rate outcomes		
Distribution of patients by disease subtype - RDEB		
Distribution of patients by age group - [6-18]		
Distribution of patients by disease subtype - DDEB		
Distribution of patients by age group - ≥18		
Bandage cost per cycle by health state (£) - Moderate		
Impact of DEB on QoL of carer - Patients ≥18 years old - Moderate		
Health states distribution by age groups - RDEB population [6-18] - Severe		
Impact of DEB on HRQoL of carer - Patients ≥18 years old - Very Mild		
DDEB=dominant dystrophic epidermolysis bullosa; DEB=dystrophic epidermolysis bullosa; HRQoL=health related quality of life; RDEB=recessive dystrophic epidermolysis bullosa		

Figure 3.9: Results of the one-way sensitivity analysis for the comparison to BBE



DDEB=dominant dystrophic epidermolysis bullosa; DEB=dystrophic epidermolysis bullosa; NMB=net monetary benefit; QoL=quality of life; RDEB=recessive dystrophic epidermolysis bullosa; WTP=willingness to pay

3.11.3 Scenario analysis

Various scenario analyses were explored and are presented in Table 3.42.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

Table 3.42: Scenario analyses explored

#	Setting	Base case	Scenario
1	Vial optimization	4 syringes per vial (max 4 per patient)	9 syringes per two vials
2	Proportion of patients to consider vial optimization for	80%	90%
3			70%
4	B-VEC discontinuation	1% per year	9.68% per year in the first year, then 1% per year onwards for B-VEC
5	Utility values	Vignette – general population sample	BBE NICE submission (EASE trial utilities)
6	Discounting on costs and outcomes	3.5% for both	1.5% for both

The results of the scenario analyses are shown in Table 3.43.

Table 3.43: Results of the scenario analysis

#	Scenario	Comparator: BSC					Comparator: BBE				
		Incremental		ICER	Threshold (for NMB) (£)	NMB (£)	Incremental		ICER	Threshold (for NMB) (£)	NMB (£)
		Discounted costs (£)	QALYs				Discounted costs (£)	QALYs			
0	Base case	████	26.23	dominant	51,000	████	████	16.48	dominant	51,000	████
1	B-VEC vial optimization: 9 syringes per two vials (maximum of 4 syringes per patient).	████	26.39	dominant	51,000	████	████	16.47	dominant	51,000	████
2	Proportion of patients to consider for vial optimization: 90%	████	26.18	dominant	51,000	████	████	16.53	dominant	51,000	████
3	Proportion of patients to consider for vial optimization: 70%	████	26.16	dominant	51,000	████	████	16.47	dominant	51,000	████
4	B-VEC discontinuation: 9.68% per year in the first year, then 1% per year onwards	████	23.94	dominant	51,000	████	████	14.19	dominant	51,000	████
5	Utility values for patients: BBE NICE submission	████	17.06	dominant	36,000	████	████	6.09	dominant	36,000	████
6	Discounting for costs and outcomes set to 1.5%	████	42.12	dominant	51,000	████	████	25.87	dominant	51,000	████
BBE=birch bark extract; BSA=Body surface area; DEB=Dystrophic Epidermolysis Bullosa; ICER=incremental cost-effectiveness ratio; NMB=Net monetary benefit; RDEB=recessive dystrophic epidermolysis bullosa; SCC=squamous cell carcinoma											

3.12 Subgroup analysis

Subgroup analyses have not been conducted, although assumptions regarding the three different age subgroups (0-6 years; 6-18 years; ≥18 years) in relation to health state distribution are examined in the scenario analyses.

3.13 Validation

The quality checklist used to assess the cost-effectiveness model of B-VEC in DEB was included in the CEM file in sheet “QC” and it is based on the report produced according to the model review by the York Health Economic Consortium.

The current CEM was validated versus the model used for the initial Company Submission for BBE, as reported in NICE HST28. This is described in detail in Section 3.3.1.

A validation of the CEM versus the B-VEC trial data unfortunately was not possible, as the model is based on total BSA affected, whilst both GEM-1 and GEM-3 are only providing data on a wound level, without any information about the total number of wounds or area affected in the patients.

An attempt was made to validate the proportion of area closed as modelled through the patient-level simulation tool versus outcomes reported in GEM-3. However, since the patient-level simulation models the total BSA affected and not single wounds, and also it considers the treatment of area not initially treated once the initially treated area has closed, the outcomes from the patient-level simulation are not comparable to those reported in GEM-3.

3.14 Interpretation and conclusions of economic evidence

This is the first economic analysis and model submitted to NICE for a targeted, corrective therapy to treat DEB. The CEM shows that the intervention (B-VEC plus BSC) was dominant compared to BSC alone at a WTP threshold of £51,000 per QALY gained. Over the lifetime time horizon, there was a substantial gain in discounted QALYs (26.23), for patients who received B-VEC compared with those who received BSC alone. From the NHS perspective, the discounted total lifetime cost in the B-VEC arm was [REDACTED] less than in the BSC arm, and the NMB was [REDACTED] when comparing B-VEC to BSC. Taken together, B-VEC is shown to be more cost-effective than BSC alone for patients with DEB. Similarly, there was a substantial gain in discounted QALYs (16.86) when comparing B-VEC to BBE; discounted costs of [REDACTED]. The NMB for the comparison to BBE was [REDACTED].

The WTP threshold was set to £51,000 considering the February 2022 update of the NICE manuals for processes and methods for HTA submissions. A notable update Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

was the introduction of a decision modifier, applicable only to medicines for severe diseases. The decision modifier permits adjustment of the standard WTP threshold for single technology appraisals (£30,000/QALY), enabling the definition of a higher threshold based on the anticipated health gains offered by new therapies. The use of £51,000 as the threshold aligns with this guidance, particularly when the technology under review (B-VEC) offers transformative benefits, such as substantial HRQoL improvements, reductions in disease burden, and potentially extended survival as demonstrated in the GEM trials and other evidence.

Health states were defined by varying BSA percentages affected by wounds in this model. This approach and the values adopted for each health state were validated by UK clinical experts. This approach also aligned with a previous NICE technology appraisal, which received positive feedback from the ERG. This appraisal also defined health states by BSA, which was noted to correlate with disease severity.

Although the GEM-3 study collected HRQoL values using the EQ-5D-5L and other instruments, this approach was not chosen as health state definitions were not based on BSA. Therefore, the EQ-5D-5L was used to derive utility values through a vignette study. This approach allows for the NICE preferred instrument to be used, EQ-5D-3L, and to align utility values with health states based on the percentage of BSA covered by wounds. The CEM also incorporates carer HRQoL values derived from the TTO instrument. The number of carers ranges from 0.5 in the Very Mild health state to 1.78 in the Severe health state as validated by UK clinical and patient experts. Should patients enter milder health states, they may require less help from carers.

To test the uncertainty around model inputs and assumptions, various sensitivity and scenario analyses were conducted. In the one-way sensitivity analysis, the variable with the greatest influence on the NMB for both comparisons (B-VEC with BSC and B-VEC with BBE) was the discount rate for outcomes and costs. Furthermore, the robustness of the base case and model results were demonstrated through a PSA, which showed that base case results were similar to the mean point in the iterations of the cost/effectiveness plane. Several scenario analyses were explored, including a discount rate of 1.5% for costs and outcomes, vial optimisation (9 syringes per 2 vials; 70% and 90% of patients participating), and different sources of utility values based on HST28.

Vial sharing (or optimisation), which includes filling multiple syringes from one vial, is a concept supported by the literature and recognised as a method to reduce wastage. To ensure the robustness of the CEM, scenario analyses that estimated varying degrees of vial sharing were run. Importantly, a conservative estimate was used in the base case, that a total of four syringes can be filled with a single B-VEC Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

vial and considering only 80% of patients would participate in vial optimisation. Considering the limited data addressing costs in DEB, outpatient costs were obtained from a structured expert elicitation from a previous NICE appraisal in EB.

B-VEC offers the most discounted QALYs gained in the Very Mild health state in the comparison with BSC (■■■■) and with BBE (■■■■), meaning B-VEC may be best administered earlier in the disease course. This could be due to B-VEC being a targeted, corrective therapy that can prevent or slow the progression of irreversible clinical manifestations, such as SCC and mitten deformities of the hands and feet, through restoration of function COL7. Considering that SCC is a leading cause for mortality in patients with DEB, B-VEC may also prolong the lifespan of patients. There are no other known targeted, corrective therapies for DEB.

Patients with DEB experience life-long clinical manifestations starting at birth that can be irreversible. In this economic analysis, treatment with B-VEC was found to be cost-effective and provided the most QALYs gained early in the disease process. This highlights the importance of the targeted and corrective nature of B-VEC, in which timely intervention may be important to prevent irreversible complications and improve the HRQoL of patients. Considering the role of B-VEC in restoring COL7, it can also halt the progression to SCC, a cause of mortality in patients with DEB. Considering the devastating nature of DEB, that there is no cure, and that there is a lack of effective treatment options, there is a significant unmet medical need to develop innovative therapies in this disease area. B-VEC could address this unmet need as a cost-effective therapy that targets the underlying cause of the debilitating symptoms DEB patients experience through a durable response and improves patients' and carers' HRQoL.

References

1. Krystal Biotech. Summary of product characteristics: Vyjuvek (beremagene geperpavec). Amsterdam, Netherlands: Krystal Biotech Netherlands, B.V.; 2023.
2. European Medicines Agency (EMA). First topical gene therapy treatment for dystrophic epidermolysis bullosa. 2025; <https://www.ema.europa.eu/en/news/first-topical-gene-therapy-treatment-dystrophic-epidermolysis-bullosa>.
3. Food and Drug Administration. FDA Approves First Topical Gene Therapy for Treatment of Wounds in Patients with Dystrophic Epidermolysis Bullosa. 2023; <https://www.fda.gov/news-events/press-announcements/fda-approves-first-topical-gene-therapy-treatment-wounds-patients-dystrophic-epidermolysis-bullosa>.
4. National Health Service (NHS) England. NHS standard contract for epidermolysis bullosa service (all ages): Particulars, schedule 2 – the services, a - Service Specification. 2013.
5. Angelis A, Kanavos P, Lopez-Bastida J, et al. Social/economic costs and health-related quality of life in patients with epidermolysis bullosa in Europe. *Eur J Health Econ*. 2016;17(Suppl 1):31-42.
6. Bruckner AL, Losow M, Wisk J, et al. The challenges of living with and managing epidermolysis bullosa: insights from patients and caregivers. *Orphanet J Rare Dis*. 2020;15(1):1.
7. Tang JY, Marinkovich MP, Lucas E, et al. A systematic literature review of the disease burden in patients with recessive dystrophic epidermolysis bullosa. *Orphanet J Rare Dis*. 2021;16(1):175.
8. Denyer J, Pillay E, Clapham J. Best practice guidelines for skin and wound care in epidermolysis bullosa. An International Consensus. Wounds International; 3 May 2017.
9. Fine JD. Inherited epidermolysis bullosa. *Orphanet J Rare Dis*. 2010;5:12.
10. Has C, Bauer JW, Bodemer C, et al. Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. *Br J Dermatol*. 2020;183(4):614-627.
11. Petrof G, Papanikolaou M, Martinez AE, et al. The epidemiology of epidermolysis bullosa in England and Wales: data from the national epidermolysis bullosa database. *Br J Dermatol*. 2022;186(5):843-848.
12. Feinstein JA, Jambal P, Peoples K, et al. Assessment of the timing of milestone clinical events in patients with epidermolysis bullosa from North America. *JAMA Dermatol*. 2019;155(2):196-203.
13. Pfendner EG, Lucky AW. Dystrophic epidermolysis bullosa. Chapter in Adam MP, Everman DB, Mirzaa GM, et al., eds. *GeneReviews((R))*. Seattle (WA):2018.
14. Cianfarani F, Zambruno G, Castiglia D, Odorisio T. Pathomechanisms of altered wound healing in recessive dystrophic epidermolysis bullosa. *Am J Pathol*. 2017;187(7):1445-1453.
15. Mellerio JE. Infection and colonization in epidermolysis bullosa. *Dermatol Clin*. 2010;28(2):267-269.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

16. Mellerio JE, Robertson SJ, Bernardis C, et al. Management of cutaneous squamous cell carcinoma in patients with epidermolysis bullosa: best clinical practice guidelines. *Br J Dermatol*. 2016;174(1):56-67.
17. Nystrom A, Bruckner-Tuderman L, Kiritsi D. Dystrophic epidermolysis bullosa: secondary disease mechanisms and disease modifiers. *Front Genet*. 2021;12:737272.
18. Fine JD, Mellerio JE. Extracutaneous manifestations and complications of inherited epidermolysis bullosa: part II. Other organs. *J Am Acad Dermatol*. 2009;61(3):387-402; quiz 403-384.
19. Chateau AV, Blackbeard D, Aldous C. The impact of epidermolysis bullosa on the family and healthcare practitioners: a scoping review. *Int J Dermatol*. 2022;62(4):459-475.
20. Ireland CJ, Pelentzov LJ, Kopecki Z. Caring for a child with epidermolysis bullosa: a scoping review on the family impacts and support needs. *Wound Pract Res*. 2021;29(2):86-97.
21. Fulchand S, Harris N, Li S, et al. Patient-reported outcomes and quality of life in dominant dystrophic epidermolysis bullosa: A global cross-sectional survey. *Pediatr Dermatol*. 2021;38(5):1198-1201.
22. Eng VA, Solis DC, Gorell ES, et al. Patient-reported outcomes and quality of life in recessive dystrophic epidermolysis bullosa: A global cross-sectional survey. *J Am Acad Dermatol*. 2021;85(5):1161-1167.
23. Mauritz P, Jonkman MF, Visser SS, et al. Impact of painful wound care in epidermolysis bullosa during childhood: an interview study with adult patients and parents. *Acta Derm Venereol*. 2019;99(9):783-788.
24. National Institute for Health and Care Excellence (NICE). Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]. Committee papers. 20 September 2023.
25. Amryt Pharmaceuticals DAC. Filsuvez (Oleogel-S10) 0.5g–1.0 g birch bark gel. Summary of Product Characteristics. 4 July 2022. Accessed 29 November 2022.
26. European Medicines Agency (EMA). EPAR Medicine Overview: Filsuvez (birch bark extract). 4 July 2022; <https://www.ema.europa.eu/en/medicines/human/EPAR/filsuvez>. Accessed 29 November 2022.
27. European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP) assessment report: Filsuvez. 4 April 2022; <https://www.ema.europa.eu/en/medicines/human/EPAR/filsuvez>. Accessed 4 December 2022.
28. Medicines and Healthcare products Regulatory Agency (MHRA). Filsuvez Gel Summary of Product Characteristics. 18 August 2022; <https://www.medicines.org.uk/emc/product/13971/smpc/print>. Accessed 3 April 2023.
29. Has C, El Hachem M, Buckova H, et al. Practical management of epidermolysis bullosa: consensus clinical position statement from the European Reference Network for Rare Skin Diseases. *J Eur Acad Dermatol Venereol*. 2021;35(12):2349-2360.
30. DEBRA UK. Epidermolysis bullosa patient insights. Quantitative research presentation. June 2023/JN4286.2023.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

31. Schrader NHB, Korte EWH, Duipmans JC, et al. Identifying epidermolysis bullosa patient needs and perceived treatment benefits: an explorative study using the Patient Benefit Index. *J Clin Med*. 2021;10(24).
32. Guide SV, Gonzalez ME, Bagci IS, et al. Trial of beremagene geperpavec (B-VEC) for dystrophic epidermolysis bullosa. *N Engl J Med*. 2022;387(24):2211-2219.
33. Gurevich I, Agarwal P, Zhang P, et al. In vivo topical gene therapy for recessive dystrophic epidermolysis bullosa: a phase 1 and 2 trial. *Nat Med*. 2022;28(4):780-788.
34. Badger KS, O'Haver J, Price H. Recommendations for a comprehensive management plan for the child diagnosed with epidermolysis bullosa. *J Dermatol Nurses Assoc*. 2013;5:72-78.
35. Tabor A, Pergolizzi JV, Jr., Marti G, et al. Raising awareness among healthcare providers about epidermolysis bullosa and advancing toward a cure. *J Clin Aesthet Dermatol*. 2017;10(5):36-48.
36. Cogan J, Weinstein J, Wang X, et al. Aminoglycosides restore full-length type VII collagen by overcoming premature termination codons: therapeutic implications for dystrophic epidermolysis bullosa. *Mol Ther*. 2014;22(10):1741-1752.
37. Fritsch A, Loeckermann S, Kern JS, et al. A hypomorphic mouse model of dystrophic epidermolysis bullosa reveals mechanisms of disease and response to fibroblast therapy. *J Clin Invest*. 2008;118(5):1669-1679.
38. Kuhl T, Mezger M, Hausser I, et al. Collagen VII half-life at the dermal-epidermal junction zone: Implications for mechanisms and therapy of genodermatoses. *J Invest Dermatol*. 2016;136(6):1116-1123.
39. Bardhan A, Bruckner-Tuderman L, Chapple ILC, et al. Epidermolysis bullosa. *Nat Rev Dis Primers*. 2020;6(1):78.
40. Bruckner-Tuderman L. Dystrophic epidermolysis bullosa: pathogenesis and clinical features. *Dermatol Clin*. 2010;28(1):107-114.
41. Wilkinson HN, Hardman MJ. Wound healing: cellular mechanisms and pathological outcomes. *Open Biol*. 2020;10(9):200223.
42. Orphanet. Dystrophic epidermolysis bullosa. May 2021; <https://www.orpha.net/>. Accessed 3 December 2022.
43. Fine JD, Bruckner-Tuderman L, Eady RA, et al. Inherited epidermolysis bullosa: updated recommendations on diagnosis and classification. *J Am Acad Dermatol*. 2014;70(6):1103-1126.
44. Paller AS, Pope E, Rudin D, et al. A prospective short-term study to evaluate methodologies for the assessment of disease extent, impact, and wound evolution in patients with dystrophic epidermolysis bullosa. *Orphanet J Rare Dis*. 2022;17(1):314.
45. National Institute for Health and Care Excellence (NICE). Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]. Response to consultee and commentator comments on the draft remit and draft scope. August 2022.
46. Office for National Statistics. Mid-2023 edition of this dataset - Estimates of the population for the UK, England, Wales, Scotland, and Northern Ireland. 2024.
47. Tong L, Hodgkins PR, Denyer J, et al. The eye in epidermolysis bullosa. *Br J Ophthalmol*. 1999;83(3):323-326.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

48. Reimer A, Hess M, Schwieger-Briel A, et al. Natural history of growth and anaemia in children with epidermolysis bullosa: a retrospective cohort study. *Br J Dermatol*. 2020;182(6):1437-1448.
49. Liy-Wong C, Tarango C, Pope E, et al. Consensus guidelines for diagnosis and management of anemia in epidermolysis bullosa. *Orphanet J Rare Dis*. 2023;18(1):38.
50. Fine JD, Johnson LB, Weiner M, et al. Eye involvement in inherited epidermolysis bullosa: experience of the National Epidermolysis Bullosa Registry. *Am J Ophthalmol*. 2004;138(2):254-262.
51. Condorelli AG, Dellambra E, Logli E, et al. Epidermolysis bullosa-associated squamous cell carcinoma: from pathogenesis to therapeutic perspectives. *Int J Mol Sci*. 2019;20(22).
52. Bonamonte D, Filoni A, De Marco A, et al. Squamous cell carcinoma in patients with inherited epidermolysis bullosa: review of current literature. *Cells*. 2022;11(8):1365.
53. Fine JD, Johnson LB, Weiner M, et al. Epidermolysis bullosa and the risk of life-threatening cancers: the National EB Registry experience, 1986-2006. *J Am Acad Dermatol*. 2009;60(2):203-211.
54. Guerra L, Odorisio T, Zambruno G, Castiglia D. Stromal microenvironment in type VII collagen-deficient skin: The ground for squamous cell carcinoma development. *Matrix Biol*. 2017;63:1-10.
55. Atanasova VS, Russell RJ, Webster TG, et al. Thrombospondin-1 Is a Major Activator of TGF- β Signaling in Recessive Dystrophic Epidermolysis Bullosa Fibroblasts. *J Invest Dermatol*. 2019;139(7):1497-1505.e1495.
56. Kim M, Li M, Intong-Wheeler LRA, et al. Epidemiology and outcome of squamous cell carcinoma in epidermolysis bullosa in Australia and New Zealand. *Acta Derm Venereol*. 2018;98(1):70-76.
57. Montaudie H, Chiaverini C, Sbidian E, et al. Inherited epidermolysis bullosa and squamous cell carcinoma: a systematic review of 117 cases. *Orphanet J Rare Dis*. 2016;11(1):117.
58. Choi S, Solis D, Nazaroff J, et al. Quality of life in recessive dystrophic epidermolysis bullosa: The AltaVoice patient registry, 2012-2015. *J Invest Dermatol*. 2017;137(5):S38.
59. Pope E, Lara-Corrales I, Mellerio J, et al. A consensus approach to wound care in epidermolysis bullosa. *J Am Acad Dermatol*. 2012;67(5):904-917.
60. Gowran RJ, Kennan A, Marshall S, et al. Adopting a Sustainable Community of Practice Model when Developing a Service to Support Patients with Epidermolysis Bullosa (EB): A Stakeholder-Centered Approach. *Patient*. 2015;8(1):51-63.
61. Angelis A, Mellerio JE, Kanavos P. Understanding the socioeconomic costs of dystrophic epidermolysis bullosa in Europe: a costing and health-related quality of life study. *Orphanet J Rare Dis*. 2022;17(1):346.
62. Kearney S, Donohoe A, McAuliffe E. Living with epidermolysis bullosa: Daily challenges and health-care needs. *Health Expect*. 2020;23(2):368-376.
63. De Stefano S, Grassi FS, Lalatta F, et al. Family burden of children suffering from epidermolysis bullosa. *Ital J Dermatol Venerol*. 2021;156(5):580-587.
64. Fine JD, Johnson LB, Weiner M, Suchindran C. Impact of inherited epidermolysis bullosa on parental interpersonal relationships, marital status and family size. *Br J Dermatol*. 2005;152(5):1009-1014.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

65. Dufresne H, Hadj-Rabia S, Bodemer C. Impact of a rare chronic genodermatosis on family daily life: the example of epidermolysis bullosa. *Br J Dermatol*. 2018;179(5):1177-1178.
66. Feinstein JA, Bruckner AL, Chastek B, et al. Clinical characteristics, healthcare use, and annual costs among patients with dystrophic epidermolysis bullosa. *Orphanet J Rare Dis*. 2022;17(1):367.
67. Wu YH, Sun FK, Lee PY. Family caregivers' lived experiences of caring for epidermolysis bullosa patients: A phenomenological study. *J Clin Nurs*. 2020;29(9-10):1552-1560.
68. Kern JS, Sprecher E, Fernandez MF, et al. Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: results from the phase III randomized double-blind phase of the EASE study. *Br J Dermatol*. 2022;188(1):12-21.
69. Amryt Pharma. Amryt to pursue formal dispute resolution for Oleogel-S10 (Filsuvez®) NDA. 24 June 2022; <https://amrytpharma.com/newsroom/>. Accessed 29 November 2022.
70. Amryt Pharma. Amryt receives complete response letter from the FDA for Oleogel-S10 NDA. 28 February 2022; <https://amrytpharma.com/newsroom/>. Accessed 29 November 2022.
71. Chiesi Global Rare Diseases. Chiesi Global Rare Diseases Receives FDA Approval for FILSUEZ® (birch triterpenes) topical gel for the Treatment of Epidermolysis Bullosa. 2023; <https://chiesirarediseases.com/media/fda-approval-for-filsuvez-topical-gel>.
72. Marinkovich MP, Gonzales ME, Guide S, et al. GEM-3: A phase 3 study of beremagene geperpavec (B-VEC), an investigational, topical gene therapy, for the treatment of dystrophic epidermolysis bullosa (DEB). [Abstract presented at the American Academy of Dermatology Annual Meeting 2022, March 25-29, 2022; Boston, MA]2022.
73. Office for Disability Issues. Equality Act 2010: Guidance on matters to be taken into account in determining questions relating to the definition of disability. 2010; <https://www.gov.uk/government/publications/equality-act-guidance>. Accessed 13 April 2023.
74. National Organization for Rare Disorders (NORD). Epidermolysis bullosa. 10 July 2015; <https://rarediseases.org/rare-diseases/epidermolysis-bullosa/>. Accessed 13 April 2023.
75. Kramer-Roy D. Supporting ethnic minority families with disabled children: learning from Pakistani families. *Br J Occup Ther*. 2012;75(10):442-448.
76. Chamba R, Ahmad W, Hirst M, et al. On the edge: Minority ethnic families caring for a severely disabled child. 1999; <https://www.york.ac.uk/inst/spru/pubs/pdf/minoritysumm.pdf>. Accessed 13 April 2023.
77. National Institute for Health and Care Excellence (NICE). Developing NICE guidelines: the manual. 2014.
78. Krystal Biotech Inc. GEM-3 Clinical Study Report. A Phase 3 Efficacy and Safety Study of Beremagene Geperpavec (B-VEC, Previously KB103) for the Treatment of Dystrophic Epidermolysis Bullosa (DEB). 24 May 2022.
79. ClinicalTrials.gov. NCT04491604: Ph 3 Efficacy and Safety of B-VEC for the Treatment of DEB (GEM-3). 17 February 2023; <https://clinicaltrials.gov/ct2/show/NCT04491604>. Accessed 3 April 2023.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

80. Krystal Biotech Inc. GEM-1 Clinical Study Report: A Phase 1/2 Study of B-VEC, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB). 24 May 2022.
81. ClinicalTrials.gov. NCT03536143: A Phase I/II Study of KB103, a Topical HSV1-COL7, on DEB Patients (GEM-1). 31 January 2023; <https://clinicaltrials.gov/ct2/show/NCT03536143>. Accessed 3 April 2023.
82. Kern JS, Schwieger-Briel A, Lowe S, et al. Oleogel-S10 Phase 3 study "EASE" for epidermolysis bullosa: study design and rationale. *Trials*. 2019;20(1):350.
83. Krystal Biotech Inc. OLE Clinical Study Report: Open label treatment of beremagene geperpavec (B-VEC). B-VEC-EX-02. 18 October 2023 2023.
84. Stratenym. Vyjuvek® (beremagene geperpavec) for the treatment of dystrophic epidermolysis bullosa: SLR report 2025.
85. Centre for Reviews and Dissemination (CRD). Systematic Reviews: Guidance for Undertaking Reviews in Health Care. York, UK:2009.
86. Solis DC, Teng C, Gorell ES, et al. Classification of 2 distinct wound types in recessive dystrophic epidermolysis bullosa: A retrospective and cohort natural history study. *J Am Acad Dermatol*. 2021;85(5):1296-1298.
87. Schwieger-Briel A, Kiritsi D, Schempp C, et al. Betulin-Based Oleogel to Improve Wound Healing in Dystrophic Epidermolysis Bullosa: A Prospective Controlled Proof-of-Concept Study. *Dermatol Res Pract*. 2017;2017:5068969.
88. D K, DF M, AL B, et al. Long-term safety and efficacy of Oleogel-S10 (birch triterpenes) in epidermolysis bullosa wounds: 24-month open-label data from the EASE study. *Pediatr Dermatol*. 2023.
89. United States Food and Drug Administration (FDA). Human gene therapy for rare diseases: guidance for industry. January 2020; <https://www.fda.gov/media/113807/download>. Accessed 30 November 2022.
90. Khan A, Riaz R, Ashraf S, Akilimali A. Revolutionary breakthrough: FDA approves Vyjuvek, the first topical gene therapy for dystrophic epidermolysis bullosa. *Ann Med Surg (Lond)*. 2023;85(12):6298-6301.
91. Scottish Medicines Consortium. birch bark extract gel (Filsuvez®).2024.
92. York Health Economics Consortium. Administration Cost of Beremagene Geperpavec: Final Report. 21 March 2025 2025.
93. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition*. 1989;5(5):303-311; discussion 312-303.
94. National Center for Health Statistics. Downloadable Charts - growthcharts. 2024; <https://www.cdc.gov/growthcharts/who-charts.html>.
95. Krystal Biotech Inc. KRYs Corporate deck - Jan 2021. January 2021; <https://ir.krystalbio.com/index.php/static-files/34687a98-89a9-4188-8f3c-72e8bd90bd98>.
96. Royal College of Paediatrics and Child Health (RCPCH). UK-WHO Growth chart - 2-18 years. 2012; <https://www.rcpch.ac.uk/resources/uk-who-growth-charts-2-18-years>.
97. Haute Autorité de Santé. AVIS SUR LES MEDICAMENTS beremagene geperpavec. 2024.
98. An introduction to the methods of cost-effectiveness analysis. *Drug Ther Bull*. 2012;50(7):81-84.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

99. Watanabe T, Go H, Saigusa Y, et al. Mortality and risk factors on admission in toxic epidermal necrolysis: A cohort study of 59 patients. *Allergol Int*. 2021;70(2):229-234.
100. Palmieri TL, Greenhalgh DG, Saffle JR, et al. A multicenter review of toxic epidermal necrolysis treated in U.S. burn centers at the end of the twentieth century. *J Burn Care Rehabil*. 2002;23(2):87-96.
101. Jeschke MG, Pinto R, Kraft R, et al. Morbidity and survival probability in burn patients in modern burn care. *Crit Care Med*. 2015;43(4):808-815.
102. Hon KL, Li JJ, Cheng BL, et al. Age and etiology of childhood epidermolysis bullosa mortality. *J Dermatolog Treat*. 2015;26(2):178-182.
103. National life tables, United Kingdom, period expectation of life, based on data for the years 2018-2020. Published September 23, 2021.
<https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/previousReleases>.
104. Office for National Statistics. National life tables – life expectancy in England and Wales: 2021 to 2023. 2024;
<https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2021to2023>.
105. van Hout BA, Shaw JW. Mapping EQ-5D-3L to EQ-5D-5L. *Value Health*. 2021;24(9):1285-1293.
106. Hussain S, Worsley C, Noble-Longster J, et al. The 2023 EB Insights Study: The Impact of Epidermolysis Bullosa on the Health-Related Quality of Life of Patients and Their Carers. Presented at the ISPOR 2024.
107. Ara R, Wailoo A. NICE Decision Support Unit Technical Support Documents. Chapter in *NICE DSU Technical Support Document 12: The Use of Health State Utility Values in Decision Models*. London: National Institute for Health and Care Excellence (NICE); 2011.
108. Lien K, Cheung MC, Chan KK. Adjusting for Drug Wastage in Economic Evaluations of New Therapies for Hematologic Malignancies: A Systematic Review. *J Oncol Pract*. 2016;12(4):e369-379.
109. Suzuki S, Gilbar P, Yu B, et al. Current status of drug vial optimization use to prevent waste associated with injectable anticancer agents. *J Oncol Pharm Pract*. 2019;25(1):244-246.
110. Pillay E.I. JE, Martinez A.E., Mellerio J.E., McGrath J., Bisquera A., Robertson S. Treatment costs for individuals with recessive dystrophic epidermolysis bullosa (RDEB): Findings of the pebles study. Presented at the 1st World Congress on Epidermolysis Bullosa, EB 2020 London United Kingdom 2020.
111. Jones KWH, Birch, S., Castelli, A., Chalkley, M., Dargan, A., Findlay, D., Forder, J., Gao, M., Hinde, S., Markham, S. Premji, S. Teo, H., . Unit Costs of Health and Social Care 2023. Kent, UK: Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York); 2024.
112. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. . Published January 31, 2022.
113. NHS England. National Cost Collection for the NHS. 2024;
<https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/>.
114. National Institute for Health and Care Excellence (NICE). Birch bark extract for treating epidermolysis bullosa: final draft guidance 2023.

Company evidence submission template for beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Single technology appraisal

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

Summary of Information for Patients (SIP)

April 2025

File name	Version	Contains confidential information	Date
ID3959_SIP	1.0	No	7 April 2025

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

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

This submission assesses a medicine called beremagene geperpavec, which is also referred to as B-VEC. B-VEC is the generic name of the active ingredient of the medicine; its brand name is VYJUVEK®.

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

This treatment will be used by people with dystrophic epidermolysis bullosa (abbreviated as DEB). Please refer to Section 2 for more details on the condition ([Section 2a](#)), how it is diagnosed ([Section 2b](#)), current treatment options ([Section 2c](#)) and the impact it has on patients and carers ([Section 2d](#)).

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.

Once a medicine has been developed, it needs to receive marketing authorisation so that it can be sold and prescribed in different countries. In the UK, the Medicines & Healthcare products Regulatory Agency (MHRA) is responsible for deciding on the use of human medicines and providing marketing authorisation. The company developing B-VEC will apply to the MHRA. It is anticipated that B-VEC will be approved to treat wounds in patients with DEB from birth.

The Committee for Medicinal Products for Human Use (CHMP) is responsible for preparing the European Medicines Agency (EMA) opinions on questions concerning the use of human medicines in the European Union (EU). In February 2025, B-VEC received a positive opinion from the CHMP. The CHMP recommended that B-VEC should receive a marketing authorisation in the EU for treating wounds in patients of all ages with DEB.¹

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 provide

Krystal Biotech has collaborated with the following patient groups:

- DEBRA UK:
 - Co-funded the epidermolysis bullosa (EB) patient insights study, published in 2023 (see Section 2d for details on this study). Krystal Biotech contributed £30,000, and had no influence on running or writing-up the study.
 - Sponsored the Members' Weekend 2024 (£3,000).
- Cure EB
 - 2023 Butterfly Run – WINGS (£2,000)
 - 2024 Butterfly Run – WINGS (£2,000)

SECTION 2: Current landscape

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.

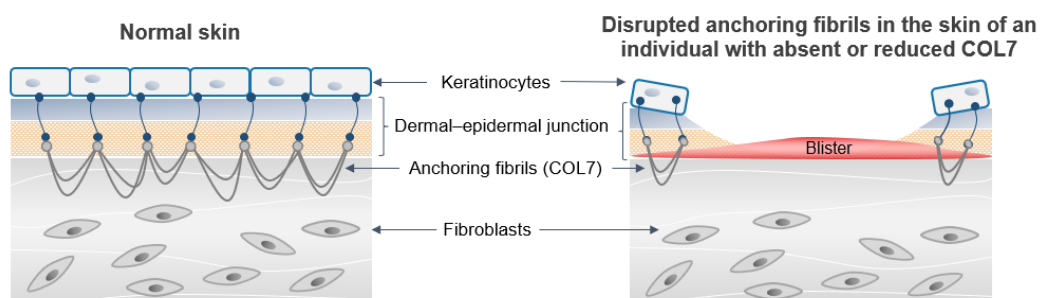
Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly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

DEB is a rare inherited skin condition caused by a faulty gene.

DEB belongs to a group of rare inherited skin conditions called EB, which cause the skin to become very fragile and damaged even with minor contact. The other skin conditions in this group, or subtypes of EB, are EB simplex, junctional EB, and Kindler EB.² These conditions are different from each other regarding what causes them, how they impact the skin, and how they can be treated. Only DEB is being discussed in this submission.

DEB is caused by a change (also called a mutation) in the COL7A1 gene that codes for a protein called type VII collagen. This protein produces anchoring fibrils that look like small threads and help the two layers of the skin to stay together (Figure 1). Because of the faulty (or mutated) COL7A1 gene, people with DEB have less type VII collagen protein or even completely lack it. As a result, the outside skin layer (epidermis) is not properly connected with the skin layer that is under (dermis).³ This causes the skin to become fragile, as the two layers of the skin can separate and slide easily. Sometimes the space between the two layers retains fluid that causes blisters, or the top layer of the skin can peel off when rubbed.^{3,4} Damage to the skin is very painful, and when blisters start to heal, they can become very itchy.⁵ DEB often presents at birth, and by the end of the first year, most babies with DEB will present signs of the condition.⁶

Figure 1. Absent or reduced type VII collagen disconnects the skin layers



In addition to causing painful wounds and blisters, DEB makes the skin unable to heal as quickly as it does in healthy people. In healthy skin, any damage is quickly repaired by a process called wound healing, which closes the wound.^{7,8} In people with DEB this process is impaired, and

wounds take much longer to close. In addition, wounds also close in a different way, with the appearance of small, white-coloured bumps called milia, and scars.⁷ As wounds take longer to heal, this can in turn cause more damage to the skin and other body tissues. Open wounds can also become infected, which leads to more complications.⁵

DEB is a hereditary condition, meaning that it can be passed from parents to their children through genes, which carry all the information that determine each person's features or characteristics. People inherit two sets of genes, one from each parent. Genes determine how people look, for instance eye or hair colour, but can also determine how healthy people are. DEB can present differently depending on whether one or both inherited genes are faulty:

- Dominant DEB (DDEB): one copy of the gene is faulty; this can be inherited from one of the parents but also happen unexpectedly even when there is no family history of the condition. Blisters can appear anywhere in the body but are more common in areas that are frequently rubbed, such as the hands and the feet.
- Recessive DEB (RDEB): both copies of the gene are faulty. RDEB is usually more severe and has higher chances of being fatal.^{2,9} Blisters can also appear in the mouth, eyes, and digestive tract (food pipe).^{3,4,6-8}

The severity of DEB depends on what caused the gene to be faulty and how much type VII collagen the person has.² There are many possible complications in severe DEB, which can cause disability and potentially lead to early death.^{4,7,10} People with severe forms of DEB may need surgery to deal with the impact of having a lot of scars, such as fused toes and fingers,¹¹ or to remove squamous cell carcinoma (SCC), which is a common type of skin cancer in people with DEB.¹²

DEB is a rare condition.

The National Health Service (NHS) estimates that there are currently 2,361 people in England and Wales living with EB.⁹ Using these EB registry data, it is estimated there are currently 617 people with DEB in England, and that every year, 15 babies are born with the condition. This means that it is expected that 632 people are eligible for treatment with B-VEC in the first year after it is approved.

DEB is a debilitating lifelong condition, which impacts the quality of life of the people who have the condition and their carers.

DEB has a profound impact on people with the condition and their carers due to recurrent and chronic wounds, acute and chronic pain, burning sensation, and intense itch.¹¹ DEB is associated with large clinical burden that starts at birth and gets worse over a person's lifetime.^{6,11,14} People with DEB experience severe complications that can impact several organs and body functions. These include hand and foot deformities, oesophageal strictures (or narrowing of the food pipe), failure to thrive, blindness, increased risk of cutaneous SCC, and premature death.^{6,11,14,15} More details on the impact of DEB are presented in [Section 2d](#).

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?

Healthcare professionals, such as doctors, nurses, and other people who provide healthcare, can use different tests to diagnose DEB, to be sure that a person has the condition. They can use different laboratory tools, such as skin biopsy, which involves removing a small bit of the skin, or taking blood to test the genes.² These tests also help to identify which specific subtype of EB the person has, for instance DEB or EB simplex. By testing the genes, the healthcare professionals will also determine if one copy or both copies of the gene are faulty. This will tell if the person has DDEB or RDEB.

Healthcare professionals who have experience with treating people with EB can sometimes do a temporary diagnosis based on clinical observation, for instance when a newborn has missing skin, but this should be confirmed by laboratory testing.

If the parents are known to carry the faulty gene, it is sometimes possible to do prenatal (that is, before the baby is born) testing at 8 to 10 weeks of gestation.³

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:
 - 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.
 - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

There is currently no cure for DEB or treatments that can address the fundamental cause of the condition. In the UK, the standard of care (which is the clinical advice on how patients with the condition should be treated) focuses on managing the symptoms and the complications associated with the condition.^{16,17} This is also sometimes called best supportive care (BSC). The British Association of Dermatologists (BAD) published a leaflet, which recommended that DEB should be managed with a combination of practical measures (such as selecting clothes and activities that reduce friction), skin care (including using dressings and lubricant ointments and eye drops when the eyes are affected), nutritional support and oral hygiene, physiotherapy and hand wrapping, and other special considerations.³ Most people with DEB (72%) need to use painkillers to manage their pain, including stronger opioids such as morphine or hydrocodone (19% of people), or topical and oral steroids (38% of people).¹⁸ There are four specialist centres in the UK (two for children, two for adults), where a team of healthcare professionals provides care for people with DEB.

Due to the lack of cure or treatments that address the fundamental cause of the condition, people with DEB and their carers become experts on how to manage the condition and learn what helps to manage the symptoms.² People also value treatment recommendations from other people with the condition.¹⁸

The only treatment that is available specifically for DEB is called birch bark extract gel (brand name Filsuvez®). It was recommended by the National Institute for Health and Care Excellence (NICE) in September 2023 for the treatment of partial thickness wounds associated with DEB or junctional EB in people aged 6 months and older.¹⁹ This treatment is a gel that can either be applied directly onto the wounds and covered with a wound dressing, or applied onto the dressing that is then used to cover the wound. It is not clear how the active ingredient in the gel, birch bark extract, works. Birch bark extract does not address the fundamental cause of the condition.^{1,20,21} This means that this medicine treats the symptoms of DEB but it does not change what is causing the condition. As such, although people may feel that they are getting better, DEB continues to progress in the same way it would even if people did not use birch bark extract. The gel cannot be used on the eyes or mucous membranes, such as the mouth.²²

When a new treatment is developed, its efficacy (which is defined as the beneficial results of a treatment under ideal conditions), and safety (which is defined as the potential of a medicine to be tolerated by people taking it) are often assessed in clinical trials. The EASE trial was implemented to assess the efficacy and safety of birch bark extract, comparing it with a control

gel. This was a gel that looked like the gel being studied, but it did not contain the active medicine; it is sometimes called placebo or dummy. People with DEB or junctional EB were given the gel with birch bark extract or the control gel, which was applied to the wound as needed for 90 days.²³ People with the condition and their carers did not know whether they were receiving the active or the control gel. When results were assessed after 45 days of treatment, a slightly higher number of people who received the birch extract gel had their wounds completely closed at any point during those 45 days, when compared with people who received the control gel.²⁴ However, the difference between the two groups of people was small.²⁰ Also, the trial did not investigate how long the wounds stayed closed, or if they remained closed during the whole 45-day period. After 90 days of treatment, there were no differences between groups for complete wound closure. This means that complete wound closure was the same for people with DEB who used birch bark extract gel and for people with DEB who used control gel.

The safety results showed that the gel did not help to avoid infections or full-thickness ulcers, or to slow down the development of skin cancer.²⁰ Finally, as people with severe DEB and junctional EB were more likely to quit the trial, there is less information about how this treatment works for them.

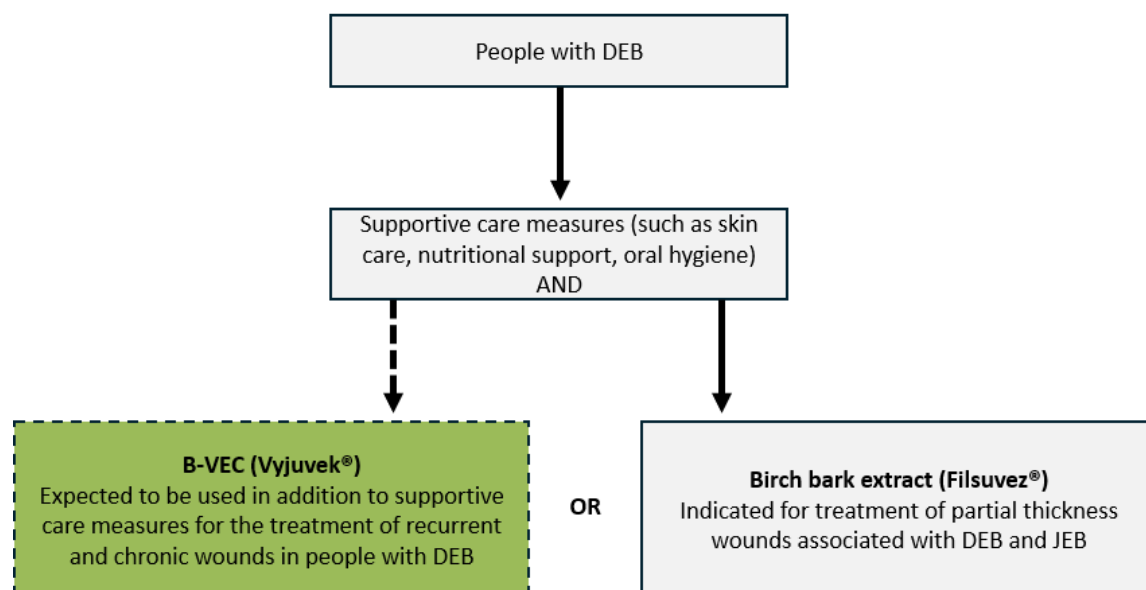
People with DEB and their carers urgently need access to treatments that address the fundamental cause of the condition and that can answer specific concerns and unmet needs:

- Reduce pain, itch, and burning sensation, which will improve quality of life and health-related quality of life (HRQoL).
- Reduce the burden of daily wound care.
- Reduce long-term complications associated with DEB and the need for additional medical procedures, such as surgery to release fused toes or fingers.
- Improve severe infection and SCC, which are associated with increased risk of death.

B-VEC is a gene therapy that delivers two new copies of the gene that is faulty in people with DEB.²⁵ [Section 3a](#) provides more details on how B-VEC works.

B-VEC is expected to be used in addition to supportive care measures (**Figure 2**) and address many of the unmet needs of people with DEB.

Figure 2. Clinical pathway of care for people with DEB in the UK



B-VEC=beremagene geperpavec; DEB=dystrophic epidermolysis bullosa; JEB=junctional epidermolysis bullosa.

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.

DEB has a profound impact on people with the condition and their carers, who are most often parents of children with DEB.

DEBRA UK, a leading UK-based EB medical research charity, conducted a large study in early 2023, called EB insights study. The goals of the EB insights study were to understand what it is like to live with EB, what care and support are available, and what are the unmet needs of people with DEB and their carers, many of whom were parents of young children. This study was conducted across the UK and surveyed more than 200 people living with EB, 97 of whom had DEB, and 100 carers.¹⁸ People with EB answered a questionnaire called EQ-5D, which measures health-related problems. Results of the questionnaire showed that EB impacted many aspects of wellbeing. Specifically, people with EB reported that the condition negatively impacted usual activities and self-care, especially their ability to move about, and caused pain and discomfort, as well as symptoms of anxiety and depression.

Of people with DEB, approximately two thirds (64%) indicated that the condition impacted their self-confidence, approximately half (55%) considered that it impacted their mental health, and for 45% their condition limited their independence. On a typical day, more than two thirds of people with EB spent up to four hours resting or recovering.¹⁸ Almost two thirds of people with DEB said that they had experienced fatigue (65%) or difficulty sleeping (61%).¹⁸

RDEB, which is the more severe form of DEB, has a particularly strong impact on people with the condition. People with RDEB have more pain and itch and worse quality of life than people with other subtypes of EB.¹¹ Most people with RDEB have wounds on at least one third of their body, and pain and intense itch are higher in those people with larger wounds,¹¹ which also happens for people with DDEB.¹⁷

DEB greatly impacts the productivity of people with the condition and their carers.

Wound care is a major part of the lives of people with DEB and their carers, with dressings being changed up to three times per day.^{11,26} Wound care can take more than four hours per day and require assistance from one or more carers.¹¹ In the EB insights study conducted by DEBRA UK, most people with EB spent on average 2.2 hours on blister/wound care and personal hygiene.¹⁸ Of the 97 people with DEB, 90% said that they had poor wound healing symptoms, while 79% had wounds that healed very slowly, 73% had leakage or discharge from wounds, 69% had infected wounds, and 66% had experienced smell or odour from wounds.

The EB insights study also showed that more people with DEB are unable to work due to ill health (23 in every 100 people with DEB were unable to work due to ill health), when compared with other subtypes of EB, such as junctional EB (17 in every 100 people with junctional EB were unable to work due to ill health) or EB simplex (eight in every 100 people with EB simplex were unable to work due to ill health).¹⁸ A survey conducted in the US found that most of those with EB had decided not to work due to their condition, and those who continued working had to reduce their hours of work.¹⁶

Given that people with EB often require a carer for wound management and support for living with consequences of DEB, EB also has a major impact on carers' lives. Most carers indicated that

looking after someone with the condition had impacted their ability to enjoy life (61%) and work or study (54%), as well as their mental health (59%), and their future plans and aspirations (58%).¹⁸ In the US study mentioned before, more than half of the 93 carers surveyed said that they had decided not to work, because they had to look after of someone with EB.¹⁶ On a typical day, carers spent up to four hours supporting the person with EB, including more than one hour checking on the person during the night. Additionally, parents of children with EB reported feeling powerless and sad at seeing their child in pain and suffering.¹⁷

SECTION 3: The treatment

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.

B-VEC is a herpes simplex virus type 1–based topical (this means that it is applied directly to the skin) gene therapy. B-VEC works in an innovative and novel way, by delivering two new copies of the gene that is faulty in people with DEB. The new copies of the gene tell the cells to make type VII collagen, the protein that is lacking in people with DEB, which will, in turn, make anchoring fibrils, the small threads that bind (glue) the two layers of skin together.²⁵ Contrary to birch bark extract, B-VEC is a treatment that addresses the fundamental mechanism that causes DEB, as it tackles the faulty gene that causes DEB and restores the protein necessary for healthy skin.²⁷

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.

It is expected that people with DEB who are treated with B-VEC will continue using those strategies and support they were already using as part of the standard of care. This can include antibiotics or pain medication ([Section 2c](#)).

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?

B-VEC is applied cutaneously (on the skin) to one or more wounds. B-VEC should be prepared at the pharmacy by mixing the B-VEC product into a gel and put into a syringe. Once it is prepared,

B-VEC should be kept at a cold temperature (between 2 and 8 Celsius degrees, which is similar to the usual temperature of a home fridge) and used within seven days of preparation. For B-VEC to last for seven days, it should be prepared in aseptic conditions, that is conditions free from germs or infections. B-VEC is given weekly, and doses are adjusted based on the person's age, wound size, and wound healing from one week to the next. B-VEC should be applied until the wound closes.

B-VEC should be given by a doctor or nurse, either at a healthcare professional setting (such as a health centre) or at the home setting. People with DEB or their carers may also apply B-VEC, once they have received training on how to apply the treatment.

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.

B-VEC has been investigated in two clinical trials (GEM-1 and GEM-3),^{25,27} which are presented in Table 1. In GEM-3, people with DEB and their carers, the healthcare providers and researchers were not aware of which treatment was being applied to the wound.

To obtain additional information on how safe B-VEC is to use, another trial was conducted, called a long-term extension, where people were followed for a longer period of time.²⁸ This included people who had participated in GEM-3, as well as people who were receiving B-VEC for the first time.

Table 1. Clinical effectiveness evidence: GEM-3 and GEM-1

Study	GEM-3; B-VEC-03 (NCT04491604) Guide et al. 2022 ²⁵	GEM-1; KB103-001 (NCT03536143) Gurevich et al. (2022) ²⁷
Population	- People aged ≥6 months with clinical diagnosis of DEB - Two cutaneous wounds similar in size, anatomical region, and appearance 31 people participated	- People aged ≥18 years (phase 1), ≥5 years (phase 2a), or ≥2 years (phase 2b and 2c) with clinical diagnosis of RDEB - Nine people participated (three people participated in more than one phase, totalling twelve people included in the analyses)
Intervention(s)	B-VEC mixed with excipient gel and applied topically once weekly	B-VEC mixed with excipient gel and applied topically (how often it was applied varied across trial phases)
Comparator(s)	Saline mixed in excipient gel and applied topically once weekly	Saline mixed with excipient gel
Reported outcomes specified in the decision problem	- Proportion of complete wound healing: - Proportion of primary wounds with complete wound closure at 6 months (Week 22+24 or Week 24+26) - Primary wounds with complete healing at 3 months (Week 8+10 or Week 10+12). - Pain: change from the beginning of the trial to Weeks 22, 24, and 26 in	- Proportion of wounds with complete wound healing (Weeks 8, 10, or 12) - Time to wound closure - Duration of wound closure - Pain: patient-reported outcome for pain (at the beginning of the trial and Days 3, 5, 15, 30, 60, and 90)

	pain severity during changes in wound dressing • HRQoL: change from the beginning of the trial to Week 26	
Study design	• Wound pairs were assigned by chance to receive once-weekly application of either B-VEC or control gel for 26 weeks until wound closure	• Wounds were assigned by chance to be treated with B-VEC or control gel
B-VEC=beremagene geperpavec; DEB=dystrophic epidermolysis bullosa; HRQoL=health-related quality of life; RDEB=recessive dystrophic epidermolysis bullosa.		

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.

People with DEB who applied B-VEC had long-lasting and consistent wound healing (defined as a wound that had 100% closure). These results were much better than those obtained with the control gel.

Complete wound closure

Results from GEM-1 and GEM-3 showed that B-VEC treatment led to complete healing of more wounds than control gel at assessment times of three^{25,27} and six²⁵ months. In GEM-1, most wounds treated with B-VEC had closed by three months (10 out of 12 wounds), which was not the case with control gel (1 out of 7 wounds). All wounds treated with B-VEC were completely closed when the treatment was repeated and remained healed when treatment was assessed at eight months.²⁷ This shows how repeated treatment with B-VEC works.

In GEM-3, two thirds (67%) of the wounds treated with B-VEC were completely closed at six months, while only about one fifth (22%) of the wounds treated with control gel were closed at that timepoint.²⁵ The researchers also looked at the results at 3 months, and found that the results also showed that B-VEC works better than control gel to close wounds caused by DEB. The results indicate that the difference between groups is likely to be caused by the treatment and not by chance.

In GEM-3, results were also assessed separately for male and female participants, as well as for different age groups (≤ 12 years; > 12 and ≤ 18 years; > 18 years). Results showed that regardless of sex or age, wounds treated with B-VEC were more likely to be closed at 6 months than wounds treated with control gel. As the number of wounds in each group was small, it is not possible to know if these results are due to chance.

Duration (or durability) of response

In GEM-1, wounds that were treated with B-VEC closed sooner than wounds treated with control gel, and they stayed closed for a longer period of time. In that trial, duration (or durability) of response was defined as the time from the first treatment to complete wound closure observed for two consecutive weeks. It took less time for wounds treated to B-VEC to close than wounds treated with control gel.

In GEM-3, response was defined as complete wound healing at least two consecutive study visits, two weeks apart. To be considered a durable response, complete wound healing had to be seen at three months and at six months.²⁵ The results showed that approximately half (49.7%) of the

wounds that were treated with B-VEC had a durable response. In contrast, only 7.1% of the wounds treated with control gel had a durable response.

Pain severity during wound dressing

Researchers in GEM-3 assessed how much pain people with DEB had when changing wound dressings. They used a scale marked 0 to 10, where 0 means no pain, and 10 means most severe pain, and asked people to complete this scale at the beginning of the trial, as well as other times during the trial. Results found that at Week 22 of treatment, people with DEB felt less pain when changing wound dressing, and that people who received B-VEC experienced a bigger difference (that is, their pain had decreased more) than people who received the control gel. Because of the small number of people involved it is not possible to know whether these results happened by chance.

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 condition 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.

Quality of life was assessed in GEM-3 using two patient-reported outcome measures; these are questionnaires completed by the person with the condition, or sometimes their carer, who can tell directly how the condition impacts their health and quality of life. The two questionnaires used in GEM-3 were the EQ-5D (a general questionnaire that can be completed by anyone even if they do not have a skin condition) and Skindex-29 (which assesses the impact that skin conditions have on quality of life). Results showed that, between the beginning of the study and at the six months assessment, quality of life had remained the same or slightly improved for most people with DEB.²⁵ As all the people participating in the trial received both treatments for different wounds, it is not possible to assess how each treatment impacted quality of life. The CHMP highlighted that treatment with B-VEC is expected to bring great benefits to people with DEB, improving their quality of life and addressing unmet needs.¹

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.

B-VEC was well accepted, and most adverse events were mild.

Adverse events (AEs) are changes to a person's health that happen or get worse after a treatment is started. AEs may or may not be related to the treatment; if AEs are found to be a direct result of the treatment, then they are called side effects or side events.

In GEM-3, eighteen people had at least one AE, most of which were mild (Table 2). The most common AEs, each reported by three people, were itch, chills, and SCC.²⁵ Cases of SCC did not happen at the places where treatment had been applied. One mild AE (erythema or redness of the skin) was possibly related to the treatment the person was receiving. Three people experienced five serious AEs (cellulitis, which is skin infection caused by bacteria; two anaemia events; diarrhoea; and positive blood culture), none of which was found to be a side effect as they were considered to be not related with the treatment those people were receiving.

In GEM-1, nine people had at least one AE, and of those only one person had a moderate AE.²⁷ There were four mild AEs that were possibly related to the treatment (fever, different taste, rash, itch) and two AEs that were probably related to the treatment (discharge where the treatment was applied). No one had to stop receiving treatment due to their AEs. As all the people participating in the trial received both treatments for different wounds, it is not possible to compare the AEs for each treatment.

Table 2. Adverse events: GEM-3 and GEM-1

Event	GEM-3	GEM-1
Total AEs, n*	45	21
People with ≥1 AE, n	18	9
Mild	15	9
Moderate	3	1
Severe	2	0
Serious	3	0
Related to B-VEC or control gel	1	6
Leading to discontinuation of B-VEC or control gel	0	0
* AEs that appear or got worse after the first application of B-VEC or control gel. AE=adverse event; B-VEC=beremagene geperpavec		

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

There are several key benefits of B-VEC for people with DEB and their carers. B-VEC is the first treatment for DEB that modifies the condition by replacing the faulty gene. It is also a benefit to the person with DEB that the treatment is given in a way that is not invasive, that is using a gel applied to the skin. The CHMP highlighted that B-VEC is a promising treatment that has the potential to address unmet needs in people with DEB.¹ The CHMP stated that B-VEC is expected to bring great benefits to people with DEB, improving their quality of life.¹

Results from clinical trials show that B-VEC led to complete wound healing at three and six months (please refer to [Section 3e](#) for more details). The wounds that were treated with B-VEC healed more quickly and wounds stayed closed for a longer period of time, when the results were compared with the control gel. Additionally, B-VEC may help reduce pain associated with

unhealed wounds that people with DEB experience. Those results also show that most of the AEs were mild and that people with DEB did not have to stop using the treatment because of the AEs. As B-VEC leads to better wound closure, then it is expected that less time is spent on wound dressing. This will benefit the person with DEB but also their carers.

When assessing the use of birch bark extract, NICE stated that people with DEB or junctional EB could only receive that treatment if their wounds were at least three weeks old and had a certain size (between 10 and 50 square centimetres, or between 1.55 and 7.75 square inches). This means that many people with DEB may not be able to receive birch bark extract. B-VEC does not have the same limitations and can thus benefit all people with DEB.

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

B-VEC needs to be applied weekly, either by a healthcare professional or a carer who has been trained on how to apply it. However, as it replaces daily treatment for certain wounds, it may lead to a care regimen that is less time-consuming. It may not be possible to apply B-VEC to all wounds with each treatment application because the maximum area on the skin covered by wounds that can be treated weekly is 200 cm².

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.

How the model reflects the condition

- A health economic model was developed to estimate health outcomes and costs of treatment for people with DEB. Health economic models are useful to understand if a new treatment offers good value for money compared with existing treatments. Models also allow researchers to simulate (that is, make additional evidence using a computer) what is the possible impact of the new treatment into the future. In this way, the researchers can simulate how the new treatment may impact people with a condition after the new

treatment has been used for several years, even when no clinical evidence has been collected for this period of time. When there is no evidence, researchers make assumptions about the health outcomes and costs associated with the treatment. Because of those assumptions, models always have some uncertainty, so it is not possible to be fully sure if the model truly describes the health costs and outcomes of the new treatment.

- When assessing if a new treatment provides good value for money, NICE also considers those uncertainties to assess the incremental cost-effectiveness ratio (ICER). This is a measure that summarises what is known about the value for money of an intervention, compared with existing treatments (comparator).
- This model compared three options to treat DEB: B-VEC, birch bark extract, and BSC. The costs of using B-VEC and birch bark extract were added to the costs of using BSC, as it is expected that B-VEC and birch bark extract are used at the same time as BSC.
- Several sources of evidence were used to inform the model, including: the GEM-1 and GEM-3 trials; the birch bark extract trials; interviews with clinical experts, people with DEB and their carers, as well as people who did not have DEB; and current costs of treatments.
- In the model, people with DEB could transition (move) across five health states (Very Mild, Mild, Moderate, Severe, and Death) based on the amount body surface area (BSA) with open wounds. People with the greatest amount of BSA with open wounds are considered to have the most severe disease. Over time, people could move more than one health state and improve (except if their health state was Death), get worse (except if their health state was Death) or stay the same.
- The model also assessed how the treatments impacted wound closure, duration of wound closure, and clinical manifestations associated with DEB (such as infections).

Modelling how much a treatment extends life

- To understand mortality (death rate) following the start of treatment, the model used evidence collected in the registry database of EB.⁹
- The model found that people with DEB treated with B-VEC would be expected to live longer than people treated with birch bark extract or BSC.

Modelling how much a treatment improves quality of life

- Quality of life in the model was assessed by how much of the body was covered by wounds (BSA) and the pain and itch that people felt because of those wounds.
- As DEB is a rare condition, there was not enough evidence from people with DEB. To get more evidence, the researchers asked a group of people who did not have DEB how they thought the condition could impact their quality of life, either if they had the condition or if they cared for someone who had it. This is called a vignette study. More than 1,100 people, all of whom lived in the UK, answered those questions. Additional evidence was gathered from people with DEB and their carers, also using a vignette study.
- Because DEB has a major impact on those who care for people with the condition, the quality of life of carers was also included in the model. It was expected that carers looking after people with more severe DEB would have worse quality of life.
- The model showed that people with DEB treated with B-VEC were more likely to remain in the mild stage of DEB compared to patients who were treated with birch bark extract, and as a result, had a better quality of life.

Modelling how the costs of treatment differ with the new treatment

- The model included costs for:

- Treatment with B-VEC, birch bark extract or BSC (this included the costs of using psychiatric medications, painkillers and medication to control itch).
- Treatment of the clinical manifestations of DEB (such as infections and SCC).
- Wound dressing and outpatient monitoring.
- The model showed that B-VEC is expected to reduce treatment costs when compared with birch bark extract. It is also expected to save costs for other medications, treatment of clinical manifestations of DEB, wound dressing and outpatient monitoring, both when compared with birch bark extract and BSC.

Uncertainty

- DEB is a rare condition and, as such, evidence on the effects of B-VEC in people with DEB is limited. This applied to different types of evidence, including efficacy, quality of life, and safety. When there was no evidence available from the B-VEC trials or the clinical literature, clinical experts or people who did not have the condition were asked about their opinions. Sometimes evidence was also simulated (reproduced) using a computer.

Additional factors

- DEB severely impacts people's self-confidence and mental health and limits their independence. As an innovative treatment that leads to wounds healing better and staying healed for longer, B-VEC has the potential to improve people's wellbeing and autonomy. This represents a benefit beyond what was assessed in the model.
- Additionally, DEB is a life-long condition that starts at a very early age and its complications accumulate over a person's lifetime. Because B-VEC is a treatment that targets and aims to correct what is causing the condition, it is expected that treatment with B-VEC as early as possible may lead to benefits that will last for the person's lifetime. Therefore, these long-term benefits of B-VEC would not be captured with the information that is currently available.

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)

B-VEC is an innovative and novel treatment that addresses the fundamental mechanism that causes DEB, as it promotes the production of a protein that is either missing or in low supply in people with DEB.²⁷ B-VEC represents a step change in treatment for people with DEB, as there are no other treatments that change what is causing the condition ([Section 3a](#) presents details on how B-VEC is an innovative treatment).

As such, the way how B-VEC works is a benefit compared with birch bark extract gel, which does not tackle what is causing DEB. It is also important to note that B-VEC led to better wound closure in all people with DEB, regardless of their age and sex.²⁵

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

No inequalities were identified related with B-VEC.

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.

Information on EB and DEB for patients:

- DEBRA UK www.debra.org.uk/
- EB Clinet www.eb-clinet.org/
- British Skin Foundation knowyourskin.britishskinfoundation.org.uk/condition/dystrophic-epidermolysis-bullosa/
- Cure EB cure-eb.org/

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:

Adverse event: An unfavourable change in the health of a participant, including abnormal laboratory findings, that happens during a clinical study or within a certain amount of time after the study has ended. This change may or may not be caused by the intervention/treatment being studied.²⁹

Clinical trial/study: A research study involving human volunteers (also called participants) that is intended to add to medical knowledge.²⁹

Eligibility criteria: The key requirements that people who want to participate in a clinical study must meet or the characteristics they must have. Eligibility criteria consist of both inclusion criteria (which are required for a person to participate in the study) and exclusion criteria (which prevent a person from participating).²⁹

Incremental cost-effectiveness ratio (ICER): A measure that summarises what is known about the value for money of an intervention, compared with existing treatments (comparator).

Marketing authorisation: Approval to sell a treatment based on its efficacy and safety. This differs from the NICE appraisal, which is about the willingness to pay for a treatment and the value for money of the new treatment is also assessed.

Mutation: Change in the DNA sequence of a cell. It can be inherited or happen by chance.

Outcome measure: For clinical trials, a planned measurement described in the protocol that is used to determine the effect of an intervention/treatment on participants.²⁹

Placebo: An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.²⁹

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:

1. European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP) Summary of opinion (initial authorisation): Vyjuvek. 27 February 2025; <https://www.ema.europa.eu/en/medicines/human/EPAR/vyjuvek>. Accessed 4 March 2025.
2. Denyer J, Pillay E, Clapham J. Best practice guidelines for skin and wound care in epidermolysis bullosa. An International Consensus. Wounds International; 3 May 2017.
3. British Association of Dermatologists. Dystrophic epidermolysis bullosa. 2023.
4. Bardhan A, Bruckner-Tuderman L, Chapple ILC, et al. Epidermolysis bullosa. *Nat Rev Dis Primers*. 2020;6(1):78.
5. Goldschneider KR, Good J, Harrop E, et al. Pain care for patients with epidermolysis bullosa: best care practice guidelines. *BMC Med*. 2014;12:178.
6. Pfendner EG, Lucky AW. Dystrophic epidermolysis bullosa. Chapter in Adam MP, Everman DB, Mirzaa GM, et al., eds. *GeneReviews((R))*. Seattle (WA):2018.
7. Cianfarani F, Zambruno G, Castiglia D, Odorisio T. Pathomechanisms of altered wound healing in recessive dystrophic epidermolysis bullosa. *Am J Pathol*. 2017;187(7):1445-1453.
8. Wilkinson HN, Hardman MJ. Wound healing: cellular mechanisms and pathological outcomes. *Open Biol*. 2020;10(9):200223.
9. Petrof G, Papanikolaou M, Martinez AE, et al. The epidemiology of epidermolysis bullosa in England and Wales: data from the national epidermolysis bullosa database. *British Journal of Dermatology*. 2022;186(5):843-848.
10. Bruckner-Tuderman L. Dystrophic epidermolysis bullosa: pathogenesis and clinical features. *Dermatol Clin*. 2010;28(1):107-114.

11. Tang JY, Marinkovich MP, Lucas E, et al. A systematic literature review of the disease burden in patients with recessive dystrophic epidermolysis bullosa. *Orphanet J Rare Dis*. 2021;16(1):175.
12. Bonamonte D, Filoni A, De Marco A, et al. Squamous cell carcinoma in patients with inherited epidermolysis bullosa: review of current literature. *Cells*. 2022;11(8).
13. National Institute for Health and Care Excellence (NICE). Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]. Response to consultee and commentator comments on the draft remit and draft scope. August 2022.
14. Fine JD. Inherited epidermolysis bullosa. *Orphanet J Rare Dis*. 2010;5:12.
15. Tong L, Hodgkins PR, Denyer J, et al. The eye in epidermolysis bullosa. *Br J Ophthalmol*. 1999;83(3):323-326.
16. Bruckner AL, Losow M, Wisk J, et al. The challenges of living with and managing epidermolysis bullosa: insights from patients and caregivers. *Orphanet J Rare Dis*. 2020;15(1):1.
17. Fulchand S, Harris N, Li S, et al. Patient-reported outcomes and quality of life in dominant dystrophic epidermolysis bullosa: A global cross-sectional survey. *Pediatr Dermatol*. 2021;38(5):1198-1201.
18. DEBRA UK. Epidermolysis bullosa patient insights. Quantitative research presentation. June 2023; www.debra.org.uk/Handlers/Download.ashx?IDMF=c8f78f54-447f-4748-b604-fc6b87124fcd.
19. National Institute for Health and Care Excellence (NICE). Birch bark extract for treating epidermolysis bullosa: final draft guidance 2023.
20. European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP) assessment report: Filsuvez. 4 April 2022; <https://www.ema.europa.eu/en/medicines/human/EPAR/filsuvez>. Accessed 4 December 2022.
21. Medicines and Healthcare products Regulatory Agency (MHRA). Filsuvez Gel Summary of Product Characteristics. 18 August 2022; <https://www.medicines.org.uk/emc/product/13971/smpc/print>. Accessed 3 April 2023.
22. European Medicines Agency (EMA). Filsuvez (Oleogel-S10) 0.5g–1.0 g birch bark gel. Summary of Product Characteristics. 4 July 2022. Accessed 29 November 2022.
23. Kern JS, Schwieger-Briel A, Lowe S, et al. Oleogel-S10 Phase 3 study "EASE" for epidermolysis bullosa: study design and rationale. *Trials*. 2019;20(1):350.
24. Kern JS, Sprecher E, Fernandez MF, et al. Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: results from the phase III randomized double-blind phase of the EASE study. *Br J Dermatol*. 2023;188(1):12-21.
25. Guide SV, Gonzalez ME, Bagci IS, et al. Trial of beremagene geperpavec (B-VEC) for dystrophic epidermolysis bullosa. *N Engl J Med*. 2022;387(24):2211-2219.
26. Eng VA, Solis DC, Gorell ES, et al. Patient-reported outcomes and quality of life in recessive dystrophic epidermolysis bullosa: A global cross-sectional survey. *J Am Acad Dermatol*. 2021;85(5):1161-1167.
27. Gurevich I, Agarwal P, Zhang P, et al. In vivo topical gene therapy for recessive dystrophic epidermolysis bullosa: a phase 1 and 2 trial. *Nat Med*. 2022;28(4):780-788.
28. Krystal Biotech Inc. OLE Clinical Study Report: Open label treatment of beremagene geperpavec (B-VEC). B-VEC-EX-02. 2023.

29. ClinicalTrials.gov. ClinicalTrials.gov Glossary Terms. 09 December 2024;
<https://clinicaltrials.gov/study-basics/glossary>. Accessed 11 February 2025.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions

May 2025

File name	Version	Contains confidential information	Date
ID3959 Beremagene EAG Clarification letter to company [CON]	1	Yes	22/05/25

Section A: Clarification on effectiveness data

Decision problem

A1. CS Section 1.3.4: Is beremagene geperpavec (B-VEC) for all dystrophic epidermolysis bullosa (DEB) patients with any wound type (recurrent and chronic, as per Table 1.3)?

B-VEC is indicated for the treatment of wounds in patients with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene, from birth as per the Summary of Product Characteristics (SmPC) attached (file name: *[ID3959]_beremagene_geperpavec_Appendix A_vyjuvek-epar-product-information_en.pdf*). The indication refers to any type of wounds, recurrent and chronic.

A2. CS Section 1.3.5.1: Please clarify if GEM-3 trial population's wounds (Table 2.6) are recurrent or chronic or both (defined as per the Table 1.3).

In the GEM-3 study, data related to wound type (chronic vs. recurrent) was not collected.

Literature searches

A3. [Priority] Appendix B, Table 8 and 'Additional searching' section: The accompanying note to the table reporting the results from the Cochrane Library search (Table 8) states that five results came from the Cochrane Database of Systematic Reviews (CDSR) and that these were excluded from the review. Please clarify whether these excluded results were systematic reviews and, if so, why they were excluded at this stage in the review given that one of the additional searching methods mentioned in the search strategy (as indicated in the 'Additional searching' section of the methodology and the PRISMA diagram at Figure 1) for the clinical SLR was to handsearch the bibliographies of systematic reviews?

The five results retrieved from CDSR were systematic reviews. As per the PICOS criteria, systematic reviews were not eligible for inclusion, hence these records were excluded.

In total, eight systematic reviews were identified from searching of which three were judged eligible for handsearching.¹⁻³ Eligibility for handsearching was based on alignment with the population, interventions and outcomes of the PICOS.

From these eligible systematic reviews, included records (identified via the bibliographies) were compared to the screened records in the SLR. Any records that had not previously been identified through the other search methods would have been added to the review and reflected in the PRISMA. Handsearching these systematic reviews did not yield any additional eligible records that had not already been identified via the main search effort.

A4. Appendix B, Table 3: The search narrative provided in this table for the MEDLINE search states the source of the study design filter used and how it was adapted for this particular search. However, it is unclear whether a published and validated filter was used in the same way for the other databases (e.g. Embase, for which such filters are available). Please provide details of the sources of any filters used and any modifications made.

The search narrative provided for the primary database, in this case MEDLINE, as suggested by Cooper et al. 2018,⁴ details use of the CADTH RCT/CCT filter with amendments made to increase the sensitivity of the filter (excerpt shown in Table 1).

Table 1 Search narrative

8 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt. (722046) 9 Randomized Controlled Trial/ (625972) 10 exp Randomized Controlled Trials as Topic/ (180017) 11 "Randomized Controlled Trial (topic)"/ (0) 12 Controlled Clinical Trial/ (95635) 13 exp Controlled Clinical Trials as Topic/ (185855) 14 "Controlled Clinical Trial (topic)"/ (0) 15 Randomization/ (107777) 16 Random Allocation/ (107777) 17 Double-Blind Method/ (181369) 18 Double Blind Procedure/ (0) 19 Double-Blind Studies/ (181369) 20 Single-Blind Method/ (34256) 21 Single Blind Procedure/ (0) 22 Single-Blind Studies/ (34256) 23 Placebos/ (36021) 24 Placebo/ (0) 25 Control Groups/ (2137) 26 Control Group/ (2137) 27 (random* or sham or placebo*).ti,ab,hw,kf,kw. or NCT*.ab. (2019097)	Study designs: Lines 8–41 represent the search filter for studies reporting randomised or controlled clinical trials, open-label extension studies, or single-arm studies. This filter is based on the CADTH RCT/CCT filter.⁵ Researchers commonly amend established search filters to increase sensitivity (i.e., to further reduce the risk of missing studies).^{4,6} The following amendments were made for this search: • Line 27—NCT* included to identify study registry identification numbers aiding in the identification of trials • Line 28—addition of “arm” or “arms” or ‘centre’ or “center” to aid with the identification of single-arm/single-centre studies • Line 34—addition of terminology for subgroups, for instance where studies report an evaluation of a subgroup of interest • Line 39—CADTH use an adapted version of the Cooper P3 filter.⁴ The full version is used here which has been amended to include truncation of phase. This covers the identification of a study which reports as a Phase 2 or a Phase 2b study, and has been

28 ((singl* or doubl*) adj (blind* or dumm* or mask* or arm or arms)).ti,ab,hw,kf,kw. (296841) 29 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. (1971) 30 (control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw. (1342041) 31 (Nonrandom* or non random* or non-random* or nRCT or quasi-random* or quasirandom*).ti,ab,hw,kf,kw. (60042) 32 allocated.ti,ab,hw. (92172) 33 ((open label or open-label) adj5 (study or studies or trial* or extension or extended)).ti,ab,hw,kf,kw. (50537) 34 ((sub* and (group adj2 anal*)) or (subgroup adj2 anal*)).ti,ab,kw,kf. (95941) 35 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw. (14216) 36 (pragmatic study or pragmatic studies).ti,ab,hw,kf,kw. (681) 37 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw. (8909) 38 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw. (14691) 39 ("Phase 3*" or "phase3*" or "phase III*" or P3* or "PIII*" or "Phase 2*" or "phase2*" or "phase II*" or P2* or "PII*").ti,ab,kw,kf. (418159) 40 (trial or trail).ti,ab,kw,kf. (869488) 41 pharmacokinetic*1.ti,ab,kf. (202921) 42 or/8-41 (3637920)	amended further to capture studies that are between stages, namely Phases 1–2 or 2–3 ⁷ - Line 40—addition of a common misspelling of trial (e.g., trail) - Line 41—addition of the term 'pharmacokinetic'

A modified CADTH RCT/CCT filter in the appropriate form was also applied to the other searches.

A5. [Priority] Appendix B, Table 6: Please clarify why the search of the CINAHL database via EBSCOhost did not include the available subject heading “Epidermolysis Bullosa” alongside the free-text terms in lines S1-S5, and comment on the potential implications for retrieval.

Since free-text terminology is more sensitive than the indexing and, given the ‘complexities’ in searching any database via EBSCO, simplicity has been favoured in the search approach for this database specifically. This search of CINAHL was implemented as part of a full-coverage, cautious approach in the context of a rare disease, to identify any studies with a specific nursing focus that report outcomes associated with the PICOS.

Given the inclusion of the trinity of resources required by Cochrane in reviews of the effects of interventions (namely, MEDLINE, Embase, Cochrane), the company are confident that there are no implications for the review in terms of missed studies, when considering that CINAHL content is also available via CENTRAL.

A6. Appendix B, Tables 3, 4, 5, 6, 7, 8; Appendix E, Tables 3, 4, 5, 6, 7, 9: In the database searches, a line has been included that uses two proximity operators within the same phrase (e.g. Appendix B, Table 3, line 6: (partial* adj3 thick* adj3 wound*).ti,ab,ot,kf.). This produces a different number of results compared to a combination of lines each with one proximity operator (see example search string below, also in MEDLINE ALL). Please comment on the discrepancy between the two approaches, and possible implications for retrieval of the use of two proximity operators together, the approach taken in this CS.

Ovid MEDLINE(R) ALL <1946 to April 25, 2025>

1	(partial* adj3 thick* adj3 wound*).ti,ab,ot,kf.	674
2	(partial* adj3 thick*).ti,ab,ot,kf.	5125
3	(thick* adj3 wound*).ti,ab,ot,kf.	5004
4	2 and 3	704

In searching, there are frequently different ways to approach a single search problem, and it is the company's view that here we observe two examples which seek to do similar things, differently.

Line 1 aims to situate the wound* within context of their definition (e.g., partial* adj3 thick*). This followed clinical advice that, occasionally in the literature, EB is referred to by the characteristic wound type (i.e., partial thickness wounds). During conceptualisation, no specific evidence was found that any studies would be missed by not adding this version of Line 1 (and other approaches were tested that were similar to the idea described in the question, at the time), therefore we retained this version of Line 1. The objective being to search for any studies in a controlled and pragmatic way, hence the use of double adj.

It is however also noted that these search lines specifically should not be considered in isolation. There are other condition terms alongside these which lessen the difference in yield overall of the two different approaches. Comparing the search proposal detailed in the question, to the approach taken, alongside the other condition terms and search filter, the difference between these is an additional 23 records retrieved in MEDLINE.

The search syntax is detailed in Table 2 to support this exploration, along with independent double-screening of the 23 records. None of these 23 records meet the

PICOS criteria. They are mostly reporting pre-clinical, animal study, and/ or burn-related data.

The company conclude there were no implications for study identification.

Table 2 Search syntax

Search syntax	Comments
Database: Ovid MEDLINE(R) ALL <1946 to May 09, 2025> Search Strategy: 1 exp *Epidermolysis Bullosa/ (5245) 2 ((epidermolysis or dystrophic or junctional adj5 bullosa*).ti,ab,ot,kf,kw. (6646) 3 ((EB or DEB or DDEB or RDEB or JEB or "RDEB-GI" or "RDEB-I" or "RDEB-GS" or "RDEB-S" or "JEB-GI" or "JEB-GS") and (wound* or thick* or skin* or bullosa*).ti,ab,kw,kf,ot. (2667) 4 "butterfly skin".ti,ab,kw,kf,ot. (1) 5 (partial* adj3 thick* adj3 wound*).ti,ab,ot,kf. (674) 6 1 or 2 or 3 or 4 or 5 (8486)	Condition terms for our original and favoured search approach
7 exp *Epidermolysis Bullosa/ (5245) 8 ((epidermolysis or dystrophic or junctional adj5 bullosa*).ti,ab,ot,kf,kw. (6646) 9 ((EB or DEB or DDEB or RDEB or JEB or "RDEB-GI" or "RDEB-I" or "RDEB-GS" or "RDEB-S" or "JEB-GI" or "JEB-GS") and (wound* or thick* or skin* or bullosa*).ti,ab,kw,kf,ot. (2667) 10 "butterfly skin".ti,ab,kw,kf,ot. (1) 11 (partial* adj3 thick*).ti,ab,ot,kf. (5127) 12 (thick* adj3 wound*).ti,ab,ot,kf. (5044) 13 11 and 12 (704) 14 7 or 8 or 9 or 10 or 13 (8516)	ScHARR's proposal (Line 10-13)
15 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt. (735353) 16 Randomized Controlled Trial/ (638966) 17 exp Randomized Controlled Trials as Topic/ (187203) 18 "Randomized Controlled Trial (topic)"/ (0) 19 Controlled Clinical Trial/ (95689) 20 exp Controlled Clinical Trials as Topic/ (193089) 21 "Controlled Clinical Trial (topic)"/ (0) 22 Randomization/ (108458) 23 Random Allocation/ (108458) 24 Double-Blind Method/ (184268) 25 Double Blind Procedure/ (0) 26 Double-Blind Studies/ (184268) 27 Single-Blind Method/ (35087) 28 Single Blind Procedure/ (0) 29 Single-Blind Studies/ (35087)	Search filter, as used.

30 Placebos/ (36112) 31 Placebo/ (0) 32 Control Groups/ (2153) 33 Control Group/ (2153) 34 (random* or sham or placebo*).ti,ab,hw,kf,kw. (2028909) 35 ((singl* or doubl*) adj (blind* or dumm* or mask* or arm or arms)).ti,ab,hw,kf,kw. (303123) 36 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. (2125) 37 (control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw. (1388337) 38 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw. (61939) 39 allocated.ti,ab,hw. (95177) 40 ((open label or open-label) adj5 (study or studies or trial* or extension)).ti,ab,hw,kf,kw. (52426) 41 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw. (15028) 42 (pragmatic study or pragmatic studies).ti,ab,hw,kf,kw. (709) 43 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw. (9432) 44 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw. (15789) 45 ("Phase 3*" or "phase3*" or "phase III*" or P3* or "PIII*" or "Phase 2*" or "phase2*" or "phase II*" or P2* or "PII*" or "Phase 1-2" or "Phase 2-3").ti,ab,kw,kf. (429493) 46 (trial or trail).ti,ab,kw,kf. (904644) 47 or/15-46 (3523639) 48 6 and 47 (653) 49 14 and 47 (670) 50 49 not 48 (23)	
48 6 and 47 (653) 49 14 and 47 (670) 50 49 not 48 (23)	Line 48 = our MEDLINE search Line 49 = SchARR's proposal Line 50 = difference between SchARR's proposal and our MEDLINE search. These records are processed below.

Table 3 Independent double-screening results for the 23 records in question

Number	Title	Reviewer 1	Reviewer 2
1	Human amniotic membranes as an allogenic biological dressing for the treatment of burn wounds: Protocol for a randomized-controlled study.	Exclude	Exclude
2	Split-Thickness Skin and Dermal Pixel Grafts Can Be Expanded up to 500 Times to Re-Epithelialize a Full-Thickness Burn Wound.	Exclude	Exclude
3	Efficacy of hydrosurgical excision combined with skin grafting in the treatment of deep partial-thickness and full-thickness burns: A two-year retrospective study.	Exclude	Exclude

4	Full- versus partial-thickness sutures: experimental models of corneal injury repair	Exclude	Exclude
5	[Effects and mechanism of exogenous tumor necrosis factor alpha on differentiation of mesenchymal stem cells of mice into sweat gland cells in three-dimensional environment]. [Chinese]	Exclude	Exclude
6	Enzymatic Debridement of Porcine Burn Wounds via a Novel Protease, SN514	Exclude	Exclude
7	Treatment of third-degree burn wounds in animal specimens: acellular dermis or partial-thickness skin graft	Exclude	Exclude
8	[Effects of unified surgical scheme for wounds on the treatment outcome of patients with extensive deep burn]. [Chinese]	Exclude	Exclude
9	Full-thickness skin wound healing using autologous keratinocytes and dermal fibroblasts with fibrin: bilayered versus single-layered substitute.	Exclude	Exclude
10	Delayed topical p38 MAPK inhibition attenuates full-thickness burn wound inflammatory signaling.	Exclude	Exclude
11	[Experimental study on the recycling of denatured acellular dermal matrix after burn]. [Chinese]	Exclude	Exclude
12	Prevalence of wet-to-dry dressings in wound care	Exclude	Exclude
13	Modulation of scarring in a liquid environment in the Yorkshire pig	Exclude	Exclude
14	Evaluating the use of hydrogel sheet dressings in comprehensive burn wound care.	Exclude	Exclude
15	Biobrane versus duoderm for the treatment of intermediate thickness burns in children: a prospective, randomized trial.	Exclude	Exclude
16	CM101 stimulates cutaneous wound healing through an anti-angiogenic mechanism.	Exclude	Exclude
17	Development of angiotensin (1-7) as an agent to accelerate dermal repair.	Exclude	Exclude
18	A multicenter clinical trial to evaluate the topical hemostatic efficacy of fibrin sealant in burn patients.	Exclude	Exclude
19	Effect of interferon-alpha2b on guinea pig wound closure and the expression of cytoskeletal proteins in vivo.	Exclude	Exclude

20	Assessment of stress fiber orientation during healing of radial keratotomy wounds using confocal microscopy.	Exclude	Exclude
21	Safety and effect of topical recombinant human interleukin-1beta in the management of pressure sores.	Exclude	Exclude
22	Pulsed microamperage stimulation: a controlled study of healing of surgically induced wounds in Yucatan pigs.	Exclude	Exclude
23	Low-dose ultrasound effects on wound healing: a controlled study with Yucatan pigs.	Exclude	Exclude

A7. Appendix E, 'Identification and selection of relevant studies' section: This section of the methodology mentioned searching trial registers, but no further details are provided of trial register searches. Please clarify whether any trial registers were searched for the economic SLR and, if they were, please provide details of the searches that were performed on these platforms.

Trials registers were not searched as part of the specific searching effort for the economic SLR but were searched as part of the combined searching effort for clinical and non-clinical, performed in November 2024. The specific resources searched for the non-clinical reviews were:

- Electronic databases
 - Embase, MEDLINE, AMED, CINAHL, PsycINFO, Retraction Watch, CRD NHS EED, and Econlit
- Conferences
 - Databases: Embase and CPCI-S
 - Handsearching: AAD, SID, BAD, ESPD, ISID, ISPOR
- Websites
 - INAHTA, NICE, SMC, CDA-AMC

However, when screening the clinical trials registers (WHO ICTRP, clinicaltrials.gov) for the clinical review, any eligible studies matching the economic PICOS were also considered for the economic review.

A8. Appendix E, 'Electronic databases' section: What is the rationale behind searching databases such as PsycInfo and CINAHL for the non-clinical SLR, given that these databases do not have a particularly economic focus, and economics-focused databases such as NHS EED and EconLit have been (appropriately) searched?

While PsycInfo and CINAHL do not have a particular economic focus, they do include economic evaluations, costs data, and data on burden of illness, and quality of life. In the context of rare disease reviews, where an absence of data is often a challenge, a broader search effort was employed.

In these specific examples, the particular interest was for any quality-of-life data (PsycInfo, for any associated mental health data) and any nursing specific studies, such as resource use with nurse-applied interventions (CINAHL), considering EB services are frequently delivered by EB clinical nurse specialists.

A9. Appendix B: please clarify the process in the event of disagreement between the two reviewers in terms of quality assessment.

In terms of quality assessment (and as with screening), as per the protocol, disagreements between researchers were resolved through discussion or, if necessary, by consulting a third researcher.

A10. Appendix B: please clarify the inclusion of the non-RCT CASP tool, given that the clinical evidence only includes RCTs.

As described in the SLR report⁸ and summarised in Appendix B (page 18), four non-RCTs were identified in the clinical SLR, including the phase 2 BEB-10 trial of Oleogel-S10, two phase 1/2 trials of gentamicin (NCT02698735, NCT03012191), and a trial of Henna (Niazi 2022).⁹⁻¹² The CASP tool was used to quality assess these included non-RCTs; however, since these do not inform the decision problem addressed by this submission, they are not described in the company submission.

B-VEC clinical effectiveness

A11. CS, Section 2.3.2.3 and Table 2.6: Demographic and baseline characteristics. Please clarify if there are data on age of the target wounds in the GEM-3 trial.

In the GEM-3 study, data on the age of the target wound (*i.e.*, how long wounds had been open prior to the study start) was not collected.

A12. CS, Section 2.3.2.4: Assessment of secondary endpoints was described but assessment of primary endpoint was not. More detailed explanations are provided regarding documentation of wounds for GEM-1 and EASE studies (e.g. WoundMatrix application) but not for GEM-3. Please confirm how wounds were documented in GEM-3. Was this done in person by blinded investigator for GEM-3, with photographic documentation required in GEM-1 because patients were unblinded? In GEM-3, was there any second investigator agreement sought on assessment of wound closure or was the judgement made by a single investigator?

In the GEM-3 study, primary wounds were imaged using a Canfield tracing and imaging system. Wound assessments were performed live by the blinded investigator after removal of the participant's dressings and prior to any potential disruption of the wounds (markings, bacterial culture of wounds for clinical purposes, or IP administration). Primary wounds were assessed by the blinded investigator for closure at Weeks 8, 10, 12, 22, 24, and 26, corresponding to timing of the primary and key secondary efficacy endpoints. There was no secondary investigator performing assessments on the primary wounds in order to reduce the potential for inter-evaluator variability.

A13. CS, Table 2.12 and Table 2.13: Please clarify why concealment of treatment allocation is described as NA for GEM-3 and GEM-1. GEM-3 is described as double blinded (both patients/carers and assessors blinded) so concealment of allocation of wounds to placebo/B-VEC is relevant to this study design. GEM-1 is described as being open label placebo controlled with blinded independent physician assessors. Why are not these information reflected in the quality assessment?

Tables 2.12 and 2.13 of the company submission present only an overview of the quality assessment of these trials. Granular detail of the full quality assessment of GEM-3 and GEM-1 are included below, as reported in the SLR report.⁸

In this context, we performed the quality assessment at the patient level denoting that concealment of allocation was not applicable. However, we accept the premise of your clarification question and have now modified the assessment to also consider concealment of allocation at the wound level (changes are highlighted in **green** in Table 4 and Table 5).

Table 4: Quality assessment for GEM-3

GEM-3		
Was randomisation carried out appropriately?	Yes	Intra-patient wound randomisation-block design, wound pairs
Was the concealment of treatment allocation adequate?	Yes	Patient level: N/A – Intra-patient design Wound level: the patients, investigators, site staff, and the sponsor were blinded to allocation of treatment to each wound.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	NA	N/A – Intra-patient design. Primary wounds were similar in size between those exposed to B-VEC and those exposed to placebo.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	All the patients, investigators, site staff, and the sponsor remained blinded to trial-group assignments, except for designated personnel, including the pharmacist who handled unblinded B-VEC or placebo.
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	NA	N/A – Intra-patient design
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Protocol available. No evidence of further outcomes collected and NR.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	ITT and mITT analysis used for all primary and secondary efficacy sensitivity analyses and baseline summaries. Multiple imputation method used to handle missing data for primary efficacy analysis.
B-VEC, beremagene geperpavec; NA, not applicable Source: Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination as detailed in section 2.5 Critical appraisal of the relevant clinical effectiveness evidence of the NICE Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template (PMG24)		

Table 5: Quality assessment of GEM-1

GEM-1		
Was randomisation carried out appropriately?	Yes	Intra-patient wound randomisation. A complete randomised-block design, with each patient designated as a block to receive all conditions, was used to assign treatment. Investigator-assigned wound numbers were randomised using a pre-generated randomisation

		schedule. Randomisation schemes were generated via a customised program prior to the study, and randomisation assignments for the treatment sites of each study patient were provided in sealed envelopes.
Was the concealment of treatment allocation adequate?	Unclear	Patient level: N/A – Intra-patient design Wound level: while participants and carers were not blinded to treatment allocation (open label), clinicians assessing wound images were blinded.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	NA	N/A – Intra-patient design, but there was variability in wound size observed across the small participant sample
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes/ unclear	Participants and direct care providers were not blinded, B-VEC and placebo were applied open-label. However, wound images were assessed by two independent blinded physician-dermatologists with bullous disease expertise to evaluate wound closure therefore impact on wound closure outcomes is likely to be small.
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	NA	N/A – Intra-patient design
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Protocol available. No evidence of further outcomes collected and NR.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Primary population analysis was ITT. For efficacy evaluation, the treatment endpoint is defined as one assessment time point, which includes the last measurement obtained during the study for a variable. No other imputation of values for missing data was performed.
B-VEC, beremagene geperpavec; NA, not applicable		
Source: Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination as detailed in section 2.5 Critical appraisal of the relevant clinical effectiveness evidence of the NICE Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template (PMG24) ¹³		

A14. CS, Section 2.5: Please provide full details of the decision-making underpinning the judgements for the risk of bias assessments reported in Table 2.12 to Table 2.14.

As per our response to A13, full details of the quality assessment of included studies are included in the SLR report, with an excerpt provided in A13 above for GEM-1 and GEM-3, and below in Table 6 for the EASE trial.

Table 6: Quality assessment of EASE

EASE		
Was randomisation carried out appropriately?	Yes	Parallel group design. Random number assignment using a blind-maintained numerical assignation system, blinding maintained by off-site Biostats team.
Was the concealment of treatment allocation adequate?	Yes	Once a randomisation number has been assigned, that number was not used again for any other patient (e.g., when the patient was withdrawn from the study, that patient's randomisation number was not reused for any other patient).
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Baseline characteristics were similar between treatment groups, and statistical analysis of primary endpoint was stratified by EB subtype and target wound size class.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Double-blind 90-day randomised phase. Participants, care providers and Investigators were blinded to treatment. An independent unblinded biostatistics team in a separate location maintained the randomisation scheme key. Key remained unavailable to all other individuals until after DBP completion and subsequent locking of the study database for the DBP.
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No/ unclear	Dropout was n=15 from control gel arm and n=9 from Oleogel-S10, with 99 and 100 completing the DBP, respectively. However, among the patients who were eligible to attend first wound closure visit at day 45; the number of patients who completed the assessment was low and imbalanced between both treatments (30 of 45 patients treated with Oleogel-S10, 13 of 33 patients treated with control gel). It is unclear what impact this had.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Protocol available. No evidence of further outcomes collected and NR.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Within the FAS and completer analysis set, patients were analysed using the ITT principle, i.e., patients assigned to the treatment regimen to which they have been randomised. LOCF approach was

		generally taken, but for primary analysis a sensitivity analysis based on multiple imputation (MI) was conducted using the tipping point approach to assess the departures from missing at random (MAR) to missing not at random (MNAR) assumptions.
NA, not applicable		
Source: Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination as detailed in section 2.5 Critical appraisal of the relevant clinical effectiveness evidence of the NICE Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template (PMG24) ¹³		

A15. CS, Section 2.5: Please clarify what adaptations were made to the CRD checklist.

The adapted CRD checklist was used as per section 2.5 *Critical appraisal of the relevant clinical effectiveness evidence of the Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template (PMG24)* - page 17.¹³

A16. CS, Section 2.5, Table 2.12: Please clarify, (i) why the judgement regarding prognostic factors was N/A, (ii) if wound duration at baseline is a potential prognostic factor (e.g. as reported in CS, Table 1.3), and (iii) whether this was controlled for in GEM-3.

GEM-3 was conducted as an intra-patient study therefore consideration of inter-patient prognostic factors was not considered applicable. For each patient, a primary wound pair was selected, with the wounds matched according to size, region, and appearance. However, as described in A11, the age of the target wounds was not collected at baseline in GEM-3.

A17. CS, Section 2.5, Table 2.14: Please clarify whether the quality assessment of EASE related only to the initial double-blind (90-day) phase of the trial.

We can confirm that the summary table in the submission and the detailed table included in the SLR report (and shown above Question A14), present the quality assessment of the EASE DBP, only.

We present an additional quality assessment of the EASE OLP below, performed using the ROBINS-I tool (Table 7).¹⁴

Table 7: ROBINS-I quality assessment of the 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) <i>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</i>	N - all participants in the EASE OLP received Oleogel-S10 and continued with usual wound care.
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) <i>If N/ PN go to 2.4</i>	PN - all participants in the EASE OLP who rolled over from the DBP were assessed within their prior allocation groups from randomisation before treatment (prior Oleogel-S10 or prior control gel). All participants in the OLP received Oleogel-S10 and no additional participants were recruited. However, the of probability trial participants entering an OLP following randomised treatment is often skewed by the treatment effect observed in the DBP so this cannot be discounted and introducing selection bias into the OLP based on prior response.
2.4 Do start of follow-up and start of intervention coincide for most participants? (Y/ PY/ N/ PN/ NI)	NI
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	MODERATE
3: Bias in classification of interventions	
3.1 Were intervention groups clearly defined? (Y/ PY/ N/ PN/ NI)	Y - All participants in the EASE OLP who rolled over from the DBP were treated with Oleogel-S10 and were assessed within their prior allocation groups (prior Oleogel-S10 or prior control gel).
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 – all OLP participants were treated with the same intervention
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 - not as reported
4.3 Were important co-interventions balanced across intervention groups? (Y/ PY/ N/ PN/ NI)	NA – no co-interventions
4.4 Was the intervention implemented successfully for most participants? (Y/ PY/ N/ PN/ NI)	Y

4.5 Did study participants adhere to the assigned intervention regimen? (Y/ PY/ N/ PN/ NI)	NI
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)	PY – based on what is currently published at the time of the review
5.2 Were participants excluded due to missing data or intervention status? (Y/ PY/ N/ PN/ NI)	NI
5.3 Were participants excluded due to missing data on other variables needed for the analysis? (Y/ PY/ N/ PN/ NI)	NI
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	NI (at this time)
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)	N – all participants received Oleogel-S10
6.2 Were the outcomes assessors aware of the intervention received by study participants? (Y/ PY/ N/ PN/ NI)	Y – all participants received open-label Oleogel-S10 during the OLP
6.3 Were the methods of outcome assessment comparable across intervention groups? (Y/ PY/ N/ PN/ NI)	Y – analysis the same regardless of prior allocation in the randomised phase
6.4 Were any systematic errors in measurement of the outcomes related to intervention received? (Y/ PY/ N/ PN/ NI)	NI
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	LOW
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)	NI
7.2 ...multiple analyses of the intervention-outcome relationships? (Y/ PY/ N/ PN/ NI)	NI
7.3 ...different subgroups? (Y/ PY/ N/ PN/ NI)	NI
Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	LOW
OVERALL Risk of bias judgement (Low/ Moderate/ Serious/ Critical/ NI)	MODERATE RISK OF BIAS
DBP, double-blind phase; 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; Y, yes.	

A18. [Priority] CS, Section 2.9 p77: Please clarify whether the inclusion of five GEM-1 patients in the GEM-3 trial presents a potential confounder of outcomes in the GEM-3 trial.

While five patients who had previously enrolled in the Phase 1/2 trial could conceivably be considered as a potential source of bias, importantly different wounds than those previously treated in GEM-1 were selected as primary wounds in the GEM-3 study, which limits any potential impact on the primary and key secondary endpoints given

the localised mechanism of action and absence of systemic distribution upon B-VEC exposure. However, to ensure that there was no unexpected impact of reenrolment of these five participants, a sensitivity analysis of the Phase 3 results was performed excluding those who had participated in the GEM-1 study; as shown in Table 8, the primary analysis remained highly significant.

Table 8 Primary Efficacy Endpoint Analysis: ITT Population (Imputed Data)—Excluding Roll-Over Patients from Phase 1/2

	B-VEC responder	B-VEC non-responder	Overall	Difference (95% CI)	p value
Placebo non-responder	13.1 (50.4)	7.5 (28.8)	20.6 (79.2)		
Placebo responder	3.2 (12.3)	2.2 (8.5)	5.4 (20.8)		
Overall	16.3 (62.7)	9.7 (37.3)			
				41.9 (17.2, 66.6)	0.01008

A19. [Priority] Please clarify differences in the 6-month results reported for the primary endpoint of the GEM-3 trial in the CS, relative to the data reported in the full publication (Guide 2022) and the FDA decision document. These are summarised in Table 1 below for reference.

Table 1: Primary endpoint: complete wound closure at 6 months,* n (%), from different sources

Results including imputation for missing data – N=31				
Document	B-VEC (n=31)	Placebo (n=31)	Absolute difference, % (95% CI)	p value
CS, Table 2.15	20.9 (67)	6.7 (22)	46 (24–68)	0.002
Guide 2022, Table S3**	19 (61.3)	6 (19.4)	41.9 (NR)	NR
FDA Summary Basis for Regulatory Action	20 (64.5)	8 (25.8)	38.7 (13.9-63.5)	0.012
Results excluding 3 patients with missing data - N=28				

Document	B-VEC (n=28)	Placebo (n=28)	Absolute difference, % (95% CI)	p value
Guide 2022, Table S1***	19 (67.9)	6 (21.4)	NR	NR
*Primary wounds were assessed at Weeks 22+24 or Weeks 24+26. ** summary statistics generated by the EAG by summing across rows for primary wound area in Table S3 of Guide 2022. *** summary statistics generated by the EAG from the patient level data reported in Table S1 of Guide 2022.				

The differences between the results shown in the CSR, the USPI, and data reported in the New England Journal of Medicine (Guide 2022),¹⁵ are based on differences in requested imputation methods to handle missing data, and how a remote wound assessment at Week 22 for Subject 02-07 was handled. The various imputation approaches used to address missing data within this study included:

- a) Multiple Imputation. This approach was pre-specified by the Statistical Analysis Plan (SAP) and is described within the Statistical Analysis section of Guide (2022). Wound closure values calculated by this method represent the mean of 10 distinct imputations of the missing data, which is why fractional (non-integer) responses are observed.
- b) “Open” Imputation. All missing wound assessments assumed the wounds were open.
- c) “Worst-Case” Imputation. Missing assessments for placebo-treated wounds assumed the wounds were closed, while missing assessments for B-VEC-treated wounds assumed the wounds were open.

Wound assessments for Subject 02-07 were initially handled differently due to potential concerns regarding a protocol deviation. Specifically, due to the subject’s inability to travel during the COVID-19 pandemic, the wound assessments for Subject 02-07 were conducted remotely at Week 22. In view of this deviation, the Week 22

wound assessment was censored (treated as missing) during the original analysis, resulting in only 19 wound closure events observed at the primary endpoint. However, in consultation with the FDA during BLA review, Subject 02-07 was considered a valid responder in the final ITT population analysis, ultimately raising the number of observed B-VEC wound closure responses to 20. Regarding the approaches used by the individual analyses:

“CS, Table 2.15” matches Guide (2022), Table 2. This analysis treats the Week 22 wound assessment for Subject 02-07 as missing and applies multiple imputation to complete missing data.¹⁵

“Guide (2022), Table S3” treats the Week 22 wound assessment for Subject 02-07 as missing and applies open imputation to complete missing data.¹⁵

“FDA Summary Basis for Regulatory Action” treats the Week 22 wound assessment for Subject 02-07 as valid and applies worst-case imputation to complete missing data.¹⁶

“Guide (2022), Table S1” treats the Week 22 wound assessment for Subject 02-07 as missing and drops all three subjects with missing data.¹⁵

Importantly, the primary endpoint is both statistically significant and clinically relevant irrespective of the imputation methodology applied.

A20. CS, Section 2.6.1.3: Please clarify whether ‘Durable wound closure’ was a post hoc assessment and was not a pre-specified endpoint (noted as a ‘supplementary analysis’ in CS, post hoc in Guide *et al* 2022, and absent from Table 2.3: summary of trial methodology).

The supplementary analysis of the primary efficacy endpoint to assess the “Durability of Response” was performed post-hoc, by considering the proportion of wounds that met the definition for wound healing at both 3 months and 6 months (simultaneously met both the primary endpoint and key secondary endpoint). This was not an analysis included in the final SAP.

A21. CS, Section 2.6.1.3: Please clarify how the Durability of response figure (49.7%) – ‘the proportion of wounds that met the definition of closure at both 3 months and 6

months (meeting both primary endpoints simultaneously)' can be higher than either the 3-month (47.7%) or the 6-month (43.2%) figures as reported in Table 2.16.

The reason why the figures for “durability of response” are higher than those referring to “complete wound closure” at 3-month (weeks 8, 10 and 12) and 6-month (weeks 22, 24 and 26) is because different definitions were used for those endpoints. For the analysis presented in table 2.16, “complete wound closure” was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin reepithelialisation without drainage, as determined by the investigator, at the 3 consecutive time points evaluated at month 3 (weeks 8, 10 and 12) or month 6 (weeks 22, 24 and 26). “Durability of response” was defined as meeting the responder definition for complete wound closure both at 3 months (Weeks 8 and 10 or Weeks 10 and 12) and at 6 months (Weeks 22 and 24 or Weeks 24 and 26).

A22. Were all patients assessed at 22, 24 and 26 weeks allowing closure to be achieved either at 22/24 weeks or 24/26 weeks? Or was only one pair of timings allowed for each patient with the flexibility for week 22 or 24 as the first assessment point just to allow for scheduling differences?

All primary wounds were assessed by the blinded investigator at Weeks 8, 10, 12, 22, 24, and 26, corresponding to timing of the primary and key secondary efficacy endpoint definitions.

A23. Please clarify why the results reported in Table 9 of the CSR for GEM-1 do not match those in Table 2.18 for the wound closure outcome (both denominators and numerators vary).

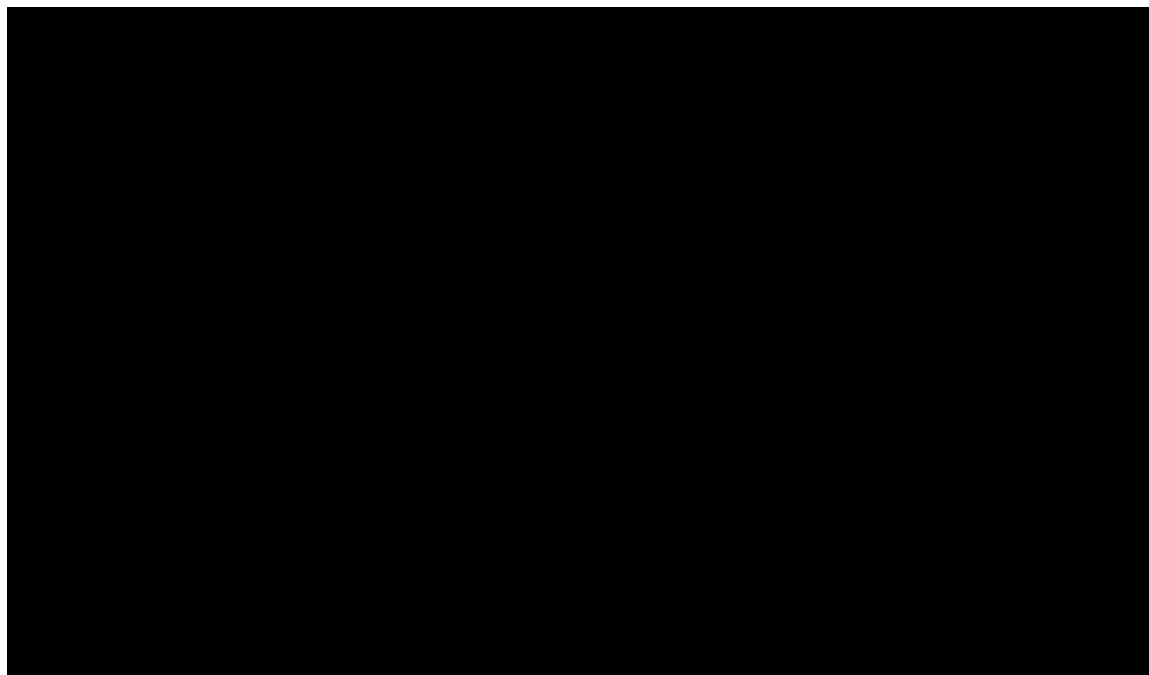
Table 9 of the CSR presents the wound closure observations for Weeks 8, 10, and 12.¹⁷ Alternatively, Table 2.18 aims to match the wounds considered for Responder Analysis and *excludes three subjects*. Two Phase 1 subjects were excluded (KB103-001-1a and KB103-001-2a) due to mismatched timepoints in data collection; wound closure data under the Phase 1 protocol occurred at Weeks 6 and 12 rather than Weeks 8 and 10. Subject KB103-001-09 in Phase 2 was excluded as there was no data collected for a placebo-treated wound, only a B-VEC-treated wound.

A24. [Priority] Median time to wound closure is reported in CSR, Table 10 for GEM-1. Please provide a Kaplan-Meier plot of time to wound closure in GEM-1

to allow the EAG to assess whether the assumption of a constant hazard is appropriate.

The Kaplan-Meier plot of time to wound closure is provided below in Figure 1.

Figure 1: Kaplan-Meier plot for time to wound closure in GEM-1

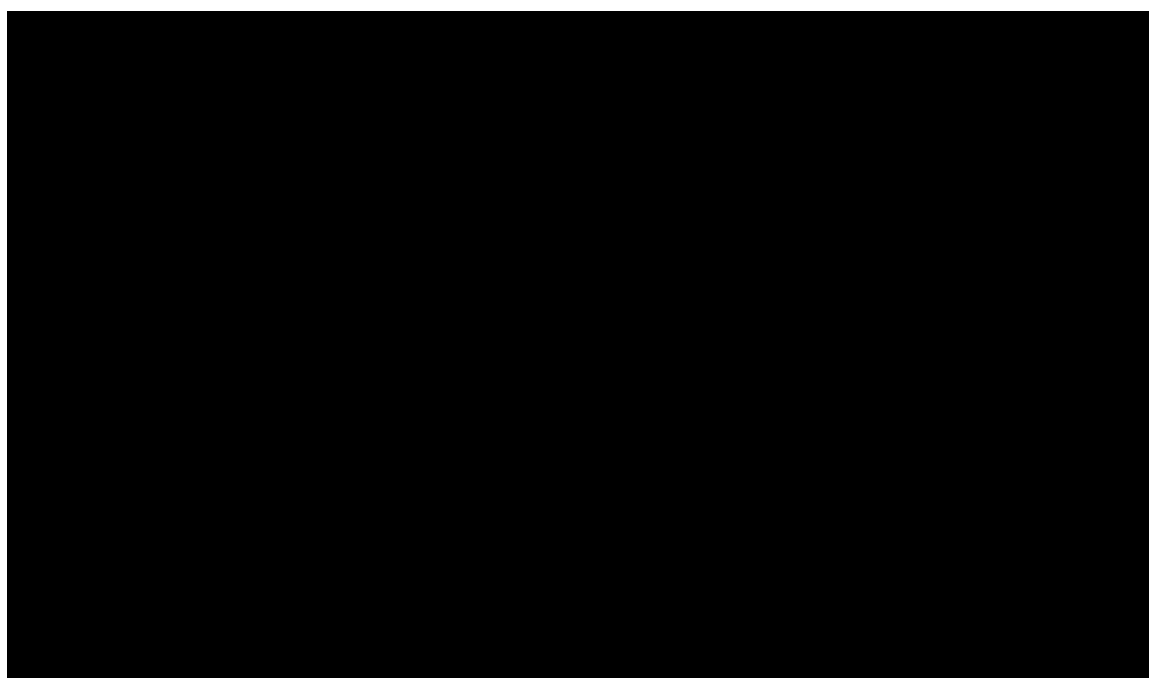


Source: Krystal Biotech, data on file.

A25. [Priority] Duration of closure is reported in CSR, Table 10 for GEM-1. Please provide a Kaplan-Meier plot for time to reopening using the data collected to calculate duration of closure to allow the EAG to assess whether the assumption of a constant hazard is appropriate.

The Kaplan-Meier plot for time to reopening, incorporating data collected to calculate duration of closure, is provided below in Figure 2.

Figure 2: Kaplan-Meier plot for time to reopening in GEM-1



Source: Krystal Biotech, data on file.

A26. Please clarify what proportion of patients in GEM-1 received the treatment via intradermal injections and what % of administrations were given via this route.

In the GEM-1 trial, there were nine patients in total; however, three subjects who were enrolled in Phase 2a contributed a different wound for the Phase 2b trial and were therefore considered as a separate subject to total 12 subjects for analysis in the study. A total of 5/12 subjects (41.7%) received treatment via intradermal injection during the GEM-1 trial. Across these 5 subjects, 40 intradermal injections were administered, representing 17.8% (40/225) of all B-VEC administrations for this study. 12/12 subjects (100%) received a total of 185 topical administrations, representing 82.2% (185/225) of all B-VEC administrations for this study.

A27. Please clarify why definition of complete closure for GEM-1 is reported as 95% in Tables 2.10 and 2.19 and Section 2.9, p.77, but 90% in Tables 2.4, 2.10 and 2.18.

In GEM-1, complete wound closure was defined as a 90% or more reduction in wound surface area from baseline (reference CSR), and this definition was provided in Tables 2.4, 2.10, and 2.18 of the company submission. Analysis using a more stringent definition of wound closure, that is, at least 95% reduction in wound surface area from baseline, was also performed (reference Gurevich et al., 2022). However, recalculating the number of wound closures for Weeks 8, 10, and 12 using either the

90% or 95% threshold does not affect the outcome. At these timepoints, no wounds exhibit a percentage reduction in wound size $\geq 90\%$ but $< 95\%$; therefore, use of either threshold will result in identical numbers of closed wounds and an identical outcome from the responder analysis.

A28. CS, Section 2.10.2: Please provide details of the moderate AE reported.

One moderate AE of itching/ facial redness was experienced, which resolved within two days.

A29. CS, Section 2.10.3: Please provide some information on average patient exposure to drug for the OLE safety findings.

Summary statistics for duration of exposure, and for the number of doses received, are provided in Table 9 below. Twenty-nine of 47 subjects (61.7%) had over one year of exposure.

Table 9 Study Treatment Exposure by Duration and Number of Doses Received (Safety Population)

Characteristic	Rollover subjects (N=24)	Naïve subjects (N=23)	All subjects (N=47)
Overall exposure duration (days)			
Mean (SD)	602.1 (229.72)	342.7 (197.09)	475.1 (249.29)
Median (min, max)	642.0 (1, 794)	344.0 (21, 664)	565.0 (1, 794)
Total number of doses received			
Mean (SD)	62.1 (32.32)	34.5 (20.06)	48.6 (30.15)
Median (min, max)	72.5 (1, 107)	36.0 (3, 73)	48.0 (1, 107)

SD=standard deviation.

Source: Krystal Biotech, 2023 (GEM-3 OLE CSR)¹⁸.

A30. The SmPC states “*Patients are expected to enrol in a non-interventional multi-country study, to assess the long-term safety of beremagene geperpavec in a real-life setting*” Please provide details of any requirements for ongoing studies made by licensing authorities (e.g. FDA/ EMA/ MHRA). Please describe how these requirements will be met in a UK setting.

Included as an Annex II condition of the Vyjuvek EU Marketing Authorization, a non-interventional post-authorisation safety study (PASS) will be implemented, to further characterise the long-term safety of Vyjuvek in patients with dystrophic epidermolysis bullosa with mutation(s) in the *COL7A1* gene, including patients less than 6 months of age. This will be a prospective, non-interventional, multi-country study in patients treated with Vyjuvek in a real-life clinical setting. The study is planned to be initially

implemented in France, Germany and the US. It is not currently planned to implement this study in the UK.

There are no additional requirements to conduct any further studies by the EMA or other regulatory agencies, at present.

A31. Why was the GEM-3 OLE study terminated early? The CSR states that ■ of patients enrolled discontinued and the most common reason (■) was study termination by sponsor.

The OLE study was conducted to provide continued access to B-VEC for Phase 3 participants, to provide new access for patients who were unable to enrol in a prior study, and to collect additional health outcomes, namely long-term safety. Once Vyjuvek was approved by the FDA and became commercially available,¹⁶ the Sponsor decided to terminate the OLE study early, as subjects now had the ability to access the therapy without the additional burden of study visits. The data collected to-date was considered sufficient to demonstrate long-term safety and effectiveness of Vyjuvek.

A32. Please present the summary of response for rollover subjects in the GEM-3 OLE study and comment on whether these show stable or fluctuating wound closure over the 12-month follow-up period.

A summary of the response for rollover subjects in the GEM-3 OLE study is provided in the Table 10. Out of the 24 rollover subjects, 19 were evaluated (five patients did not consistently attend follow-up visits). The responder rate ranged from 61.1% to 89.5% in the OLE study (up to Month 12) and was comparable to the rates observed at Months 3 and 6 in the Phase 3 study.

Table 10 Summary of Responders for Rollover Subjects

Visit	Responders/Subjects (%)
Month 3 (Phase 3)	13/19 (68.4)
Month 6 (Phase 3)	14/19 (73.7)
Week 1	17/19 (89.5)
3 Months	16/19 (84.2)
6 Months	11/18 (61.1)
9 Months	14/17 (82.4)
12 Months	10/16 (62.5)

Note: responders were subjects with complete wound closure for primary wounds previously treated with B-VEC during the phase 3 study (B-VEC-03).

Source: Krystal Biotech, Data on File (GEM-3 OLE CSR, Table 14.2).¹⁸

A33. Please present the mean number of vials received for GEM-3 and the OLE phase for rollover and naive participants across years 1, 2, and 3 since the start of treatment for either group.

Vial consumption was not collected in the GEM-1, GEM-3, OLE trials of B-VEC.

Indirect treatment comparisons

A34. [Priority] In the economic model, B-VEC and birch bark extract (BBE) were compared naively. Please present the naive indirect treatment comparison between B-VEC and BBE for complete wound closure, time to wound closure and change in target wound size.

The endpoint definitions implemented in the trials assessing BBE (BEB-10 and EASE) and those implemented in trials assessing B-VEC (GEM-1 and GEM-3) are strikingly different, preventing a meaningful indirect treatment comparison (ITC).

Complete wound closure

While all four studies reported on complete wound closure, they did so at different timepoints. For the purpose of analysis (relative effectiveness of B-VEC versus BBE), only timepoints reported in both at least one B-VEC and one BBE trial were considered—restricting the evaluation to complete wound closure at 3 months (GEM studies) and 90 days (EASE).

Crucially, the definition of "complete wound closure" differed so substantially between the studies that a valid comparison is not possible. The GEM studies only considered wounds that were still closed at the 3-month visit and required confirmation of closure across two consecutive visits. Further, closure was defined as $\geq 90\%$ in GEM-1 and 100% in GEM-3, adding additional stringency. The primary endpoint of the EASE trial required a target wound to remain closed after 7 days of the initial closure for it to be considered a responder.

This discrepancy introduces an unavoidable bias: a wound counted as "closed" in EASE would not qualify as closed in the GEM trials, and wounds that reopened before the Month 3 visit (but were previously closed) would still be considered successful in EASE, but not in GEM. Likewise, GEM-3 required that a wound remain closed for two weeks after the 3-month visit to be counted—a criterion absent in EASE.

Given these major methodological differences, no meaningful or scientifically valid ITC can be made between B-VEC and BBE on this outcome. Any attempt to do so would be methodologically unsound.

Time to wound closure

A valid comparison of time to wound closure across studies is not possible due to critical differences in endpoint definitions. In GEM-1, wound closure was rigorously defined as closure sustained over two consecutive visits, ensuring durability of the outcome. In contrast, neither EASE nor BEB-10 required confirmation of closure, a wound observed to be closed once was counted as closed, even if it reopened soon after. This discrepancy biases the results in favour of BBE, as transient closures are counted as treatment successes in EASE and BEB-10 but not in GEM-1.

Change in target wound size

Change in target wound size was reported in GEM-1, EASE, and BEB-10. While the endpoint definition was generally consistent, minor differences exist in the statistical summaries used (i.e., mean vs. median). These differences are less critical than in other outcomes but still require caution when interpreting study outcomes.

Even though it is not feasible to indirectly compare B-VEC and BBE based on wound dynamics data from the GEM and EASE trials, due to the reasons outlined above, we conducted an ITC using the Bucher method based on the relative change in the proportion of the cohort in each health state over two consecutive model cycles. This analysis was implemented within the replicated version of the HST28 model, adapted to a 4-health-state structure plus death, with 3-month cycle lengths to align with the B-VEC modelling framework.

The analysis incorporated data from both B-VEC and BBE trials to inform the modelled health-state distributions and estimate relative treatment effects. The full methodology and results of this Bucher ITC are presented in the response to Question B15.

A35. CS, Section 2.9: BEB-10 is first mentioned on page 75. Please provide a fuller description of this trial if it is relevant to the CS.

BEB-10 is the phase 2 monocentric case series pilot trial of Oleogel-S10 (BBE), which enrolled ten participants.⁹ While it was identified in the SLR and included in the ITC feasibility assessment for completeness, it was not deemed relevant to the decision problem addressed by the company submission since Phase 3 RCT evidence from EASE is available.

A36. CS, Section 2.9, p.77: Please clarify the statement: *‘Importantly, the definitions of complete wound closure differed between studies. EASE measured all wounds that had complete closure (definition not reported)’* in light of the definition for closure reported in Kern *et al.* 2022, pp.13-14: *‘The primary efficacy endpoint of the study was the proportion of patients with first complete closure of the EB target wound, determined by clinical assessment, within 45 days ($\pm$ 7days) of treatment... Complete wound closure was defined as skin re-epithelialization without drainage’.*

Further clarity is needed with respect to why the definitions of the primary endpoints are substantially different between these studies. In the EASE trial, the primary efficacy endpoint was the proportion of patients with first complete closure of the EB target wound within 45 days of treatment with Oleogel-S10 compared with control gel based on clinical assessment by the investigator (the wound was to be rated as “closed” at first appearance of complete re-epithelialisation without drainage). In the GEM-3 study, the primary endpoint was the proportion of wounds demonstrating complete wound healing at 6 months (~180 days), defined as 100% wound closure from the exact wound area selected at baseline, specified as skin reepithelialisation without drainage, as determined by the Investigator; only wounds healed for at least two consecutive weeks were counted as responders (*i.e.*, healed at Weeks 22 and 24 or Weeks 24 and 26). It is important to emphasise that both the primary and secondary endpoints of the GEM-3 trial required a wound to be closed at two consecutive visits (Weeks 22 and 24 or Weeks 24 and 26 for the primary endpoint; Weeks 8 and 10 or Weeks 10 and 12 for the key secondary endpoint) for it to be considered a responder. Differently, the primary and secondary endpoints of the EASE trial only considered a single time point for a wound to be considered closed. The impact of the higher threshold required in the GEM-3 trial for a wound to be considered closed is well illustrated in the sensitivity analysis of the primary endpoint of the EASE trial, which

required a target wound to remain closed after 7 days of the initial closure for it to be considered a responder. With this change in the definition, noteworthy in still being less stringent than the responder definition used for the primary and key secondary endpoints in the GEM-3 study, the proportion of responders to Oleogel-S10 (BBE) dropped from 41.3% to 17.4% at 45 days; for comparison, at 3 and 6 months, 70.6% and 67.4%, respectively, of B-VEC treated wounds were closed in two consecutive visits spaced 2 weeks apart.

A37. CS, Section 2.9, p.77: It is stated that, “*no confirmation of closure of wounds was required in EASE,*” whereas in CS, Section 2.3.4.4 (p56) which describes the assessment of outcomes in the EASE trial, it is stated, “*Once the wound was deemed closed, complete closure of the EB target wound was confirmed at 1 week plus 2 days after first complete closure.*” Please clarify if the definition of wound closure did or did not require confirmation after 1 week plus 2 days for the EASE study. If this was the case, then please clarify whether the difference between closure at 1 week plus 2 days versus 2 weeks is a clinically important difference. For context, the EAG notes that the guidance for BBE (HST28) states, “*The clinical expert submission stated that a clinically significant benefit for people 10 years and older would be for a wound to heal and to remain healed for 3 months,*” and both 2 weeks and 1 week plus 2 days are substantially lower than 3 months.

When considering partial thickness wounds in DEB, wound dynamics are an important consideration in terms of the severity of disease, with both time to wound closure and duration of wound closure playing an important but distinct part. Here we are referring to wound closure and confirmation of that closure, not the durability of closure which we believe was being referred to in the clinical expert submission in the guidance for HST28.

In terms of wound closure and confirmation of that closure, we do not believe there is a clinically important difference between 1 week $\pm$ 2 days and 2 weeks. However, we do not have this information from the primary analysis from EASE. The closure endpoint in GEM-3 was more stringent than EASE since in EASE, wounds closed at any time were presented. Furthermore, closure did not have to be confirmed in following visit. The number of patients who completed the assessment was low and imbalanced between treatment arms.

Section B: Clarification on cost-effectiveness data

Markov model structure

B1. [Priority] Please provide a revised base case and supplementary analyses if there have been any amendments based on the clarification process.

Incremental changes to the initial company base case, resulting in the updated company base case are presented in Table 11, with the detailed results of the updated company base case in Table 12. The outcomes of the updated base case remain broadly consistent with those of the original base case submitted in the CS.

Two key changes contributed most to the lower total cost savings for B-VEC versus comparators. First, adjusting the baseline distribution of patients between RDEB and DDEB (see response to Question B6) resulted in a greater proportion of patients being distributed in more severe health states at baseline. This led to a longer time to reach the very mild health state, thereby increasing costs in the B-VEC arm. Second, correcting the mortality calculation for the moderate health state (see response to Question B49) resulted in a higher mortality rate, which reduced the time spent in this relatively costly state. As more patients reside in the moderate health-state in BBE and BSC arms than in B-VEC, this correction reduced costs more significantly in those arms, contributing to the reduced cost saving for B-VEC vs comparators.

The incremental QALYs in the updated base case are slightly lower than in the original submission. This is primarily due to the correction of the caregiver utility calculation (see responses to Questions B43–B45).

As requested by the EAG, the total QALYs have been disaggregated by patient and caregiver contributions. As shown, the patient's quality-of-life gains remain the primary driver of the total incremental QALYs.

The results of scenario analyses are presented in Table 13, with a detailed description of the methodology for each scenario provided in the corresponding response to the relevant EAG question (also referenced in Table 13).

Table 11 Incremental changes to original company base case to derive updated company base case

#	Change	In response to question	B-VEC vs BSC				B-VEC vs BBE			
			ΔQALYs	ΔCosts	ICER	iNMB	ΔQALYs	ΔCosts	ICER	iNMB
0	Original company submission base case	NA	26.23	████	Dominant	████	16.48	████	Dominant	████
1	Distribution over RDEB and DDEB based on overall sample of Bruckner et al	B6	26.87	████	Dominant	████	16.56	████	Dominant	████
2	Updated mapping from 6 to 4 health states for inputs from HST28	B36	26.85	████	Dominant	████	16.75	████	Dominant	████
3	Including caregiver QALYs also after the patient dies	B43	21.97	████	Dominant	████	16.82	████	Dominant	████
4	Apply age adjustment for caregiver utilities	B44	21.91	████	Dominant	████	16.80	████	Dominant	████
5	Set baseline age of caregivers to 43.3	B45	22.54	████	Dominant	████	16.36	████	Dominant	████
6	Correcting mortality calculation for moderate health state	B49	22.47	████	Dominant	████	16.43	████	Dominant	████
7	Correcting calculations for irreversible clinical manifestations UPDATED COMPANY BASE CASE	B51	22.47	████	Dominant	████	16.43	████	Dominant	████

Table 12 Updated discounted base case results

	Life-Years	Patient QALYs	Caregiver QALY	Total QALYs	Cost (£)	ICER (£)	iNMB (£)
B-VEC	25.19	10.97	40.37	51.34	████		
BSC	20.65	-4.87	33.74	28.87	████		
BBE	23.07	-2.07	36.98	34.91	████		
Comparisons							
B-VEC vs BSC	4.54	15.84	6.63	22.47	████	Dominant	████
B-VEC vs BBE	2.13	13.04	3.39	16.43	████	Dominant	████
BBE=birch bark extract; BSC=best supportive care; QALY: quality-adjusted life-year							

Table 13 Scenario analysis results

#	Scenario	In response to question	B-VEC vs BSC					B-VEC vs BBE				
			ΔQALYs	ΔCosts (£)	ICER (£)	Threshold for NMB (£)	iNMB (£)	ΔQALYs	ΔCosts (£)	ICER (£)	Threshold for NMB (£)	iNMB (£)
0	Updated company base case	NA	22.47	████	dominant	51,000	████	16.43	████	dominant	51,000	████
1	B-VEC vial optimization: 9 syringes per two vials (maximum of 4 syringes per patient).	NA (scenario in CS)	22.47	████	dominant	51,000	████	16.43	████	dominant	51,000	████
2	Proportion of patients to consider for vial optimization: 90%	NA (scenario in CS)	22.47	████	dominant	51,000	████	16.43	████	dominant	51,000	████
3	Proportion of patients to consider for vial optimization: 70%	NA (scenario in CS)	22.47	████	dominant	51,000	████	16.43	████	dominant	51,000	████
4	B-VEC discontinuation: 9.68% per year in the first year, then 1% per year onwards	NA (scenario in CS)	19.36	████	dominant	51,000	████	13.32	████	dominant	51,000	████
5	Utility values for patients: BBE NICE submission	NA (scenario in CS)	14.27	████	dominant	36,000	████	7.24	████	dominant	36,000	████
6	Discounting for costs and outcomes set to 1.5%	NA (scenario in CS)	36.75	████	dominant	51,000	████	26.65	████	dominant	51,000	████
7	████ compliance	B11	22.42	████	dominant	51,000	████	16.37	████	dominant	51,000	████
8	Inclusion of utility decrements for clinical manifestations	B12	23.16	████	dominant	51,000	████	16.97	████	dominant	51,000	████
9	ITC scenario 1 • Baseline health-state distribution derived from Bruckner et al.; • BBE transitions through Bucher ITC • B-VEC and BSC transitions from the patient-level simulation	B15	22.47	████	dominant	51,000	████	20.23	████	dominant	51,000	████
10	ITC scenario 2 • Baseline health-state distribution derived from Bruckner et al.;	B15	20.56	████	████	51,000	████	16.59	████	dominant	51,000	████

#	Scenario	In response to question	B-VEC vs BSC					B-VEC vs BBE				
			ΔQALYs	ΔCosts (£)	ICER (£)	Threshold for NMB (£)	iNMB (£)	ΔQALYs	ΔCosts (£)	ICER (£)	Threshold for NMB (£)	iNMB (£)
0	Updated company base case	NA	22.47	████	dominant	51,000	████	16.43	████	dominant	51,000	████
	• BBE and BSC health-state transitions from the replicated HST28 model. • B-VEC transitions through Bucher ITC											
11	ITC scenario 3 • Baseline health-state distributions based on HST28 model; • BBE transitions through Bucher ITC • B-VEC and BSC transitions from the patient-level simulation	B15	18.77	████	dominant	51,000	████	15.07	████	dominant	51,000	████
12	ITC scenario 4 • Baseline health-state distributions based on HST28 model; • BBE and BSC health-state transitions from the replicated HST28 model. • B-VEC transitions through Bucher ITC	B15	18.96	████	████	51,000	████	14.74	████	dominant	51,000	████
13	████% weekly reduction in open area treated with placebo	B16	22.52	████	dominant	51,000	████	16.44	████	dominant	51,000	████
14	█████% weekly reduction in open area treated with placebo and █████% weekly reduction in open area treated with B-VEC	B16	22.06	████	████	51,000	████	15.98	████	dominant	51,000	████
15	B-VEC duration of closure: █████ days	B19	22.47	████	dominant	51,000	████	16.43	████	dominant	51,000	████
16	B-VEC duration of closure: █████ days	B19	22.48	████	dominant	51,000	████	16.44	████	dominant	51,000	████
17	B-VEC duration of closure: █████ days	B19	22.43	████	████	51,000	████	16.40	████	dominant	51,000	████
18	B-VEC duration of closure: █████ days	B19	22.46	████	████	51,000	████	16.42	████	dominant	51,000	████

B2. [Priority] Please provide an updated model with a log of changes if there have been any amendments to the model based on the clarification process.

A log of changes is provided in Table 14. This log is also included in the model on sheet 'Change log'.

Table 14 Summary of amendments to the base-case

Sheet	Range	Change	In response to question
Clinical data	f14:G20	Added distribution including also care-giver reported data	B6
Clinical data	B15:B16	Added choose function to select appropriate data source depending on setting	B6
Lookups	K33:M37	Added setting for selecting data for distributions over disease types	B6
Results	F13:J13	Added dropdown for selecting data for distributions over disease types	B6
Clinical data	H11:H67	Added adjustment factor for OWSA values for Dirichlet distributions	B13
Markov B-VEC	Columns G, Q	Added to track caregiver mortality probability	B43
Markov B-VEC	Columns AE, AO, BK, EI, EW	Added to track caregivers of deceased patients	B43
Markov B-VEC	Columns EJ and EX	Included to include also the new columns DJ and DW in totals	B43
Lookups	K39:M43	Added setting to in/exclude carer utilities after a patient dies	B43
Results	L15:O15	Added dropdown for selecting setting to in/exclude carer utilities after a patient dies	B43
Markov BSC	Columns G, P	Added to track caregiver mortality probability	B43
Markov BSC	Columns AD, AO, AV, BH, EF, ET	Added to track caregivers of deceased patients	B43
Markov BSC	columns EG and EU	Included to include also the new columns DQ and EC in totals	B43
Markov Filsuvez	Columns G, P	Added to track caregiver mortality probability	B43
Markov Filsuvez	Columns AD, AO, AV, BO, EM, FA	Added to track caregivers of deceased patients	B43
Markov Filsuvez	columns EN and FB	Updated to include also the new columns DO and EB in totals	B43
Transitions	Columns A	Added columns for total populations to use in ITC analyses	A34/B15
ITC	Entire sheet	Added the sheet	A34/B15
Lookups	O41:Q46	Added setting to use ITC output	A34/B15
Markov Filsuvez	column L	Replaced < with <= to include 1 more cycle for ITC transitions before freezing the cohort	A34/B15
Markov Filsuvez	Columns AV:BD	Added to implement ITC input	A34/B15
Markov Filsuvez	Columns BF:BJ and BM	Added choose function to select appropriate data source depending on setting	A34/B15
Markov B-VEC	Column M	Added to track whether or not to use ITC output	A34/B15
Markov B-VEC	Columns AR:AZ	Added to implement ITC input	A34/B15
Markov B-VEC	Columns W:AP	Adjusted to account for ITC functionality	A34/B15

Results	F19:J19	Added dropdown for selecting whether to use ITC based on transitions	A34/B15
Lookups	K45:M49	Added setting to in/exclude age adjustment for caregiver QALYs	B44
Results	L17:O17	Added dropdown for selecting setting to in/exclude age adjustment for caregiver QALYs	B44
Lookups	K51:M55	Added setting to set baseline age of carers	B45
Results	L17:O17	Added dropdown for selecting baseline age of carers	B45
QoL Data	B66	Added choose function to change baseline age of caregiver dependent on selection	B45
Markov B-VEC	EE:EH	adjusted to account for age adjustment for caregivers	B44
Markov BSC	EB:EE	adjusted to account for age adjustment for caregivers	B44
Markov Filsuvez	EI:EL	adjusted to account for age adjustment for caregivers	B44
Lookups	KO48:Q52	Added setting for fixing error in Moderate health state survival calculation	B49
Results	L24:O24	Added dropdown for fixing error in Moderate health state survival calculation	B49
Mortality	T1291:T1771	Adjusted to fix error in calculation of Moderate health state survival calculation	B49
Lookups	K57:Q61	Added setting for adjusting health state mapping	B36
Results	L24:O24	Added dropdown for adjusting health state mapping	B36
Clinical data	C65	Added choose function to change value based on setting	B36
Markov B-VEC	Columns CK, CR, CY	Added to show total patients with the respective irreversible clinical manifestations	B51
Markov BSC	Columns CH, CO, CV	Added to show total patients with the respective irreversible clinical manifestations	B51
Markov Filsuvez	Columns CO, CV, DC	Added to show total patients with the respective irreversible clinical manifestations	B51
Lookups	O54:Q58	Added setting for correction of clinical manifestation calculations	B51
Results	L24:O24	Added dropdown for correction of clinical manifestation calculations	B51
Markov B-VEC	Columns CM:CP	Adjusted to fix error where the calculations were using values from CF:CI in the previous cycle instead of CM:CP	B51
Markov B-VEC	Columns CT:CW	Adjusted to fix error where the calculations were using values from CF:CI in the previous cycle instead of CT:CW	B51
Markov BSC	Columns CJ:CM	Adjusted to fix error where the calculations were using values from CC:CF in the previous cycle instead of CJ:CM	B51
Markov BSC	Columns CQ:CT	Adjusted to fix error where the calculations were using values from CC:CF in the previous cycle instead of CQ:CT	B51
Markov Filsuvez	Columns CQ:CT	Adjusted to fix error where the calculations were using values from CJ:CN in the previous cycle instead of CQ:CT	B51
Markov Filsuvez	Columns CX:DA	Adjusted to fix error where the calculations were using values from CJ:CN in the previous cycle instead of CX:DA	B51
QoL data	rows 56:100	Added to include utility decrements from clinical manifestations	B12
HRQoL	Rows 33:42	Added to include utility decrements from clinical manifestations	B12
OWSA_data	Rows 178:183	Added to include utility decrements from clinical manifestations	B12
Lookups	K63:M67	Added to include utility decrements from clinical manifestations	B12

Results	L21:O21	Added to include utility decrements from clinical manifestations	B12
Markov B-VEC	Columns DA:DI, EA, EP	Added to include utility decrements from clinical manifestations	B12
Markov B-VEC	Columns EB, EQ	Adjusted to include utility decrements from clinical manifestations	B12
Markov BSC	Columns CX:DF, DX, EM	Added to include utility decrements from clinical manifestations	B12
Markov BSC	Columns DY, EN	Adjusted to include utility decrements from clinical manifestations	B12
Markov Filsuvez	Columns DE:DM, EE, ET	Added to include utility decrements from clinical manifestations	B12
Markov Filsuvez	Columns EF, EU	Adjusted to include utility decrements from clinical manifestations	B12
Results	H115:H122 and H133:H140	Added to include utility decrements from clinical manifestations	B12
Results	J115:J122 and J133:J140	Adjusted to include utility decrements from clinical manifestations	B12

B3. [Priority] CS Section 3.2 (p87): It is stated that the data from GEM-1 was used to populate the model because of the more frequent measurements of wound outcomes, with only 3- and 6-month data available from GEM-3 and weekly data from GEM-1. But then a 3-monthly cycle length was chosen for the Markov model to align with outcome collection in GEM-3 (see Table 3.3). Given the larger size of GEM-3 and the alignment of outcome measurement from GEM-3 with the cycle length, why wasn't the data from GEM-3 used to inform transition probabilities?

While GEM-3 included a larger patient population, it collected wound outcomes only at 3- and 6-month intervals, which limited its suitability for extrapolating the dynamic wound-healing process to the body surface area affected over time. In contrast, GEM-1/2 provided weekly-level wound data, which were essential for accurately characterising wound closure dynamics and extrapolating from individual wound outcomes to total BSA with open wounds.

B-VEC is administered once weekly to open wounds, with a maximum weekly dose. Treatment continues until wounds are closed, and reapplication is required if wounds reopen. Importantly, the volume of B-VEC administered varies as wounds increase or decrease in size. Therefore, not all wounds may be treated at each visit.

To appropriately estimate both transition probabilities between health states (i.e., changes in total BSA with open wounds) and B-VEC vial consumption, it was necessary to simulate wound-level healing trajectories on a weekly basis, capturing

how individual wounds respond to treatment and when they close or recur. This level of temporal granularity is not available from GEM-3 and could not be derived from its 3-monthly outcome measurements.

Therefore, weekly data from GEM-1/2 were the only data suitable for informing a patient-level simulation (PLS) that could extrapolate wound-level healing dynamics to changes in BSA with open wounds, while accounting for the weekly maximum area treatable with B-VEC. This simulation enabled the projection of health state transition probabilities and B-VEC vial requirements within each 3-month model cycle. Although GEM-3 contributed to informing other components of the model, only GEM-1/2 provided the necessary temporal granularity to robustly and plausibly simulate the clinical and resource utilisation impact of B-VEC.

B4. [Priority] Please clarify why the modelling approach for the evaluation of BBE (HST28) of considering 6 health states based on body surface area percentage (BSAP) covered was not considered as the basis for the economic modelling for this appraisal of B-VEC. Such an approach would have allowed the transition matrices from HST28 to have been used directly in the economic model reducing uncertainty in the indirect comparison.

The development of the de novo model for B-VEC was informed by the mechanism of action of B-VEC that targets the underlying mechanism of the disease. B-VEC is a topical, redosable gene therapy designed to restore the structural stability of the skin for directly treated wounds, via delivery of the COL7A1 gene and functional correction of COL7 expression. Given that B-VEC targets the underlying cause of DEB and not only accelerates wound closure but also largely improves the durability of wound closure, it is expected to prevent or revert clinical manifestations associated with DEB. Therefore, the model approach aimed to capture the benefit of B-VEC treatment in both accelerating and maintaining wound closure, and consequently preventing the clinical manifestations associated with the presence of open wounds. The reduction of clinical manifestations is therefore an important aspect of the benefit of B-VEC treatment. In contrast, given that BBE treatment is aimed at treating symptoms of the disease without addressing the underlying cause of DEB, the HST28 model included health states representing different levels of body surface area percentage (BSAP) covered by partial-thickness wounds, without considering clinical manifestations.

Health states were defined as Very Mild, Mild, Moderate, and Severe primarily to align with published literature (i.e., Bruckner et al., Eng et al.)¹⁹ and to allow the model to incorporate both reversible and irreversible complications. The literature reporting the prevalence of clinical manifestations in DEB stratifies the disease into mild, moderate, and severe. Eng et al. specifically reported on the correlation between these levels of disease severity defined by increasing size of open wounds area and the associated increasing prevalence of clinical manifestations¹⁹. Having a model that is more closely aligned with these levels of disease severity and that allows linking the clinical manifestations of DEB is appropriate to reflect the clinical course of DEB and to accurately assess the clinical and economic value of BVEC.

While we agree that a 6-health state model that was used in HST28 would have facilitated the direct inclusion of BBE transitions in the simulation without requiring any mapping approach, the decision to adopt the 4 health-states model was driven by its stronger clinical grounding and clearer alignment with published evidence on disease severity defined by open wound area, and associated manifestations. Furthermore, the clinical rationale for the 6-health state model used in HST28 could not be elucidated.

B5. CS, Tables 3.16 and 3.17: Outputs from these TP matrices suggest that all patients achieve the very mild state on B-VEC by week 39 and remain there as long as they are on treatment. It also suggests that patients aged under 18 do not transition between health states at any time on best supportive care (BSC), and those over 18 years old can only transition between the moderate and severe state in the first 6 months.

- a) Please explain the clinical plausibility of such transitions (i.e. why in clinical practice patients need to be sustained on B-VEC after achieving the very mild state where BSC can serve the same function).
- b) Please explain the discrepancies between the TP matrices used for BSC from the GEM/OLE trials and the ones from the EASE trial. For example, the TP matrix from the latter suggests that every 3 months 96% transition from the very mild to the mild state and that 76% transition from the severe to the moderate state.

a) B-VEC is a topical, redosable gene therapy designed to restore the structural stability of the skin for directly treated wounds, via delivery of the COL7A1 gene and functional correction of COL7 expression. Clinical trial data demonstrate that B-VEC not only accelerates wound closure but also significantly enhances the durability of healing compared to BSC, representing a transformative improvement in the management of DEB.

The transition to the Very Mild health state reflects this durability of response, as patients experience substantial reductions in wound burden. However, DEB is a chronic, genetic condition, and skin fragility persists even after wound closure due to ongoing cellular turnover and trauma-related injury. While B-VEC is not applied on closed wound areas, reapplication is needed when wounds reopen to ensure that healing is promptly reinitiated and sustained. This approach prevents disease progression and reversal to more severe health states, and helps patients maintain long-term benefits and avoid complications associated with more severe health states.

In contrast, to B-VEC, BSC does not address the underlying cause of the disease and therefore, patients treated with BSC experience wound recurrence and progression. The modelled transitions are consistent with the mechanism of action of B-VEC and clinical evidence, which shows that B-VEC enables sustained improvement but requires intermittent use in response to wound recurrence to maintain optimal outcomes.

As the skin cells regenerate, the cells present during delivery of the COL7A1 gene are being replaced and therefore, intermittent redosing with B-VEC is required to ensure that reopened wounds are promptly closed again and to sustain the restored structural integrity of the skin over the long term. Given that DEB wounds are dynamic and can reopen without treatment, maintenance treatment with B-VEC is required to keep patients in the Very Mild health state and ensure that patients receive optimal benefit.

b) The TP matrix from the EASE trials is based on monthly cycles, whereas the current model simulates transitions using 3 months cycles. In the BSC arm, improvement is observed in the first month, but in the second month, most patients return to the worse health state. Improvement observed in the first month likely represents regression to

the mean/placebo effect, which is no longer observed by 3 months. Figure 2.c page 68 of the CS demonstrates this perceived placebo effect.

Additionally, this is supported by data reported in HST28 Committee Papers, Table 10 (Page 46 of 173). This table shows that the distribution of patients by BSA with open wounds (<10%, 10–25%, >25%) in the control (BSC) arm remained largely unchanged between the baseline of EASE double-blind study and the baseline of the OLE phase. This suggests that any improvement seen early in treatment was not sustained, consistent with our modelling approach.

We would like to highlight that the BSC TP in the HST28 model result in the entire cohort in the severe health state transitioning out of that state after a single monthly cycle, with no return to the severe state over the remaining model time horizon. This pattern does not align with the observed distribution of patients by BSA with open wounds reported in Table 10 of the company submission (Page 46 of 173 of HST28 Committee Papers), where the proportion of patients with >25% BSA open wounds in the BSC arm remains relatively stable between the baseline double-blind and OLE phases of EASE. This should also be taken into consideration when comparing the TP matrices used for BSC from the GEM/OLE trials and the ones from the EASE trial.

B6. CS, p88: The split between RDEB and DDEB is based on Bruckner *et al.* However, this considers only the 33 respondent patients and not the overall sample including respondent caregivers (i.e. 31 DDEB and 53 RDEB). Please amend the model and update the results.

We have amended the model to use the overall sample of Bruckner *et al* and updated the results.²⁰ This modification changed the iNMB in the model base case from £[REDACTED] to £[REDACTED] in the comparison versus BSC and from £[REDACTED] to £[REDACTED] in the comparison versus BBE.

B7. CS, Section 3.3.4: Please explain why different per-cycle rates by severity were given for complete mitten deformity of hand although the p-value in Table 3.18 was not significant.

While the p-value did not reach statistical significance, likely due to the limited sample size, clinical expert input has confirmed that B-VEC treatment is expected to have an impact on the occurrence of mitten deformity due to the B-VEC mechanism of action.

In DEB, mitten hand deformity is a result of progressive blistering and scarring. As treatment with B-VEC is expected to lead to consistent and durable wound closure, it is also expected that the occurrence of mitten deformities would be less likely. Additionally, a study of patients with RDEB demonstrated that the cumulative risk of pseudosyndactyly of the hands is the highest in patients with the severe subtype.²¹ Given these observations, clinical expert input, and the finding that the occurrence of complete mitten deformity of hand was numerically higher in more severe health states in Eng et al., it was deemed appropriate to model rates of complete mitten hand deformity according to health state.

B8. CS, Figure 3.3: Please explain how the parametric RDEB-NS and RDEB-S survival curves were obtained. Was a survival analysis undertaken?

The Kaplan-Meier curves from the publication by Petrof et al (2022)²² were digitised, pseudo-patient level data were constructed using the Guyot algorithm, and then parametric survival curves were fitted to the data. Exponential, Weibull, log-normal, log-logistic, Gompertz and Generalized Gamma curves were fitted. Model fit statistics are presented in Table 15. Based on these the Exponential curve was selected for the model base case as it had the best statistical fit to the RDEB-Non-Severe curve.

In addition, the curves in the publication by Petrof et al represent survival from birth.²² As patients enter the model at a later age (depending on the age subgroup), it would not be appropriate to use a parametric curve that does not represent a constant hazard of death. Therefore, the exponential curve was then selected for the RDEB-Severe curve.

Alternative parametric curves can be selected in the executable model in Excel on the Mortality sheet, in row 75, although these alternatives are technically not appropriate.

Table 15 Parametric model fit statistics

	Exponential	Weibull	Log-Normal	Log-Logistic	Gompertz	Generalized Gamma
RDEB-Non-severe						
AIC	221.22	222.95	224.95	222.94	222.88	224.93
BIC	223.83	228.16	230.16	228.15	228.09	232.75
RDEB-Severe						
AIC	865.32	828.21	855.40	847.73	824.50	822.16
BIC	867.93	833.42	860.61	852.94	829.71	829.98

AIC= akaike information criterion; BIC= bayesian information criterion; RDEB=recessive dystrophic epidermolysis bullosa.

B9. CS, Table 3.28: Eng *et al.* states that “*there was no significant trend between severity and use of medications for itch, constipation, or topical antibiotics*”. Please justify why differences were assumed for such medications between the different health states.

While Eng *et al.* (2021) reported no statistically significant trend in the use of medications for itch, constipation¹⁹, or topical antibiotics across severity groups, this likely reflects the limitations of the study design, including relatively small sample sizes, reliance on binary (yes/no) reporting rather than dosage/frequency, and as acknowledged by the authors, its design may have lacked the sensitivity to detect meaningful trends in medication use.¹⁹

RDEB patients included in Eng *et al.* suffered from chronic and recurrent wounds (937 recurrent wounds and 289 chronic open wounds in 85 patients), severe and chronic pain, itch, infections, anaemia, malnutrition, and life-limiting complications.¹⁹ Under BSC, even when wounds appear closed, they often reopen quickly due to their inherently recurrent nature, leading to persistent cycles of wound opening and healing. As a result, the use of symptomatic medications such as topical antibiotics, anti-itch treatments, and pain relief often remains high. Thus, the absence of a statistical trend in Eng *et al.* does not indicate that there are no differences in the use of these medications by disease severity in real-world clinical practice; in fact, in the current clinical practice, some treatments such as topical antibiotics or anti-itch medications, are used so often by all patients that it can be hard to see how their use change across disease severity levels. In contrast, B-VEC's mechanism of action is expected to interrupt this cycle, thereby reducing both the frequency of wound recurrence and the associated need for symptomatic treatment.

By addressing the underlying genetic cause of skin fragility, rather than merely managing symptoms, B-VEC has been shown to result in durable wound closure. As a consequence, patients are likely to experience a reduced need for symptomatic treatments, including topical antibiotics (used to manage infected wounds), anti-itch agents (for chronic pruritus), and pain relief medications, which are commonly required in the context of open or recurrent wounds.

Thus, while Eng *et al.* did not report statistically significant trends for some medications, it seemed appropriate to include them in the model to reflect this

plausible shift in healthcare resource use, which is essential to assess the full clinical and economic impact of a disease-modifying therapy like B-VEC.¹⁹

B10. Please comment on why mortality, non-cutaneous clinical manifestations and concomitant medications not related to the wounds would differ between the health states considering that B-VEC acts only on the skin level, and not on the other organs such as the ones listed in Table 1.5.

The larger the BSA with open wounds, the greater the clinical complications, symptoms, impairment, and consequently, the disease severity. In general, the more severe and widely distributed the blistering on the skin, the more likely it is for multiple extracutaneous sites to also be involved.²³ In the study by Eng et al., 2021, the self-reported disease severity was significantly correlated with occurrence of extracutaneous manifestations such as anaemia, complete or partial mitten deformity of foot, use of gastrostomy tube, infections, osteoporosis and SCC.¹⁹

While B-VEC is topical, it modifies the underlying cause of DEB by introducing a functional copy of the COL7A1 gene and therefore, has an indirect impact on systemic complications of DEB. Some complications of DEB, such as mitten hand and foot deformities result from a persistent cycle of blistering, altered wound healing, and reopening. Because B-VEC improves wound healing and reduces the probability of wound reopening, it is expected that it may lead to a reduced occurrence of mitten hand and foot deformities.

Similarly, SCC occurs after continuous opening and closing of wounds and infections over time, with increasing incidence with age due to the recurring wound cycles in patients with DEB. Additionally, the prevalence and aggressiveness of SCC in DEB may be a direct consequence of COL7 deficits.²⁴⁻²⁶ Therefore, B-VEC would reduce the probability of SCC by restoring the function of the COL7 gene and reducing the recurrence of wound cycles. Given that SCC is a leading cause of mortality in patients with DEB, reduced occurrence of SCC is expected to lead to prolonged survival.

Although B-VEC does not directly address extracutaneous manifestations of DEB, it keeps patients in less severe health states, which are associated with a lower rate of these complications. Based on this information, it was appropriate to model mortality, extracutaneous complications and associated use of medications according to health

state. Accordingly, modelled mortality curves were validated by UK clinicians. Additional details regarding the relationship between wound burden and the sequelae of DEB are presented in response to question B18.

B11. Why does the modelling assume 90% compliance when the CSR for GEM-3 states that “ [REDACTED] ”.

The proportion in the intention to treat population that had treatment compliance greater than 90% was indeed [REDACTED]. However, the mean compliance in this population was [REDACTED] (CSR table 14.1.4.2). The mean compliance in the CS base case analysis was based on the per-protocol population in GEM-3, where the mean compliance was [REDACTED]% (CSR table 14.1.4.3). We have provided a scenario analysis using [REDACTED] instead of [REDACTED] compliance in response to question B1.

B12. Please explain why only the costs associated with clinical manifestations were considered in the economic analysis, but not the associated impact on quality of life.

The health-state utilities used in the model were derived from a vignette-based study, developed to capture the overall impact of DEB on patient quality of life. This study was conducted in the UK general population and included a discrete choice experiment (DCE) embedded alongside vignette-based valuation. Participants (n=909) evaluated health-state descriptions that already integrated the typical clinical and functional burden associated with each severity level of DEB (e.g., wound area, pain, disability, infection risk).

Given that these health-state utilities likely already reflect much of the QoL burden from key clinical manifestations, including additional disutility values linked to those same manifestations would risk double counting.

Nonetheless, the DCE provided disutility estimates for specific clinical features of DEB, including:

- Hand function impairment
- Fatigue
- Burning sensation

- Infection
- Loss of independence (as a psychosocial attribute)

These were valued at three severity levels (none, some, severe)—except for burning sensation, which was binary. The table below (Table 16) summarises the resulting disutility values from the DCE and their 95% confidence intervals. Full details on the method of the DCE is reported in the Vignette study report attached to these response document.

Table 16 Anchored general population disutility values obtained from the DCE

Attribute	Level*	Disutility**	95% CI	
			LL	UL
Hand Function	3	0.000	-	-
	2	-0.165	-0.216	-0.119
	1	-0.357	-0.418	-0.304
Fatigue	3	0.000	-	-
	2	-0.019	-0.061	0.018
	1	-0.110	-0.155	-0.070
Burning Sensation	2	0.000	-	-
	1	-0.137	-0.175	-0.104
Infection	3	0.000	-	-
	2	-0.074	-0.117	-0.036
	1	-0.165	-0.213	-0.122
Loss of Independence	3	0.000	-	-
	2	-0.165	-0.216	-0.119
	1	-0.376	-0.436	-0.322

CI, confidence interval; LL, lower level; UL, upper level.

* Levels: (3) No problems; (2) Some problems; (1) Severe problems, aside from 'Burning Sensation', where the levels were binary: (2) No burning sensation; (1) Burning sensation.

** The disutility value for each level was calculated by dividing the interaction coefficients () by the duration coefficient.

To explore the potential additional utility burden associated with clinical manifestations of DEB, a scenario analysis was incorporated into the revised version of the model. In this scenario, the utility decrements related to both reversible and irreversible clinical manifestations were applied using the multiplicative approach recommended by Ara and Brazier (2017),²⁷ ensuring an appropriate adjustment to baseline health-state utilities while avoiding overestimation of combined disutility effects.

Separate calculation was performed for reversible and irreversible clinical manifestations due to differences in how their prevalence evolves over time. For reversible manifestations, the model assumes a fixed proportion of the cohort affected within each health state, meaning the prevalence does not change over time. This

reflects the transient nature of these events, which can resolve and recur without accumulating over the model horizon. Differently for the irreversible manifestations, the proportion of cohort with irreversible manifestation changes over the time horizon of the analysis. This reflects the irreversible nature of these manifestations—once developed, patients do not recover from them even if they subsequently transition to a milder health state. As a result, the prevalence of irreversible manifestations increases over the model time horizon, accounting for both patients who had the complication at baseline and those who develop it during the simulation.

The two sources of utility decrements used to reflect the quality-of-life impact of clinical manifestations were:

- The discrete choice experiment (DCE) conducted alongside the vignette study (as described above), and
- The study by Sullivan et al., which reports EQ-5D-based utility values for a wide range of conditions in the UK general population.²⁸

The multiplicative approach was then used to estimate the utility decrements of the multiple co-occurring reversible and irreversible DEB manifestations. We applied this method by multiplying the baseline utility (in the absence of any clinical manifestation = general population) by the product of ratios of the utility for a given condition relative to the utility of the general population. Table 17 below provides a summary of the utility decrements for each individual clinical manifestation, as reported in the respective source, and the combined utility decrements associated with each possible combination of manifestations, after applying the multiplicative method.

Table 17 Utility decrement associated with clinical manifestations of DEB included in the CS model

Clinical manifestation	Utility decrement	Source, notes on calculation
<i>Reversible clinical manifestations</i>		
Infections	-0.120	DCE – Infection, average between severe problem (-0.165) and some problem (-0.074). See Table 16
Anaemia	-0.036	Sullivan et al, 2011 - Iron Deficiency Anemias
Osteoporosis	-0.042	Sullivan et al. 2011 - Osteoporosis

Infections and anaemia	-0.150	Ara and Brazier 2017 – multiplicative approach: = $-(u_{GP} - (u_{GP} * (u_{INF} / u_{GP}) * (u_{ANE} / u_{GP})))$
Infections and osteoporosis	-0.156	Ara and Brazier 2017 – multiplicative approach: = $-(u_{GP} - (u_{GP} * (u_{INF} / u_{GP}) * (u_{OST} / u_{GP})))$
Anaemia and osteoporosis	-0.076	Ara and Brazier 2017 – multiplicative approach: = $-(u_{GP} - (u_{GP} * (u_{ANE} / u_{GP}) * (u_{OST} / u_{GP})))$
Infections and anaemia and osteoporosis	-0.186	Ara and Brazier 2017 – multiplicative approach: = $-(u_{GP} - (u_{GP} * (u_{INF} / u_{GP}) * (u_{ANE} / u_{GP}) * (u_{OST} / u_{GP})))$
Irreversible clinical manifestations		
SCC	-0.013	Sullivan et al. 2011 - Other Malignant Neoplasm of the Skin
Complete or partial mitten deformity of foot	-0.036	Sullivan et al. 2011 - Acquired foot deformities
Complete mitten deformity of hand	-0.261	DCE – Hand function, average between severe problem (-0.357) and some problem (-0.165). See Table 16
SCC and deformity of foot	-0.049	Ara and Brazier 2017 – multiplicative approach: = $-(u_{GP} - (u_{GP} * (u_{SCC} / u_{GP}) * (u_{FOOT} / u_{GP})))$
SCC and deformity of hand	-0.271	Ara and Brazier 2017 – multiplicative approach: = $-(u_{GP} - (u_{GP} * (u_{SCC} / u_{GP}) * (u_{HAND} / u_{GP})))$
Deformity of foot and hand	-0.287	Ara and Brazier 2017 – multiplicative approach: = $-(u_{GP} - (u_{GP} * (u_{FOOT} / u_{GP}) * (u_{HAND} / u_{GP})))$
SCC and deformity of foot and deformity of foot and hand	-0.296	Ara and Brazier 2017 – multiplicative approach: = $-(u_{GP} - (u_{GP} * (u_{SCC} / u_{GP}) * (u_{FOOT} / u_{GP}) * (u_{HAND} / u_{GP})))$

DCE, discrete choice experiment; GP, general population; SCC, squamous cell carcinoma; u, utility.

For the reversible manifestation, starting from the per-cycle probability associated to each manifestation reported in Table 3.19 of the CS, we calculated the proportion of the cohort in a given health state with one but not the other two clinical manifestation as in the following example, in which P signifies prevalence: $P_{infection\_only} = P_{infection} \times (1 - P_{Anemia}) \times (1 - P_{Osteoporosis})$. Similarly, the proportion of the cohort in a given health state with two conditions was calculated as, for example, $P_{infection\&Anemia} = P_{infection} \times P_{Anemia} \times (1 - P_{Osteoporosis})$. The proportion of the cohort in a given health state with all three conditions was calculated as $P_{infection} \times P_{Anemia} \times P_{Osteoporosis}$. The proportion of the cohort without any of the conditions was given by $(1 - P_{infection}) \times (1 - P_{Anemia}) \times (1 - P_{Osteoporosis})$. These were assigned a utility decrement of 0.

To estimate weighted utility decrements by health state, we multiplied the disutility values for each individual reversible manifestation—or combinations of manifestations—by the proportion of the cohort experiencing those manifestations within each health state. This produced a composite disutility adjustment for each health state, reflecting the QoL burden attributable to reversible clinical manifestations

(Table 18). These weighted utility decrements were then applied to the proportion of the cohort in each health state across the model time horizon.

Table 18 Utility decrements due to reversible clinical manifestation, by health state

Health-state	Utility decrement
Very mild	-0.088
Mild	-0.089
Moderate	-0.093
Severe	-0.095

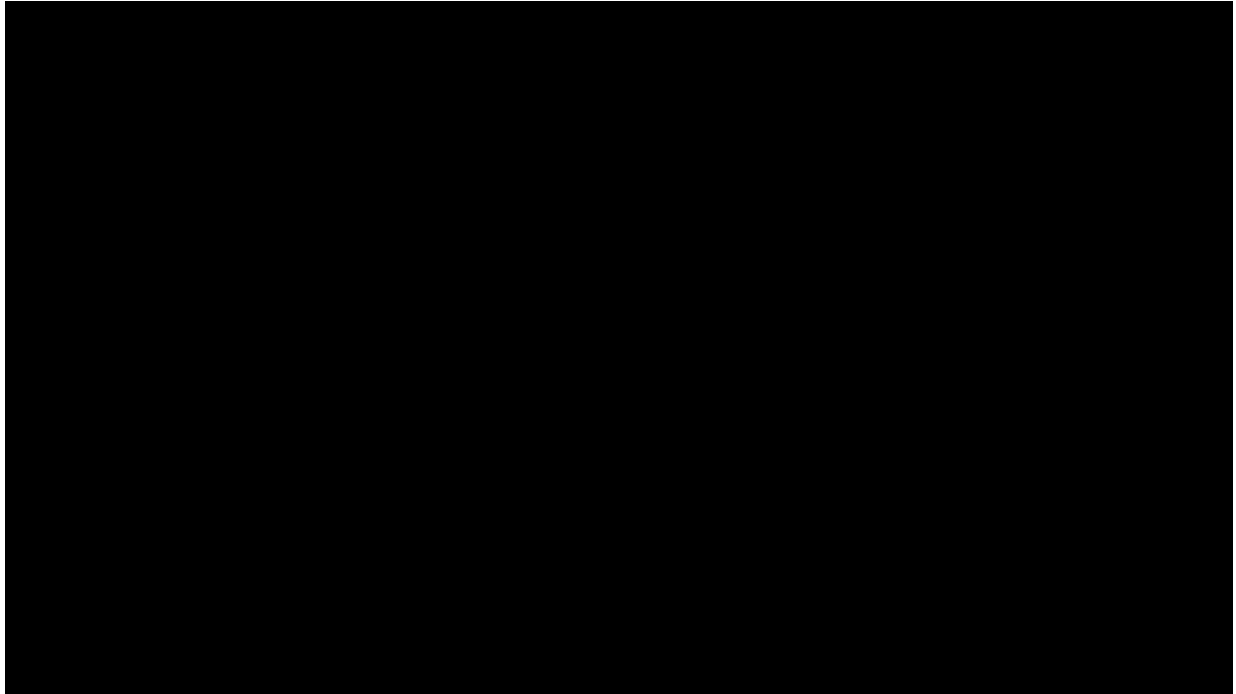
A similar approach was used for irreversible manifestations. However, the proportion of the cohort affected by each irreversible manifestation was based on the cumulative prevalence within each health state at each model cycle accounting both for patients who had the complication at baseline and for those who develop it during the simulation. The calculation was therefore done within the Markov engine of each comparator arm. This time-varying prevalence of irreversible manifestations — individual or cooccurring — was then combined with the corresponding disutility values (Table 18) to derive dynamic utility decrements, which were applied throughout the model time-horizon.

Including the impact of clinical manifestations of DEB on the quality of life, the incremental QALYs for B-VEC increase to 16.97 and 223.16 in the comparison vs. BBE and BSC, respectively. The ICER remains dominant. A more detailed overview of the results of this scenario analysis are presented as part of the response to question B1.B13. Table 3.40 and Table 3.41: Please explain how using the lower value for either distribution of patients for RDEB or DDEB moves the NMB in the same direction.

We thank the EAG for noticing the respective parameters for the proportion of RDEB and DDEB patients were not linked when the one-way sensitivity analysis (OWSA) was run, causing the analysis to increase or decrease one of the proportions without adjusting the other one accordingly. We noticed that this was the case in all places where the Dirichlet distribution was used (i.e., distribution over age subgroups, distribution over disease subtypes, and baseline distribution over the health states). These updates have been implemented in the model. The updated tornado diagrams

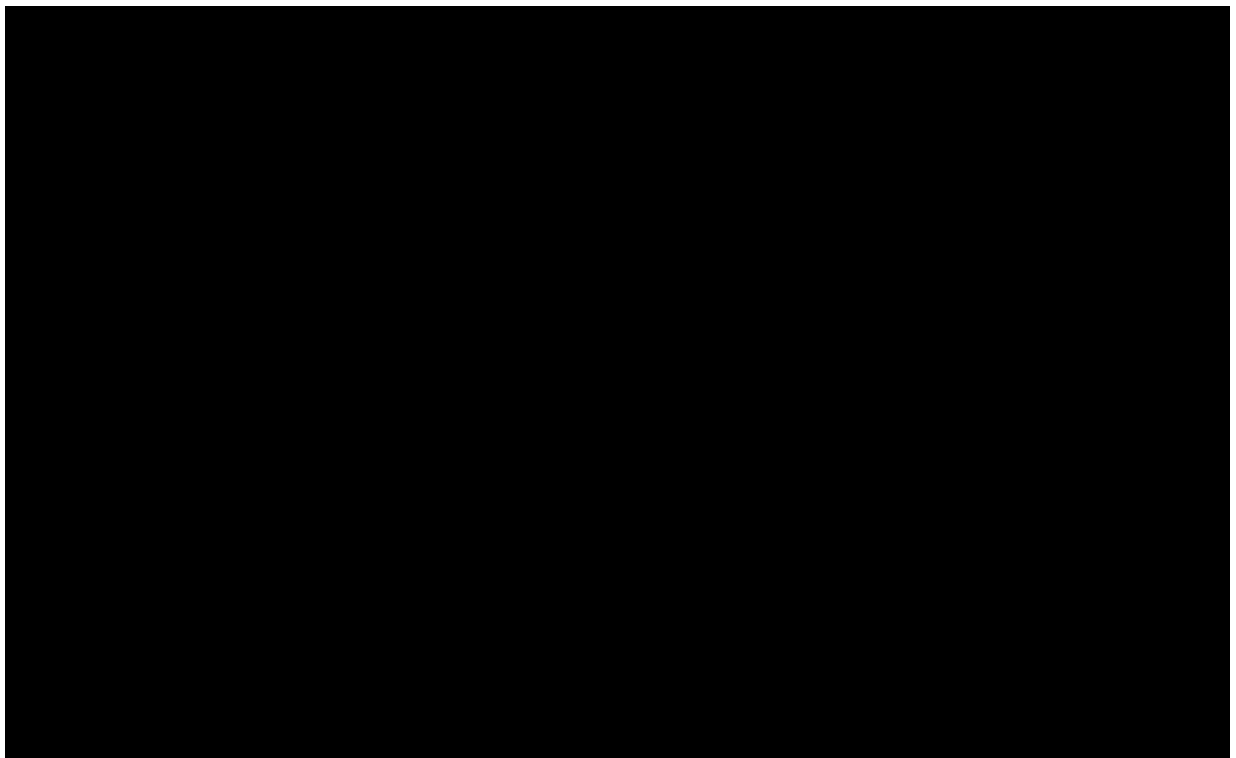
are provided in Figure 3 for the comparison to BSC and in Figure 4 for the comparison vs BBE.

Figure 3 Tornado diagram for B-VEC vs BSC



B-VEC=beremagene geperpavec; BSC=best supportive care; DEB=dystrophic epidermolysis bullosa; NMB=net monetary benefit; WTP=willingness to pay.

Figure 4 Tornado diagram for B-VEC vs BBE



B-VEC=beremagene geperpavec; BBE=birch bark extract; DEB=dystrophic epidermolysis bullosa; NMB=net monetary benefit; WTP=willingness to pay.

B14. Model, 'Mortality' AC1287: The proportion of RDEB-S (2.43%) was estimated from a cohort of patients including 26.65% JEB; which is outside the scope of this appraisal. Please reweight the proportions and use the new estimate in the model base-case.

Although patients with JEB are outside of the scope of this appraisal, the proportion of patients with RDEB-S used to calculate survival for the overall population in the model was only applied for the validation of the replication of the HST28 model. As discussed in CS Section 3.3.1.2, this proportion is not relevant for the current model analyses, as it does not differentiate survival by the model health states. As detailed in the response to question, B10, B-VEC would be expected to have an (indirect) impact on mortality, given that it acts by addressing the underlying cause of the disease (i.e., by introducing a functional copy of the COL7A1 gene). Therefore, it is not appropriate to use the same approach for mortality as used in HST28, given that BBE is not expected to affect mortality.

Patient level simulation

B15. [Priority] The company's patient level simulation should be sufficiently flexible to generate transition matrices for an alternative set of health states. Please use the patient level simulation to estimate transition matrices for BSC and B-VEC for the 6 health states employed in the HST28 model. Please use these to conduct an indirect comparison (as requested at question A34) between BSC, B-VEC and BBE using the HST28 model structure. The EAG's rationale for requesting this is that it would significantly reduce the number of assumptions required to make the indirect comparison.

Inclusion of B-VEC in the replicated HST28 model

As agreed with the NICE team and EAG during the meeting on 14 May 2025, we will provide the transition matrices with 6 health states at a later date. In the meantime, we have included a B-VEC arm in the replicated HST28 model, to allow for a cost-effectiveness analysis of B-VEC vs BBE within the same modelling framework as was used for HST28 (Table 19). Since the HST28 model does not include separate cohorts for the age groups, we have weighted the transition probabilities for each age group by the respective distribution at baseline.

Using the reproduced HST28 model, adapted to reflect a 4-health-state structure and incorporating the adjustments detailed in the response to Question B36, the resulting cost-effectiveness outcomes are presented in Table 20. These results include the application of a back-calculated PAS discount on the BBE list price of 74%.

It is important to note that using the same modelling framework as HST28 is not appropriate for the evaluation of B-VEC, as several key elements included in our current model—critical for assessing the clinical and economic value of B-VEC—are not captured in the HST28 model, as outlined in the response to Question B4. These differences are key drivers of variation in QALYs, costs, and the ICER between the two models. The primary differences include:

- **Utility Values:** in the current submission, utilities were derived from the vignette study, in which utilities were gathered through EQ-5D-3L, the NICE-preferred instrument, with utilities from HST28 presented in a scenario analysis. Justification of this approach is provided in CS, in Section 3.4.5.
- **Inclusion of Clinical Manifestations:** our model aimed to capture the benefit of B-VEC treatment in both accelerating and maintaining wound closure, and consequently preventing the irreversible clinical manifestations and reducing the risk of reversible manifestations associated with the presence of open wounds. The inclusion of clinical manifestations is therefore an important aspect of the benefit of B-VEC treatment. Clinical manifestations were not included in the in the HST28 model. A more detailed discussion on this topic is provided in the response to question B4.
- **Mortality:** our model differentiate mortality by health state, recognizing that patients in more severe states face higher mortality risk. Similarly to the rationale on the inclusion of clinical manifestation, this is important when assessing the value of B-VEC, which is associated with durable response. In contrast, the HST28 model applies a uniform mortality rate across the cohort.
- **Baseline Health-State Distribution:** the baseline distribution in our model is based on real-world observational data from RDEB and DDEB patients,²⁰ leading to a higher proportion of patients in more severe health states at baseline. In HST28, patients are evenly distributed across six health states,

resulting in more patients in mild states in the comparator arms, who are then assumed to remain stable for the entire time horizon.

To enhance transparency, we conducted a scenario analysis where the following parameters were adjusted in our model to align with those used in the HST28 model:

- Utilities: HST28 utility values used (impacts QALYs)
- Clinical manifestations: excluded from the model (impacts costs)
- Mortality: modelled uniformly across the cohort, not by health state (impacts costs and QALYs)
- Baseline health-state distribution: taken from HST28 model (impacts costs and QALYs)
- BSC arm: the transition probabilities were set equal to CCM arm in HST28 model (impact costs and QALYs in comparison vs BSC only)
- Bandage costs: based on HST28 model
- Inflation removal: monitoring and bandage costs were not applied price inflation (impacts costs)
- Concomitant medications: excluded (impacts costs)
- BBE price: includes the estimated PAS discount of [REDACTED] (impacts costs)

The results (discounted) of this scenario analysis showed a lower total cost of by [REDACTED] compared with BBE and an incremental cost of [REDACTED] versus BSC, with incremental QALYs of 5.14 and 7.43, respectively (Table 21 and Table 22).

A relatively small residual difference remains between the results in the two models. This is attributable to a structural difference: in our model, the cohort is simulated by age group, while in the HST28-replicated model, a single cohort is simulated. This is primarily impacting the B-VEC arm, which when included in the HST28 model was simulated via aggregated transition probabilities and vial consumption, rather than by age cohort.

Table 19 Discounted Base-case results from replicated HST28 model (including back-calculated PAS discount for BBE)

	Life-Years	Patient QALYs	Caregiver QALYs	QALY	Cost (£)
B-VEC	23.61	13.09	37.57	50.66	██████
BSC	23.62	9.22	33.76	42.99	██████
BBE	23.62	10.33	35.04	45.36	██████
Comparisons					
B-VEC vs BSC	-0.01	3.86	3.81	7.68	██████
B-VEC vs BBE	-0.01	2.76	2.54	5.30	██████

BBE=birch bark extract; BSC=best supportive care; QALY: quality-adjusted life-year

Table 20 Results of base-case incremental cost-effectiveness analysis from replicated HST28 model (including back-calculated PAS discount for BBE)

Comparison	Inc. cost (£)	Inc. QALY	ICER (£/QALY)	NMB ((ΔQALYs*WTP - Δcost)), WTP = £ 51,000 (£)
B-VEC vs BSC	██████	7.68	██████	██████
B-VEC vs BBE	██████	5.30	██████	██████

BBE=birch bark extract; BSC=best supportive care; ICER=incremental cost-effectiveness ratio; NMB=net monetary benefit; WTP=willingness-to-pay

Table 21 Discounted Base-case results from current CEM with settings aligned to HST28 (including back-calculated PAS discount for BBE)

	Life-Years	Patient QALYs	Caregiver QALYs	QALY	Cost (£)
B-VEC	25.38	13.42	40.50	50.66	██████
BSC	25.49	9.45	37.02	42.99	██████
BBE	24.59	10.59	38.19	45.36	██████
Comparisons					
B-VEC vs BSC	-0.01	3.96	3.47	7.43	██████
B-VEC vs BBE	-0.01	2.83	2.31	5.14	██████

BBE=birch bark extract; BSC=best supportive care; QALY: quality-adjusted life-year

Table 22 Results of base-case incremental cost-effectiveness analysis from current CEM with settings aligned to HST28 (including back-calculated PAS discount for BBE)

Comparison	Inc. cost (£)	Inc. QALY	ICER (£/QALY)	NMB ((ΔQALYs*WTP - Δcost)), WTP = £ 51,000 (£)
B-VEC vs BSC	██████	7.43	██████	██████
B-VEC vs BBE	██████	5.14	Dominant	██████

BBE=birch bark extract; BSC=best supportive care; ICER=incremental cost-effectiveness ratio; NMB=net monetary benefit; WTP=willingness-to-pay

Indirect treatment comparison between B-VEC and BBE

To further explore the relative efficacy of B-VEC versus BBE, we conducted an ITC using the Bucher method, based on the proportion of cohort in each health state over

time. This analysis was performed within the replicated version of the HST28 model (adapted to include 4 health states plus death and a 3-month cycle length), and incorporated data from both B-VEC and BBE trials that inform the modelled distribution across health states.

The selected outcome for this indirect comparison was the difference versus BSC in the relative change in the proportion of patients in each health state over two consecutive model cycles. It was deemed infeasible to conduct a comparison on direct transition probabilities, as the original BBE and CCM transitions in HST28 are structured around monthly cycles and six health states, which are not directly compatible with the four-state, 3-month transition matrices obtained from the patient level simulation used in the B-VEC model.

The change in patient distribution across health states over time was calculated for the following arms:

- BBE: Using transition data from the HST28 model, which are based on changes in BSA with open wounds observed in the EASE trial.
- CCM (placebo): Using comparator data from HST28, also informed by the EASE trial.
- B-VEC: Using transition probabilities from the patient-level simulation, based on wound dynamics observed in GEM-1, GEM-3 and the OLE study.
- BSC (placebo): Also based on the patient-level simulation, informed by wound dynamics in the placebo arm of GEM-1 study.

The relative changes in health state distribution were computed for:

- Month 3 vs Baseline
- Month 6 vs Month 3
- Month 9 vs Month 6
- Month 12 vs Month 9

Beyond Month 12, the HST28 model applies a continuity matrix in the BBE arm. To avoid incorporating model-driven extrapolations rather than data-derived transitions, the comparison was therefore limited to the first 12 months of treatment.

The adjusted indirect comparison was then performed using the Bucher method, with the assumption that CCM and BSC placebo arms are comparable. This Bucher ITC may be considered an improvement compared to a naïve comparison, as it allows for the estimation of the relative efficacy of B-VEC vs BBE, preserving the within-study randomisation.

The relative treatment effect of B-VEC vs BBE was calculated as:

$$\hat{\gamma}_{BB} = \gamma_{BVEC} - \gamma_{BBE}$$

Where:

- γ_{BB} is the estimated difference in the relative change in the proportion of patients in each health state over two consecutive cycles between B-VEC and BBE.
- γ_{BVEC} is the estimated difference vs BSC (placebo) in the relative change in the proportion of patients in each health-state over two consecutive cycles for B-VEC, based on transitions derived from the patient level simulation used in our model (for both B-VEC and BSC).
- γ_{BBE} is the estimated difference vs CCM (placebo) in the relative change in the proportion of patients in each health-state over two consecutive cycles for BBE, based on HST28 model transitions (for both BBE and CCM).

Separate Bucher comparisons were conducted for each of the four health states: very mild, mild, moderate, and severe. The results from each Bucher indirect comparison are presented in Table 23.

Table 23 Bucher adjusted indirect comparison between B-VEC and BBE on the difference in the relative change in proportion of patients in each health-state over time

	Relative change in proportion of patients in health-state over two consecutive model cycles						
	Transitions from PLS based on GEM1, GEM3 and OLE in replicated HST28 model			Transitions from EASE in replicated HST28 model			Bucher ITC
	B-VEC	Placebo (BSC)	B-VEC vs placebo mean, SE ^a (95%CI ^c)	BBE	Placebo (CCM)	BBE vs placebo mean, SE ^a (95%CI ^c)	BBE vs B-VEC mean, SE ^b (95%CI ^c) p-value
Very mild health-state							
Baseline to day 90	■	■	■	1.16	0.67	0.49, 0.05 (0.4, 0.59)	■
Day 90 to day 180	■	■	■	1.07	1.00	0.07, 0.01 (0.06, 0.08)	■
Day 180 to day 270	■	■	■	1.08	1.00	0.08, 0.01 (0.06, 0.09)	■
Day 270 to day 360	■	■	■	1.06	1.00	0.06, 0.01 (0.05, 0.07)	■
Mild health-state							
Baseline to day 90	■	■	■	1.20	0.71	0.49, 0.05 (0.39, 0.59)	■
Day 90 to day 180	■	■	■	1.09	1.00	0.09, 0.01 (0.07, 0.11)	■
Day 180 to day 270	■	■	■	1.07	1.00	0.07, 0.01 (0.06, 0.08)	■
Day 270 to day 360	■	■	■	1.06	1.00	0.06, 0.01 (0.05, 0.07)	■
Moderate health-state							
Baseline to day 90	■	■	■	1.20	1.54	-0.33, 0.03 (-0.4, -0.27)	■
Day 90 to day 180	■	■	■	0.94	1.00	-0.06, 0.01 (-0.07, -0.05)	■
Day 180 to day 270	■	■	■	0.94	1.00	-0.06, 0.01 (-0.07, -0.04)	■
Day 270 to day 360	■	■	■	0.95	1.00	-0.05, 0.01 (-0.06, -0.04)	■
Severe health-state							
Baseline to day 90	■	■	■	0.00	0.00	0, 0 (0, 0)	■
Day 90 to day 180	■	■	■	0.00	0.00	0, 0 (0, 0)	■

Day 180 to day 270	■	■	■	0.00	0.00	0, 0 (0, 0)	■
Day 270 to day 360	■	■	■	0.00	0.00	0, 0 (0, 0)	■

B-VEC=beremagene geperpavec; BBE=birch bark extract; BSC=best supportive care; CCM=current clinical management; CI: confidence interval, ITC=indirect treatment comparison; OLE=open-label extension; SE: standard error.

Notes: Bold p-value indicates statistical significance. a) SE was calculated assuming 10% of mean difference. b) the SE was calculated as square root of the sum of $SE_{B-VEC \text{ vs placebo}}^2$ and $SE_{BBE \text{ vs placebo}}^2$. c) The 95% CI was calculated assuming a normal distribution

The adjusted differences (Table 23) between B-VEC and BBE obtained from the Bucher ITC were subsequently implemented within the executable cost-effectiveness model in the current submission to estimate the proportion of the cohort transitioning between health states and to assess the impact on the cost-effectiveness between B-VEC, BBE and BSC (placebo). Four alternative scenarios were developed to assess the robustness of model outcomes to different assumptions regarding baseline distributions and source of transition probabilities. The results of these scenario analyses are presented in the response to Question B1.

The following scenarios were tested:

- Scenario 1
 - The baseline health-state distribution was derived from Bruckner et al. (in line with the assumption in the current submission, provided in Table 3.8 of CS);
 - The cohort distribution across health states in the BBE arm was estimated by applying the adjusted relative effect obtained from the Bucher ITC to the relative changes in the proportions of patients in each health-state over two consecutive cycles in the B-VEC arm (Table 24). This method was applied specifically to the very mild, mild, and moderate health states. The proportion of patients in the severe health state was then estimated as the remainder, i.e. 1 minus the sum of the proportions in the other health states. An alternative approach, using the very mild state as the residual category, was also tested. However, this resulted in 0% of patients in the very mild state, which was deemed less conservative. Therefore, the chosen method, calculating the severe state as the residual, was retained as the more conservative and aligned with original transitions from EASE. To maintain consistency with the base case model, a continuity matrix was applied for the BBE arm beyond Month 12, as per current model assumptions. The cohort distribution across health states in the B-VEC and BSC arms (Table 25) was estimated based on transition probabilities derived from the patient-

level simulation, as per current submission (provided in Tables 3.16 and 3.17 of company submission).

- Scenario 2
 - The baseline health-state distribution was derived from Bruckner et al.²⁰ (in line with the assumption in the current submission, provided in Table 3.8 of company submission);
 - The cohort distribution across health states in the BBE and BSC arms (Table 24 and Table 26) was based on transition probabilities from the replicated HST28 model (provided in Tables 3.12 and 3.13 of company submission).
 - The B-VEC health-states distribution was calculated by applying the adjusted relative effect obtained from the Bucher ITC to the relative changes in the proportions of patients in each health-state over two consecutive cycles in BBE arm (Table 25). Beyond month 12, transitions derived from the patient-level simulation, as per current submission.
- The B-VEC health-state distribution was calculated by applying the adjusted relative effect obtained from the Bucher indirect treatment comparison (ITC) to the relative changes in the proportion of patients in each health state over two consecutive cycles observed in the BBE arm (Table 24). This method was applied specifically to the mild, moderate and severe health states. The proportion of patients in the very mild health state was then estimated as the remainder (i.e., 1 minus the sum of the proportions in the other health states). An alternative approach, using the severe health-state as the residual category, was also tested. However, this resulted in immediately 0% of patients in the severe state and a greater proportion of patients in the very mild health-state, which was deemed less conservative. Therefore, the chosen method, calculating the very mild state as the residual, was retained as the more conservative. For time points beyond Month 12, transitions derived from the patient-level simulation were applied, as per the current submission assumptions. Scenario 3

- The baseline health-state distribution was taken directly from the original HST28 model (provided in Table 3.11 of CS); The cohort distribution across health states in the BBE arm was estimated by applying the adjusted relative effect obtained from the Bucher ITC to the relative changes in the proportions of patients in each health-state over two consecutive cycles in B-VEC arm (Table 25). The same methodological approach described for Scenario 1 was taken. Beyond month 12, continuity matrix is applied, as per current model assumption.
 - The cohort distribution across health states in the B-VEC and BSC arms (Table 25 and Table 26) was based on the transition probabilities derived from the patient-level simulation, as per current submission (provided in Table 3.16 and 3.17 of CS).
- Scenario 4
 - The baseline health-state distribution was taken directly from the original HST28 model (provided in Table 3.10 of CS);
 - The cohort distribution across health states in the BBE and BSC arms (Table 24 and Table 26) was estimated based on transitions from the replicated HST28 model (provided in Tables 3.12 and 3.13 of CS).
 - The B-VEC health-states distribution (Table 25) was calculated by applying the adjusted relative effect obtained from the Bucher ITC to the relative changes in the proportions of patients in each health-state over two consecutive cycles in BBE arm. The same methodological approach described for Scenario 2 was taken. Beyond month 12, transitions derived from the patient-level simulation, as per current submission.

Table 24 Distribution of the cohort between health-states in the BBE arm, across the four scenarios explored

	Very Mild	Mild	Moderate	Severe
Derived based on relative effect B-VEC vs BBE from Bucher ITC, baseline distribution from Bruckner et al. (Scenario 1)				
Baseline	0.0%	21.6%	29.0%	49.3%
Month 3				
Month 6				

Month 9				
Month 12				
Derived based on transition probabilities from replicated HST28, baseline distribution from Bruckner et al. (Scenario 2)				
Baseline	0.0%	21.6%	29.0%	49.3%
Month 3	0.6%	26.0%	73.4%	0.0%
Month 6	0.7%	31.5%	67.8%	0.0%
Month 9	0.9%	36.2%	63.0%	0.0%
Month 12	1.0%	40.2%	58.8%	0.0%
Derived based on relative effect B-VEC vs BBE from Bucher ITC, baseline distribution from original HST28 model (Scenario 3)				
Baseline	0.8%	33.0%	49.5%	16.7%
Month 3				
Month 6				
Month 9				
Month 12				
Derived based on transition probabilities from replicated HST28, baseline distribution from original HST28 model (Scenario 4)				
Baseline	0.8%	33.0%	49.5%	16.7%
Month 3	1.0%	39.6%	59.4%	0.0%
Month 6	1.0%	43.2%	55.7%	0.0%
Month 9	1.1%	46.3%	52.6%	0.0%
Month 12	1.2%	49.0%	49.9%	0.0%

B-VEC=beremagene geperpavec; BBE=birch bark extract; ITC=indirect treatment comparison. Note for Scenario 1 and Scenario 3: the proportion of cohort in each health-state at a month 3 was calculated as: cohort in each health-state at baseline * (relative change in cohort month3 vs baseline in B-VEC arm – relative effect from Bucher ITC B-VEC vs BBE). Similarly this was done for month 6 vs month 3, month 9 vs month 6 and month 12 vs month 9. Example, Scenario 1 mild health-state month 3 vs baseline: 21.6% * (0.14 ‘see Table 23, B-VEC arm’ - (-1.35) ‘Table 23, Bucher ITC results’)

Table 25 Distribution of the cohort between health states in the B-VEC arm, across the four scenarios explored

	Very Mild	Mild	Moderate	Severe
Derived based on transition BSC probabilities from PLS in CS model, baseline distribution from Bruckner et al. (Scenario 1)²⁰				
Baseline	0.0%	21.6%	29.0%	49.3%
Month 3				
Month 6				
Month 9				
Month 12				
Derived based on relative effect B-VEC vs BBE from Bucher ITC, baseline distribution from Bruckner et al. (Scenario 2)²⁰				
Baseline	0.0%	21.6%	29.0%	49.3%
Month 3				
Month 6				
Month 9				
Month 12				
Derived based on transition BSC probabilities from PLS in CS model, baseline distribution from original HST28 model (Scenario 3)²⁹				
Baseline	0.8%	33.0%	49.5%	16.7%
Month 3				

	Very Mild	Mild	Moderate	Severe
Month 6				
Month 9				
Month 12				
Derived based on relative effect B-VEC vs BBE from Bucher ITC, baseline distribution from original HST28 model (Scenario 4)²⁹				
Baseline	0.8%	33.0%	49.5%	16.7%
Month 3	36.8%	0.0%	60.8%	2.5%
Month 6	73.2%	0.0%	26.8%	0.0%
Month 9	79.2%	0.0%	20.8%	0.0%
Month 12	87.6%	0.0%	12.4%	0.0%

B-VEC=beremagene geperpavec; BBE=birch bark extract; ITC=indirect treatment comparison. Note for Scenario 2 and Scenario 4: the proportion of cohort in each health-state at a month 3 was calculated as: cohort in each health-state at baseline * (relative change in cohort month 3 vs baseline in BBE arm + relative effect from Bucher ITC B-VEC vs BBE). Similarly this was done for month 6 vs month 3, month 9 vs month 6 and month 12 vs month 9. If the resulting proportion was a negative number, 0% was applied. Example, Scenario 2 mild health-state month 3 vs baseline: max (21.6% *(1.20 'see Table 23,, BBE arm' + (-1.35) 'see Table 23, Bucher ITC results')),0%)

Table 26 Distribution of the cohort between health states in the BSC arm, across the four scenarios explored

	Very Mild	Mild	Moderate	Severe
Derived based on transition BSC probabilities from PLS in CS model, baseline distribution from Bruckner et al. (Scenario 1)²⁰				
Baseline	0.0%	21.6%	29.0%	49.3%
Month 3				
Month 6				
Month 9				
Month 12				
Derived based on transition probabilities from replicated HST28, baseline distribution from Bruckner et al. (Scenario 2)²⁰				
Baseline	0.0%	21.6%	29.0%	49.3%
Month 3	0.4%	15.6%	84.1%	0.0%
Month 6	0.4%	15.6%	84.0%	0.0%
Month 9	0.4%	15.6%	84.0%	0.0%
Month 12	0.4%	15.7%	84.0%	0.0%
Derived based on transition BSC probabilities from PLS in CS model, baseline distribution from original HST28 model (Scenario 3)²⁹				
Baseline	0.8%	33.0%	49.5%	16.7%
Month 3				
Month 6				
Month 9				
Month 12				
Derived based on transition probabilities from replicated HST28, baseline distribution from original HST28 model (Scenario 4)²⁹				
Baseline	0.8%	33.0%	49.5%	16.7%
Month 3	0.6%	23.5%	76.0%	0.0%
Month 6	0.6%	23.5%	75.9%	0.0%
Month 9	0.6%	23.5%	75.9%	0.0%
Month 12	0.6%	23.6%	75.8%	0.0%

BSC=best supportive care; CS=company submission; PLS=patient-level simulation.

The results from the four scenario analyses are presented in Table 13, Scenarios 9 to 12. These show that the ICER for B-VEC versus BBE remains dominant across all scenarios, consistent with the results of the base case analysis. For B-VEC versus BSC, the ICER ranges from dominant to £17,694 per QALY, depending on the scenario tested. These findings confirm that B-VEC remains cost-effective across all tested scenarios, regardless of the source of the baseline health state distribution (Bruckner et al. vs. HST28), whether BSC arm is modelled using transition probabilities from our GEM wound dynamics or from EASE (replicated HST28 model), and whether ITC-adjusted or original model transitions are used for B-VEC and BBE.

B16. CS, Section 3.2.2.1.2.1: when describing wound closure in the BSC arm states, *“Using the average proportion of area closed per week and considering only the weeks where at least 50% of the wounds are still open (until week 6), it was found that 14.17% of the recurrent area that was open, closed spontaneously on a weekly basis.”* Does this mean that the rate of wound closure for BSC is based only on the first 6 weeks of data from GEM-1? If so, why is it necessary to discard data on wound closure after 6 weeks? Does this approach mean that wounds that closed more slowly than the median wound do not contribute to the estimate of rate of wound closure?

To calculate the weekly rate of closure for wounds treated with placebo in GEM-1, the area open of all wounds treated with BSC was summed, as if they were the total area open in a single patient. This was done for every week, and the change in area open from one week to another was calculated. The average across the weeks was then calculated. Wounds were censored from this analysis after they had closed for the first time, as for this specific analysis we were only interested in the rate of closure, and wound reopening was modelled separately. Due to censoring, the number of open wounds decreased over time, and after 6 weeks less than half of the wounds had not yet closed (i.e., were open) and contributed to the analysis. As each week was given the same amount of weight for this analysis, it was considered to only include weeks with a sufficient number of wounds contributing to the analysis.

Wounds that closed more slowly were contributing to the estimate, as their size was included in the total area open each week and therefore contributed to lowering the reduction in size.

To address the EAGs concern, we have conducted an alternative analysis, where the average over the entire period of GEM-1 was calculated by weighting each week by the number of wounds that contributed to the analysis, which resulted in an average rate of closure of 5.75% for wounds treated with placebo. A scenario analysis using 5.75% instead of 14.17% has been provided in response to Question B1.

For consistency, we have also conducted the same alternative analysis for wounds treated with B-VEC, which resulted in an average proportion of 33.53% of the wounds that closed every week instead of the 42.54% used for the company base case. The response question B1 also provides a scenario analysis where the rate of closure for both arms has been adjusted to use the alternative approach.

B17. CS, Section 3.2.2.1.2.2: “A normal distribution was assumed and the 25th and 75th percentiles were used to provide the lower-bound of the Moderate and Severe health states, respectively, while the average defined the lower-bound of the Moderate health state (Table 3.5).” Please provide the rationale for such an assumption and how this relates to Table 3.6. For example, the average number of chronic wounds seems to double from 1.5 in mild patients to 3.5 in moderate, however this is not the case for BSAP with open wounds (averages of 0.1 to 1% in mild and 1 to 10% in moderate, which is an increase by a factor of 10). Is this disconnect due to the fact the data in Table 3.6 are based on estimates from clinicians whereas the data in Table 3.5 are based on arbitrary cut-offs (e.g. 25th percentile) in the distribution of number of wounds from Eng *et al.* Please clarify if the clinical experts were shown the assumptions on the number of wounds in Table 3.5 before making the estimates in Table 3.6.

The number of wounds is not related to the size of the wounds, and the number of wounds and BSAP open do not necessarily need to be linked. Based on Eng *et al.* (Table IV) patients with milder disease have predominantly smaller wounds than patients with more severe disease.¹⁹ Clinicians who validated the model health states were shown the estimates for the number of wounds before estimating the BSAP definitions for the health states, and indicated that these estimates were reasonable, given the limited evidence.

B18. CS, Table 3.5: The EAG notes that Eng *et al.* uses patient self-report to classify severity, and this is not based on number of wounds but on, “impact on performing

activities of daily living and need for treatment.” On page 98 it is stated, “*the larger the BSA with open wounds, the greater the clinical complications, symptoms, impairment, and, consequently, the disease severity,*” citing Eng *et al.* to support his statement. Please clarify whether any of the data from Eng *et al.* provide information on the correlation between the clinical manifestations reported in Table 3.18 and either the number of wounds (as severity is defined in the model) or the BSAP with open wounds.

The study by Eng *et al.* 2021 provides evidence supporting a correlation between larger wound burden and increased clinical manifestations, which justifies the assumption made in the model.¹⁹ Specifically:

- Total wound area is associated with disease severity in DEB. Table IV reports the number of wounds and size category by disease severity level. Based on these numbers, we can observe that moderate and severe disease account for over 70% of all wounds, and nearly all large wounds. Severe disease alone accounts for approximately 50% of large wounds.
- Table III and accompanying text show that severe disease was significantly associated with multiple clinical complications, including anaemia, infections, osteoporosis, mitten deformity, SCC, and greater use of systemic medications like opiates and gabapentin.

Therefore, although clinical manifestations are not directly linked to wound number or BSAP in the publication, the observed pattern suggests that larger wound burden correlates with higher disease severity, which in turn correlates with a higher prevalence of clinical complications.

Moreover, Eng *et al.* state that their data demonstrate a clear link between larger wound size, worsening severity, and clinical burden, noting: “This study shows a significant correlation between larger wound size with worsening skin disease severity and quality of life in participants with RDEB. Worsening skin disease severity significantly correlated with key clinical manifestations” (see Conclusions in pp 1161 of Eng *et al.* 2021).¹⁹

In this context, the modelling assumption that larger BSA with open wounds is associated to greater prevalence of clinical complications is supported by the data

from Eng et al., even if a direct statistical correlation between BSAP or wound number and complications was not reported.

B19. CS, Section 3.2.2.1.3.2 provides a list of seven assumptions to calculate the median duration of wound closure for B-VEC.

- a) Please provide clinical rationale for the assumptions used.
- b) Based on this analysis, a median duration of closure was [REDACTED]. Please justify why such a difference exists between this duration and median duration of closure reported in Table 2.19 for GEM-1 (103 days).
- c) Why wound reopening for patients on B-VEC was not modelled in the same way as described for BSC in Section 3.2.2.1.2.2?
- d) Did patients enrolled in both GEM-3 and the OLE receive B-VEC between these studies? If not, then it is not appropriate to include the period between studies when calculating the wound reopening rate for B-VEC. Please provide an analysis in which patients who had their treatment interrupted are censored from the point treatment is interrupted and for the remainder of the analysis.

a) The assumptions used and their rationale for each are listed below:

Assumption 1: If the wound status (i.e., open or closed) remained the same during two consecutive visits (this includes the period between the last observation in GEM-3 and the first observation in OLE), it was assumed it had remained the same in the period between these visits.

Rationale: B-VEC acts by addressing the root cause of the disease, by delivering a functional copy of the COL7A1 gene. This effect is lost only when skin cells are renewed, and the wound is at risk of reopening spontaneously

Assumption 2: If the wound status was different during two consecutive visits, then a pro rata probability of it being open or closed was applied in the months in between

Rationale: This was done to extrapolate data between two consecutive observations. To address the EAGs concerns, we analysed data assuming that all wounds are either closed or open in all months between observations. The analysis resulted in a median duration of closure of [REDACTED] and [REDACTED] days respectively.

Assumption 3: Data were extrapolated to 25 months for all wounds, as this was the maximum duration of follow up;

- a. If a wound had closed and remained closed (under the assumptions 1 and 2) until the final visit, it was assumed to remain closed until Month 25;
- b. If a wound had had reopenings at any point in time, it was assumed that reopening occurred after 3 months, as this was the pattern typically observed. The period in between was imputed as per assumption 2;

Rationale: This assumption was made to have the same follow-up for each wound considered in the analysis. To address the EAGs concerns, we have analysed the data without any extrapolations, which did not change the median duration of closure from the ■ days in the base case. Additionally, when removing the extrapolations was combined with the extreme assumptions discussed under Assumption #2, the duration of closure was still ■ days when assuming that wounds were open in the months between observations during one of which a wound was open and during the other it was closed, and ■ days when assuming the wound was closed in the months between.

Assumption 4: The months where the probability of the wound being closed was at least 50% (i.e., 'likely to be closed'), were counted for each period that a wound was closed;

Rationale: This was the way to use the interpolations and extrapolations.

Assumption 5: One wound could have multiple periods during which it was closed, with a period in between where it had reopened

Rationale: It was observed that some wounds opened and closed more than once. Each of these episodes contributed to the analysis.

b) Considering the differences in study design between the GEM-1/2 and GEM-3 studies, it is not adequate to directly compare the duration of closure observed in the GEM-1/2 study and our analysis that combines the GEM-3 and OLE studies. Importantly, the phase 1/2 study consisted of various dosing regimens and treatment cycles alternating with observation periods over the course of approximately 12 weeks. Target wounds were monitored for off-administration closure duration through a wound monitoring application for up to 12 weeks post-administration. As such, considering the limited treatment duration (approximately 12 weeks) and the limited follow-up time (up to 12 weeks) in the GEM-1/2 it is expected that the median duration of wound closure (103 days) is lower than that observed in our analysis (■■■■■). As a reminder, in the phase 3 study patients were treated for 26 weeks, using a standardised weekly

administration regimen, followed by a 30 day-safety observation period. Additionally, after completion of the phase 3 study, patients had the option to enroll in an open-label study. In our analysis, the overall observation period was up to 26 months, including GEM-3, the interval up to enrolment in the OLE and the OLE period.

c) We wanted to maximise the available data using the maximum possible follow-up. Some patients from the B-VEC patients rolled over from GEM-3 to OLE, and a long follow-up is available for these patients. The ■ days estimate is in line with the decision by Haute Autorité de Santé in France, in which wounds were assumed to remain closed for 12 months.³⁰ To address the EAGs concern, we are providing a scenario analysis where we use the duration of closure of 103 days as observed in GEM-1.

d) Patients who were enrolled in both GEM-3 and OLE did not receive B-VEC between the two studies. However, given that B-VEC acts by addressing the underlying cause of the disease by delivering a functional copy of the COL7A1 gene, the assumption that the wound remained closed is reasonable. To address the EAGs concern, we are providing a scenario analysis based on only the OLE data (and not also GEM-3 and the period between the studies), which resulted in a median duration of closure of ■ days.

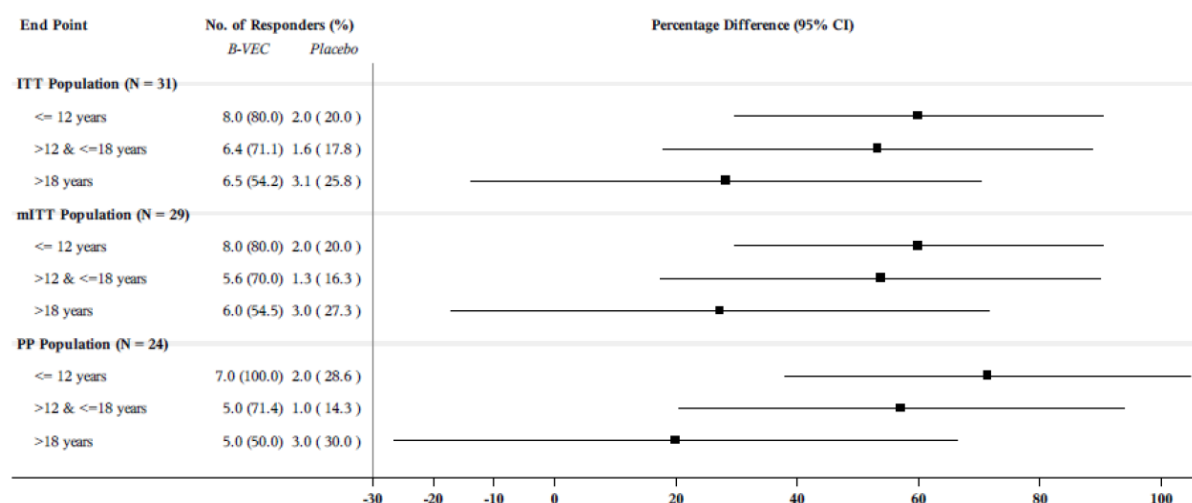
In summary, in response to this question, we are providing several additional scenario analyses for the duration of wound closure, results of which are presented in response to question B1:

- ■ days (GEM-3 + OLE without extrapolation and with conservative assumptions about wound closure between two visits during one of which the wounds was closed, and during the other the wound was open)
- ■ days (GEM-3 + OLE without extrapolation and with optimistic assumptions about wound closure between two visits during one of which the wounds was closed, and during the other the wound was open)
- 103 days (GEM-1)
- 150 days (OLE only)

B20. CS, Section 3.2.2.1.2.1 and 3.2.2.1.3.1: Assumptions for wound closure were based on a percentage decrease in wound area regardless of its initial size or patient's age group. Please provide clinical rationale for such an assumption.

Subgroup analysis of the primary efficacy endpoint at 6 months (GEM-3 CSR, Figure 5) showed that B-VEC demonstrated efficacy across all age categories: ≤12 years, >12 to ≤18 years, and >18 years (Figure 5). The responder rates were consistently in favour of B-VEC in each group, and the 95% confidence intervals overlapped, indicating no statistically significant differences in efficacy between age subgroups.

Figure 5 Forest plot of primary efficacy responder subgroup analysis by age category (imputed data)



B-VEC= beremagene geperpavec; CI=confidence interval; ITT=Intention-to-treat; mITT=modified intention to treat; PP=per protocol.

Source: Krystal Biotech, Data on File, GEM-3 CSR.³¹

Similarly, baseline wound size did not appear to influence wound healing. An exploratory analysis of GEM-3 data evaluated wound healing at 6 months across all primary and secondary wounds. This analysis showed a numerically higher proportion of wounds closed in wounds with larger baseline size (Table 27). However, as with the age subgroup analysis, the overlapping confidence intervals suggest no significant difference in wound healing based on baseline wound size. This was supported by a correlation analysis on the same data, which found no statistically significant relationship between wound size and proportion of wounds healed (correlation coefficient $r = 0.09$; p -value = 0.27).

Table 27 Proportion of wound healing in GEM-3 by baseline wound size among primary and secondary wounds, pooled B-VEC and placebo

Baseline wound size	N by category	Wound healing at 6 months, % (95% CI)
<20 cm ²	124	25.8 (8.2-43.4)
20 to <40 cm ²	31	41.9 (24.3-59.6)
40 to 60 cm ²	10	60.0 (28.0-92.0)

B-VEC= beremagene geperpavec; CI=confidence interval.

Source: Krystal Biotech, Data on File, GEM-3 CSR.³¹

Further evidence was obtained from GEM-1/2 data, where a correlation analysis between baseline wound size and time to wound closure, pooling B-VEC and placebo-treated wounds, produced a negative correlation coefficient that was not statistically significant (correlation coefficient $r = -0.24$; p -value = 0.23). This further confirms that initial wound size does not predict healing time.

Based on these findings, it is clinically justified to assume a consistent closure rate regardless of a wound initial size or patient's age group. Importantly, it should also be clarified that in the model, wounds are not modelled individually. Instead, wound closure is applied as a weekly probability, derived from the average proportion of wound area closed per week in GEM-1/2, which is applied to the total area of open wounds rather than individual wounds.

B21. CS, Section 3.2.2.1.2.2: Please comment on the validity of assuming that reopened wounds would grow back (one-off increase) to a fixed area regardless of any of the following factors: initial wound size, patient's BSA, and age group.

Given the low number of patients and wounds enrolled in the trial, there is not sufficient data available to assume different wound sizes by baseline wound or patient characteristics. We have evaluated the correlation between wound size at baseline and wound size at the time of wound reopening in GEM-1, and the correlation coefficient was 0.223 ($p=0.250$). Additionally, we have evaluated the correlation between patient age and size of wounds at the time of reopening in GEM-1, and the correlation coefficient was 0.250 ($p=0.274$). As data on about patient's BSA is not available from either of the trials, analyses for the correlation with wound sizes for that baseline characteristic was not possible.

Based on these findings we think it is appropriate to assume the same size of wounds at time of reopening, regardless of wound or patient characteristics at baseline.

B22. CS, Section 3.2.2.1.2.3: It's assumed that a fixed proportion of the recurrent wound area would become chronic every week where chronic wounds never close on BSC. The EAG does not understand the rationale for this assumption. If a wound is healing at a rate of 14% per week, then it cannot be classed as a chronic wound at 8 weeks simply because a proportion of the wound is not healed at 8 weeks. This is contrary to the estimation of the rate of wound healing which is assuming that the rate of change is constant over time (hence the exponential distribution applied by the company to estimate percent closed at week 8) and does not stabilise at 8 weeks. In addition, this assumption applies the same to all age groups; however, our clinician stated that younger patients are less liable to their wounds becoming chronic than older patients. Please provide the clinical rationale on the validity of assuming a constant rate of wound healing (at all ages) but only up until 8 weeks at which point wound healing abruptly stops.

The 14% healing per week is an average across all wounds, and is not applied to individual wounds, but rather to the entire BSA that is open with wounds. Some wounds heal faster than 14% per week, and some heal slower, or not at all, which are then considered to become chronic. The wounds that do not become chronic are still considered to heal at a rate of 14% each week.

B23. CS, Section 3.2.2.1.2.2: Please comment on the validity of assuming the same range for number of wounds per health state regardless of the patient's age group or BSA.

Because of the design of the GEM-3 trial, where each patient served as their own control, the data on the number of wounds could not be collected.³¹ Therefore, the number of wounds was taken from Eng et al. 2021, who did not stratify the data by the patient's age group or overall BSA.¹⁹ Due to a lack of data from clinical trials, data obtained from the literature were considered to be appropriate to use in the model. Additionally, as detailed in response to question B17, the estimates for the number of wounds were validated by clinicians. Clinicians were shown the estimates for the number of wounds before estimating the BSAP definitions for the health states and indicated that these estimates were reasonable.

B24. CS, Section 3.2.2.1.4 suggests that average BSAP per simulated patient could be tracked in the model. Please provide these model outputs for each modelled arm throughout the time horizon.

The updated version of the patient-level simulation now outputs a file with weekly values of the BSAP per simulated patient. The output file has two sheets; one for the B-VEC arm and one for the placebo arm.

B25. The CS description of the PLS does not mention any assumptions regarding the appearance of new wounds. Please explain how this was handled.

The appearance of new wounds was not considered in the PLS. Clinical expert input suggests that, although wounds are dynamic and there is opening, closing, and re-opening of wounds, the overall BSAP of open wounds stay relatively stable from observations in clinical practice. To not complicate the model, the appearance of new wounds has not been incorporated.

B26. The EAG understands that the four scenarios present within the output file for the patient level simulation relate to the base case (scenario 1), the scenario using 9 syringes (scenario 2) and the two scenarios exploring alternative proportions for vial sharing (scenarios 3 and 4). The EAG can see that these scenarios would impact on the consumption of vials predicted by the patient level simulation. However, the EAG does not understand why the transition matrices generated for these scenarios vary. Please clarify how the assumptions regarding vial usage and vial sharing impact on the transition matrices. Please also explain why the total number of transitions informing the probabilities in the matrices varies from scenario to scenario as well as the distribution of the probabilities within the rows and columns. Is it because some scenarios required more simulations to converge?

Indeed, some scenarios may require more simulations to converge, resulting in small differences in transition probabilities between scenario runs. However, that does not fully explain the difference in transition probabilities between the scenarios. Upon investigating, we realised the random seed was set only before the start of the first scenario, and not between the different scenarios, which are included in the same run of the simulation. We have now updated the code so that the random seed is set at the start of each scenario, resulting in the same transition matrices between scenarios where the only difference is in the assumptions around vial optimization.

B27. Please explain how the number of vials are calculated when assumptions of vial optimisation and vial sharing are differed.

In the reference case, 80% of patients were assumed to be participating in vial optimisation and sharing, whereby patients were able to maximise vial usage so that [REDACTED] syringes were obtained from [REDACTED] vial. The remaining 20% of patients were assumed to use one (1) entire vial regardless of the number of syringes required. Several scenario analyses were included in the submission to test alternative assumptions. One scenario assumed that vial optimisation produced [REDACTED] [REDACTED] instead of the [REDACTED] assumed in the reference case. Two additional scenarios tested the alternative assumptions of 70% and 90% of patients would participate in the vial optimisation and sharing versus the 80% assumed in the reference analysis.

B28. CS, Section 3.2.3.1: *“For patients under 3 years of age, the weekly dose is up to 2.5×10^9 PFU (2.5 billion) of B-VEC.”* Please clarify if the dose for patients under 3 years of age was considered.

Section 3.2.3.1 of the CS describes that as the younger age subgroup in the current CEM has a mean age of 2.25 years at baseline (based on GEM-3), in the first three cycles, the recommended dose would be the lower one. However, to simplify the model we made a conservative assumption, and the higher dose was considered for all patients.

B29. The input subfolder in the Patient level simulation vignettes appears to contain only flags to indicate the choice of input for the four scenarios modelled. Please tabulate all data points which inform the patient level simulation indicating their source, where they are described within the CS, and the variable name they are given within the R code.

Please see Table 28. for a list of datapoints informing the patient-level simulation (PLS), their variable name in the R code, value (in base case and, in case relevant, scenario analyses), their source and where in CS and/or response to the clarification questions they are discussed.

Table 28 Datapoints informing the PLS

Variable	Name in R code	Value	Source	Section in CS
Proportion of patient to consider vial sharing for	m_optimization_prop_value	70%, 80% (base case) or 90%	Assumption	3.5.2.2
Area that can be treated with a syringe	m_area_syringe	50 cm ²	SmPC	3.5.2.2
Number of syringes that can be filled from a vial	M_syringes_per_vial	4 (base case) or 4.5)	SmPC	3.5.2.2
Lower bound of area covered in chronic wounds, mild health state	M_LB_chro_mild	0.001	Expert elicitation	3.2.2.2
Lower bound of area covered in chronic wounds, moderate health state	M_LB_chro_mod	0.01	Expert elicitation	3.2.2.2
Lower bound of area covered in chronic wounds, severe health state	M_LB_chro_sev	0.01	Expert elicitation	3.2.2.2
Lower bound of area covered in recurrent wounds, mild health state	M_LB_recur_mild	0.02	Expert elicitation	3.2.2.2
Lower bound of area covered in recurrent wounds, moderate health state	M_LB_recur_mod	0.04	Expert elicitation	3.2.2.2
Lower bound of area covered in recurrent wounds, severe health state	M_LB_recur_sev	0.15	Expert elicitation	3.2.2.2
Upper bound of area covered in chronic wounds, severe health state	M_UB_chro_sev	0.2	Assumption	3.2.2.2
Upper bound of area covered in recurrent wounds, severe health state	M_UB_recur_sev	0.2	Assumption	3.2.2.2
Proportion of patients with RDEB	m_distr_RDEB_type	57.6% (original base case) or 61.5% (updated base case)	Bruckner et al	3.2.1 and Question B6
Proportion of patients with DDEB	m_distr_DDEB_type	1- m_distr_RDEB_type	Bruckner et al	3.2.1 and Question B6
Duration of wound closure for wounds not treated with B-VEC	duration_closure_pbo	16.5 days	GEM-1	3.2.2.1.2.1
Weekly probability of a wound treated with placebo reopening	m_PBO_recur_reopen_prob	$1 - \exp(-(\log(2)/\text{duration\_closure\_pbo}) * 7)$	Calculation	3.2.2.1.2.1
Maximum area to be treated with B-VEC each week	m_max_dose_perwk	200 cm ²	SmPC	3.2.2.1.3.1
Percentage increase in size of reopened wounds after initial reopening, B-VEC treated wounds	M_increase_size_B-VEC	0%	GEM-1	3.2.2.1.3.3
Percentage increase in size of reopened wounds after initial reopening, placebo treated wounds	M_increase_size_PBO	█%	GEM-1	3.2.2.1.2.3 and Question C6
Average size at which a wound reopens, B-VEC treated wounds	m_size_open_BVEC	█ cm ²	GEM-1	3.2.2.1.2.2
Average size at which a wound reopens, placebo treated wounds	m_size_open_PBO	█ cm ²	GEM-1	3.2.2.1.2.2
Minimum area open to commence treatment with B-VEC	m_min_area_treat	0 cm ² (obsolete)	SmPC	NA
Proportion of weeks without B-VEC treatment due to lack of compliance	Setting_compliance_weeks	10% (base case) or 15%	GEM-3	3.2.2.1.3.1 and

				Question B11
Weekly reduction in size of open area with recurrent wounds treated with B-VEC	m_BVEC_recur_clos_prob	42.54% (base case) or 33.53%	GEM-1	3.2.2.1.3.1 and Question B16
Weekly reduction in size of open area with chronic wounds treated with B-VEC	m_BVEC_chro_clos_prob	42.54% (base case) or 33.53%	GEM-1	3.2.2.1.3.1 and Question B16
Weekly reduction in size of open area with recurrent wounds treated with placebo	m_PBO_recur_clos_prob	14.17% (base case) or 5.75%	GEM-1	3.2.2.1.2.1 and Question B16
Weekly reduction in size of open area with chronic wounds treated with placebo	m_PBO_chro_clos_prob	0%	GEM-1	3.2.2.1.2.1
Weekly probability of a wound treated with B-VEC reopening	m_BVEC_recur_reopen_prob	$1 - \exp(-(\log(2)/\blacksquare) * 7)$ or 345, 240, 103 or 150 instead of $\blacksquare$	GEM-3 and OLE	3.2.2.1.3.2 and Question B19
Weeks of wound being open after which it is considered to become chronic	M_weeks_chronic	8	Eng et al (2021)	3.2.2.1.2.3
Proportion males	Percent_male	65%	GEM-3	3.2.1
3 rd percentile of weight of male RDEB children	Males_weight_3 in BSA_children_percentile	7.83 kg	Reimer et al (2020)	3.2.1
50 th percentile of weight of male RDEB children	Males_weight_50 in BSA_children_percentile	10.78 kg	Reimer et al (2020)	3.2.1
97 th percentile of weight of male RDEB children	Males_weight_97 in BSA_children_percentile	15.42 kg	Reimer et al (2020)	3.2.1
3 rd percentile of weight of female RDEB children	females_weight_3 in BSA_children_percentile	8.35 kg	Reimer et al (2020)	3.2.1
50 th percentile of weight of female RDEB children	females_weight_50 in BSA_children_percentile	11.58 kg	Reimer et al (2020)	3.2.1
97 th percentile of weight of female RDEB children	females_weight_97 in BSA_children_percentile	14.82 kg	Reimer et al (2020)	3.2.1
3 rd percentile of height of male RDEB children	Males_height_3 in BSA_children_percentile	73.25 cm	Reimer et al (2020)	3.2.1
50 th percentile of height of male RDEB children	Males_height_50 in BSA_children_percentile	88.02 cm	Reimer et al (2020)	3.2.1
97 th percentile of height of male RDEB children	Males_height_97 in BSA_children_percentile	103.43 cm	Reimer et al (2020)	3.2.1
3 rd percentile of height of female RDEB children	females_height_3 in BSA_children_percentile	74.34 cm	Reimer et al (2020)	3.2.1
50 th percentile of height of female RDEB children	females_height_50 in BSA_children_percentile	88.15 cm	Reimer et al (2020)	3.2.1
97 th percentile of height of female RDEB children	females_height_97 in BSA_children_percentile	101.97 cm	Reimer et al (2020)	3.2.1
2 nd percentile of weight of male DDEB children	Males_weight_2 in BSA_DDEB_children_percentile	10 kg	UK growth curves	3.2.1
50 th percentile of weight of male DDEB children	Males_weight_50 in BSA_DDEB_children_percentile	13.5 kg	UK growth curves	3.2.1
98 th percentile of weight of male DDEB children	Males_weight_98 in BSA_DDEB_children_percentile	17.5 kg	UK growth curves	3.2.1
2 nd percentile of weight of female DDEB children	females_weight_2 in BSA_DDEB_children_percentile	9.5 kg	UK growth curves	3.2.1
50 th percentile of weight of female DDEB children	females_weight_50 in BSA_DDEB_children_percentile	12 kg	UK growth curves	3.2.1

98 th percentile of weight of female DDEB children	females_weight_98 in BSA_DDEB_children percentile	15.5 kg	UK growth curves	3.2.1
2 nd percentile of height of male DDEB children	Males_height_2 in BSA_DDEB_children percentile	83 cm	UK growth curves	3.2.1
50 th percentile of height of male DDEB children	Males_height_50 in BSA_DDEB_children percentile	89.5 cm	UK growth curves	3.2.1
98 th percentile of height of male DDEB children	Males_height_98 in BSA_DDEB_children percentile	96 cm	UK growth curves	3.2.1
2 nd percentile of height of female DDEB children	females_height_2 in BSA_DDEB_children percentile	85.5 cm	UK growth curves	3.2.1
50 th percentile of height of female DDEB children	females_height_50 in BSA_DDEB_children percentile	93 cm	UK growth curves	3.2.1
98 th percentile of height of female DDEB children	females_height_98 in BSA_DDEB_children percentile	100.5 cm	UK growth curves	3.2.1
3 rd percentile of weight of male RDEB adolescents	Males_weight_3 in BSA_adolescents percentile	17.19 kg	Reimer et al (2020)	3.2.1
50 th percentile of weight of male RDEB adolescents	Males_weight_50 in BSA_adolescents percentile	26.00 kg	Reimer et al (2020)	3.2.1
97 th percentile of weight of male RDEB adolescents	Males_weight_97 in BSA_adolescents percentile	42.07 kg	Reimer et al (2020)	3.2.1
3 rd percentile of weight of female RDEB adolescents	females_weight_3 in BSA_adolescents percentile	13.65 kg	Reimer et al (2020)	3.2.1
50 th percentile of weight of female RDEB adolescents	females_weight_50 in BSA_adolescents percentile	24.33 kg	Reimer et al (2020)	3.2.1
97 th percentile of weight of female RDEB adolescents	females_weight_97 in BSA_adolescents percentile	35.01 kg	Reimer et al (2020)	3.2.1
3 rd percentile of height of male RDEB adolescents	Males_height_3 in BSA_adolescents percentile	113.39 cm	Reimer et al (2020)	3.2.1
50 th percentile of height of male RDEB adolescents	Males_height_50 in BSA_adolescents percentile	140.60 cm	Reimer et al (2020)	3.2.1
97 th percentile of height of male RDEB adolescents	Males_height_97 in BSA_adolescents percentile	169.20 cm	Reimer et al (2020)	3.2.1
3 rd percentile of height of female RDEB adolescents	females_height_3 in BSA_adolescents percentile	111.73 cm	Reimer et al (2020)	3.2.1
50 th percentile of height of female RDEB adolescents	females_height_50 in BSA_adolescents percentile	132.45 cm	Reimer et al (2020)	3.2.1
97 th percentile of height of female RDEB adolescents	females_height_97 in BSA_adolescents percentile	153.17 cm	Reimer et al (2020)	3.2.1
2 nd percentile of weight of male DDEB adolescents	Males_weight_2 in BSA_DDEB_adolescents percentile	29.5 kg	UK growth curves	3.2.1
50 th percentile of weight of male DDEB adolescents	Males_weight_50 in BSA_DDEB_adolescents percentile	41 kg	UK growth curves	3.2.1

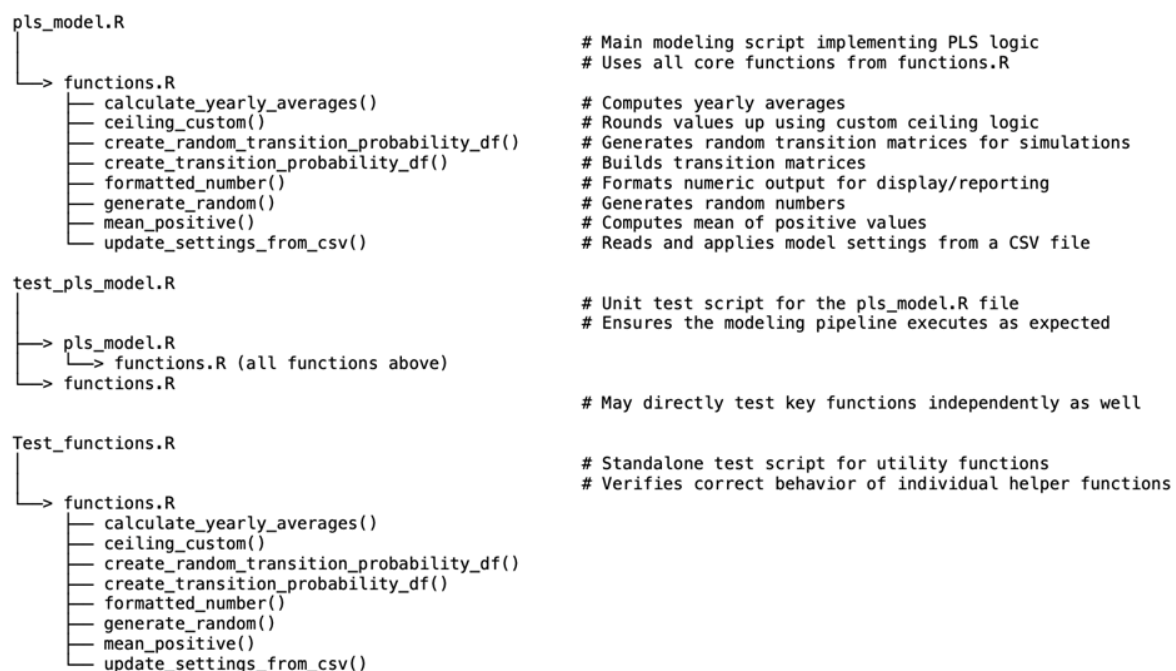
98 th percentile of weight of male DDEB adolescents	Males_weight_98 in BSA_DDEB_adolescents_percentile	61.5 kg	UK growth curves	3.2.1
2 nd percentile of weight of female DDEB adolescents	females_weight_2 in BSA_DDEB_adolescents_percentile	30 kg	UK growth curves	3.2.1
50 th percentile of weight of female DDEB adolescents	females_weight_50 in BSA_DDEB_adolescents_percentile	43.75 kg	UK growth curves	3.2.1
98 th percentile of weight of female DDEB adolescents	females_weight_98 in BSA_DDEB_adolescents_percentile	63 kg	UK growth curves	3.2.1
2 nd percentile of height of male DDEB adolescents	Males_height_2 in BSA_DDEB_adolescents_percentile	131 cm	UK growth curves	3.2.1
50 th percentile of height of male DDEB adolescents	Males_height_50 in BSA_DDEB_adolescents_percentile	151 cm	UK growth curves	3.2.1
98 th percentile of height of male DDEB adolescents	Males_height_98 in BSA_DDEB_adolescents_percentile	166 cm	UK growth curves	3.2.1
2 nd percentile of height of female DDEB adolescents	females_height_2 in BSA_DDEB_adolescents_percentile	139 cm	UK growth curves	3.2.1
50 th percentile of height of female DDEB adolescents	females_height_50 in BSA_DDEB_adolescents_percentile	153 cm	UK growth curves	3.2.1
98 th percentile of height of female DDEB adolescents	females_height_98 in BSA_DDEB_adolescents_percentile	167 cm	UK growth curves	3.2.1
3 rd percentile of weight of male RDEB adults	Males_weight_3 in BSA_adults_percentile	24.30 kg	Reimer et al (2020)	3.2.1
50 th percentile of weight of male RDEB adults	Males_weight_50 in BSA_adults_percentile	41.68 kg	Reimer et al (2020)	3.2.1
97 th percentile of weight of male RDEB adults	Males_weight_97 in BSA_adults_percentile	80.66 kg	Reimer et al (2020)	3.2.1
3 rd percentile of weight of female RDEB adults	females_weight_3 in BSA_adults_percentile	11.51 kg	Reimer et al (2020)	3.2.1
50 th percentile of weight of female RDEB adults	females_weight_50 in BSA_adults_percentile	33.60 kg	Reimer et al (2020)	3.2.1
97 th percentile of weight of female RDEB adults	females_weight_97 in BSA_adults_percentile	55.68 kg	Reimer et al (2020)	3.2.1
3 rd percentile of height of male RDEB adults	Males_height_3 in BSA_adults_percentile	142.74 cm	Reimer et al (2020)	3.2.1
50 th percentile of height of male RDEB adults	Males_height_50 in BSA_adults_percentile	156.83 cm	Reimer et al (2020)	3.2.1
97 th percentile of height of male RDEB adults	Males_height_97 in BSA_adults_percentile	170.93 cm	Reimer et al (2020)	3.2.1
3 rd percentile of height of female RDEB adults	females_height_3 in BSA_adults_percentile	151.5 cm	Reimer et al (2020)	3.2.1
50 th percentile of height of female RDEB adults	females_height_50 in BSA_adults_percentile	163.5 cm	Reimer et al (2020)	3.2.1
97 th percentile of height of female RDEB adults	females_height_97 in BSA_adults_percentile	171.5 cm	Reimer et al (2020)	3.2.1
2 nd percentile of weight of male DDEB adults	Males_weight_2 in BSA_DDEB_adults_percentile	52 kg	UK growth curves	3.2.1
50 th percentile of weight of male DDEB adults	Males_weight_50 in BSA_DDEB_adults_percentile	67 kg	UK growth curves	3.2.1
98 th percentile of weight of male DDEB adults	Males_weight_98 in BSA_DDEB_adults_percentile	90.5 kg	UK growth curves	3.2.1

2 nd percentile of weight of female DDEB adults	females_weight_2 in BSA_DDEB_adults_percentile	45 kg	UK growth curves	3.2.1
50 th percentile of weight of female DDEB adults	females_weight_50 in BSA_DDEB_adults_percentile	57.5 kg	UK growth curves	3.2.1
98 th percentile of weight of female DDEB adults	females_weight_98 in BSA_DDEB_adults_percentile	78.25 kg	UK growth curves	3.2.1
2 nd percentile of height of male DDEB adults	Males_height_2 in BSA_DDEB_adults_percentile	163 cm	UK growth curves	3.2.1
50 th percentile of height of male DDEB adults	Males_height_50 in BSA_DDEB_adults_percentile	177 cm	UK growth curves	3.2.1
98 th percentile of height of male DDEB adults	Males_height_98 in BSA_DDEB_adults_percentile	191 cm	UK growth curves	3.2.1
2 nd percentile of height of female DDEB adults	females_height_2 in BSA_DDEB_adults_percentile	151.5 cm	UK growth curves	3.2.1
50 th percentile of height of female DDEB adults	females_height_50 in BSA_DDEB_adults_percentile	163.5 cm	UK growth curves	3.2.1
98 th percentile of height of female DDEB adults	females_height_98 in BSA_DDEB_adults_percentile	171.5 cm	UK growth curves	3.2.1
Lower bound of number of recurrent wounds in Very Mild health state	Recurrent_Lower[1] in wounds_severity_data	0	Eng et al (2021)	3.2.2.1.2.2
Lower bound of number of recurrent wounds in Mild health state	Recurrent_Lower[2] in wounds_severity_data	5	Eng et al (2021)	3.2.2.1.2.2
Lower bound of number of recurrent wounds in Moderate health state	Recurrent_Lower[3] in wounds_severity_data	11	Eng et al (2021)	3.2.2.1.2.2
Lower bound of number of recurrent wounds in Severe health state	Recurrent_Lower[4] in wounds_severity_data	18	Eng et al (2021)	3.2.2.1.2.2
Upper bound of number of recurrent wounds in Very Mild health state	Recurrent_Upper[1] in wounds_severity_data	4	Eng et al (2021)	3.2.2.1.2.2
Upper bound of number of recurrent wounds in Mild health state	Recurrent_Upper[2] in wounds_severity_data	10	Eng et al (2021)	3.2.2.1.2.2
Upper bound of number of recurrent wounds in Moderate health state	Recurrent_Upper[3] in wounds_severity_data	17	Eng et al (2021)	3.2.2.1.2.2
Upper bound of number of recurrent wounds in Severe health state	Recurrent_Upper[4] in wounds_severity_data	45	Eng et al (2021)	3.2.2.1.2.2
Lower bound of number of chronic wounds in Very Mild health state	Chronic_Lower[1] in wounds_severity_data	0	Eng et al (2021)	3.2.2.1.2.2
Lower bound of number of chronic wounds in Mild health state	Chronic_Lower[2] in wounds_severity_data	1	Eng et al (2021)	3.2.2.1.2.2
Lower bound of number of chronic wounds in Moderate health state	Chronic_Lower[3] in wounds_severity_data	3	Eng et al (2021)	3.2.2.1.2.2
Lower bound of number of chronic wounds in Severe health state	Chronic_Lower[4] in wounds_severity_data	5	Eng et al (2021)	3.2.2.1.2.2

Upper bound of number of chronic wounds in Very Mild health state	Chronic_Upper[1] in wounds_severity_data	0	Eng et al (2021)	3.2.2.1.2.2
Upper bound of number of chronic wounds in Mild health state	Chronic_Upper[2] in wounds_severity_data	2	Eng et al (2021)	3.2.2.1.2.2
Upper bound of number of chronic wounds in Moderate health state	Chronic_Upper[3] in wounds_severity_data	4	Eng et al (2021)	3.2.2.1.2.2
Upper bound of number of chronic wounds in Severe health state	Chronic_Upper[4] in wounds_severity_data	9	Eng et al (2021)	3.2.2.1.2.2
Maximum area open to trigger full closure of all open area	Sim_max_area_total_closure	2 cm ²	Assumption	Question B33
Standard deviation of the average size of wounds at time of reopening	M_size_open_SD		GEM-1	3.2.2.1.2.2 and Question C7

B30. Please describe the purpose of the following R files: b-vec_Markov_v1.0.0.R; Test_functions.R; test_pls_model.R; functions.R; pls_model.R. Please provide a hierarchy diagram showing which of these programmes call on other R programmes. Please see Figure 6 for a hierarchy diagram for the R programmes. Please note that the script in source/b-vec_Markov_v1.0.0.R is the source legacy script used to extract package components (i.e., the individual functions initial formulation). It is not used by the current package. It shall not be executed or evaluated. It is included in the package only as the initial reference legacy code.

Figure 6 Hierarchy diagram for R codes



B31. Please clarify what are the file types for the files named “DESCRIPTION” and “NAMESPACE” and which programmes can be used to open these files. The EAG is currently unable to open these files.

The DESCRIPTION file in an R package provides metadata like its name, version, author and dependencies. The NAMESPACE file controls which functions are exported to users and imported from other packages, managing the package environment. Both are plain text files found in a package root directory and have no file extension by default. They are viewable with any text editor (e.g., Notepad, TextEdit).

B32. Please specify the attributes that are simulated for each patient in the patient level simulation used to generate the transition matrices. For example, does the model account for the number of wounds, the BSA for each wound, the chronicity status of each wound (e.g. recurrent/chronic)? and whether it falls within the maximum treated surface area (i.e. treated vs untreated)? Are there any other patient/wound attributes specified that inform the health state allocation or the vial consumption? Please provide the formulae used in the patient level simulation to calculate the wound areas per wound for each cycle and the total BSA covered by wounds in each cycle.

Define BSA parameters

- For each age group and subpopulation (RDEB and DDEB), calculate the mean, lower bound and upper bound weight across males and females, weighted by the proportion males
- For each age group and subpopulation (RDEB and DDEB), calculate the mean, lower bound and upper bound height across males and females, weighted by the proportion males
- For each age group and subpopulation (RDEB and DDEB), calculate the mean, lower bound and upper bound BSA by using the Dubois formula: $BSA = 0.007184 * height^{0.725} * weight^{0.425}$
- Calculate SD of mean BSA by doing (upper bound – lower bound)/(1.96*2)
- Calculate mean and SD of BSA for each age group by weighting the RDEB and DDEB values by the proportion of RDEB and DDEB patients respectively

Define patient characteristics for current patient

- Define random number parameters for
 - Age group
 - Baseline health state
 - Total BSA
 - Chronic BSAP
 - Recurrent BSAP

- Define patient age group: If random number parameter for age group is less than 1/3, then age group 1 (0-6), if the random number parameter for age group is between 1/3 and 2/3, then age group 2 (6-18), if the random number parameter for age group is greater than 2/3, then age group 3 (18+)
- Define total BSA of patient: sample from normal distribution with random number parameter for total BSA, and mean and SD of BSA for the defined age group

Define general simulation inputs

- Probability of B-VEC treated wounds becoming chronic each week = $(1 - \text{closing probability of wounds treated with B-VEC})^{\text{number of weeks of being open after which wounds are considered chronic}}$
- Probability of placebo treated wounds becoming chronic each week = $(1 - \text{closing probability of wounds treated with placebo})^{\text{number of weeks of being open after which wounds are considered chronic}}$
- Area open with chronic wounds if current patient is in Mild health state at baseline = $\text{random number for Chronic BSAP} * (\text{lower bound of area covered in chronic wounds, moderate health state} - \text{lower bound of area covered in chronic wounds, mild health state}) + \text{lower bound of area covered in chronic wounds, mild health state}$
- Area open with chronic wounds if current patient is in Moderate health state at baseline = $\text{random number for Chronic BSAP} * (\text{lower bound of area covered in chronic wounds, Severe health state} - \text{lower bound of area covered in chronic wounds, Moderate health state}) + \text{lower bound of area covered in chronic wounds, Moderate health state}$
- Area open with chronic wounds if current patient is in Severe health state at baseline = $\text{random number for Chronic BSAP} * (\text{upper bound of area covered in chronic wounds, Severe health state} - \text{lower bound of area covered in chronic wounds, Severe health state}) + \text{lower bound of area covered in chronic wounds, Severe health state}$
- Area open with recurrent wounds if current patient is in Mild health state at baseline = $\text{random number for Recurrent BSAP} * (\text{lower bound of area covered in recurrent wounds, moderate health state} - \text{lower bound of area covered in recurrent wounds, mild health state}) + \text{lower bound of area covered in recurrent wounds, mild health state}$
- Area open with recurrent wounds if current patient is in Moderate health state at baseline = $\text{random number for Recurrent BSAP} * (\text{lower bound of area covered in recurrent wounds, Severe health state} - \text{lower bound of area covered in recurrent wounds, Moderate health state}) + \text{lower bound of area covered in recurrent wounds, Moderate health state}$
- Area open with recurrent wounds if current patient is in Severe health state at baseline = $\text{random number for Recurrent BSAP} * (\text{upper bound of area covered in recurrent wounds, Severe health state} - \text{lower bound of area covered in recurrent wounds, Severe health state}) + \text{lower bound of area covered in recurrent wounds, Severe health state}$
- Number of B-VEC treated wounds that reopen for patient in Very Mild health state = $(\text{mean of lower and upper bound of number of recurrent wounds in Very Mild health state} * \text{mean of lower and upper bound of number of chronic wounds in Very Mild health state}) * \text{weekly probability of a wound treated with B-VEC reopening}$

- Number of B-VEC treated wounds that reopen for patient in Mild health state = (mean of lower and upper bound of number of recurrent wounds in Mild health state * mean of lower and upper bound of number of chronic wounds in Mild health state) * weekly probability of a wound treated with B-VEC reopening
- Number of B-VEC treated wounds that reopen for patient in Moderate health state = (mean of lower and upper bound of number of recurrent wounds in Moderate health state * mean of lower and upper bound of number of chronic wounds in Moderate health state) * weekly probability of a wound treated with B-VEC reopening
- Number of B-VEC treated wounds that reopen for patient in Severe health state = (mean of lower and upper bound of number of recurrent wounds in Severe health state * mean of lower and upper bound of number of chronic wounds in Severe health state) * weekly probability of a wound treated with B-VEC reopening
- Number of placebo treated wounds that reopen for patient in Very Mild health state = (mean of lower and upper bound of number of recurrent wounds in Very Mild health state * mean of lower and upper bound of number of chronic wounds in Very Mild health state) * weekly probability of a wound treated with placebo reopening
- Number of placebo treated wounds that reopen for patient in Mild health state = (mean of lower and upper bound of number of recurrent wounds in Mild health state * mean of lower and upper bound of number of chronic wounds in Mild health state) * weekly probability of a wound treated with placebo reopening
- Number of placebo treated wounds that reopen for patient in Moderate health state = (mean of lower and upper bound of number of recurrent wounds in Moderate health state * mean of lower and upper bound of number of chronic wounds in Moderate health state) * weekly probability of a wound treated with placebo reopening
- Number of placebo treated wounds that reopen for patient in Severe health state = (mean of lower and upper bound of number of recurrent wounds in Severe health state * mean of lower and upper bound of number of chronic wounds in Severe health state) * weekly probability of a wound treated with placebo reopening

Define Week 0 – B-VEC arm

- Chronic BSAP open = Area open with chronic wounds defined above for the health state defined above
- Recurrent BSAP open = Area open with recurrent wounds defined above for the health state defined above
- Chronic area open = chronic BSAP open * total BSA
- Recurrent area open = recurrent BSAP open * total BSA
- Total area open = chronic area open + recurrent area open
- Flag for treatment (Y/N) = if total area open >0 then 1, else 0
- Treated BSA = minimum of total area open and max area to be treated per week * flag for treatment (Y/N)
- Total BSAP open = Chronic BSAP open + recurrent BSAP open
- Health state (HS) = if total BSAP open < (Lower bound of area covered in chronic wounds, mild health state + Lower bound of area covered in

recurrent wounds, mild health state), then 1, else if total BSAP open < (Lower bound of area covered in chronic wounds, moderate health state + Lower bound of area covered in recurrent wounds, moderate health state), then 2, else if total BSAP open < (Lower bound of area covered in chronic wounds, severe health state + Lower bound of area covered in recurrent wounds, severe health state), then 3, else 4

- Vials = (Proportion of patient to consider vial sharing for * ceiling((treated BSA/area that can be treated with a syringe) / number of syringes that can be filled with a vial, (1/number of syringes that can be filled with a vial)) + (1- Proportion of patient to consider vial sharing for) * (if treated BSA = 0, then 0, else 1)
- Chronic treated BSA = minimum of chronic area open and treated BSA
- Recurrent treated BSA = if recurrent area open if smaller or equal than (treated BSA – chronic treated BSA), then recurrent area open, else treated BSA – chronic treated BSA
- Area closed through treatment with B-VEC in current week = if treated BSA is smaller or equal than maximum area open to trigger full closure of all open area, then chronic treated BSA + recurrent treated BSA, else (chronic treated BSA * Weekly reduction in size of open area with chronic wounds treated with B-VEC + recurrent treated BSA * Weekly reduction in size of open area with recurrent wounds treated with B-VEC)
- Cumulative area closed through treatment with B-VEC = 0
- Area closed through treatment with placebo in current week = (chronic area open – chronic area treated) * Weekly reduction in size of open area with chronic wounds treated with placebo + (recurrent area open – recurrent area treated) * Weekly reduction in size of open area with recurrent wounds treated with placebo
- Cumulative area closed through treatment with placebo = 0
- Reopened = 0

Define weeks 1-156 – B-VEC arm

- Define random number parameters for
 - Compliance
 - Reopening wounds treated with B-VEC
 - Size of reopened wounds treated with B-VEC
 - Reopening wounds treated with placebo
 - Size of reopened wounds treated with placebo
- Chronic area open =
 - maximum of 0 and (chronic area open in previous week
 - (if treated BSA in previous week is smaller than maximum area open to trigger full closure of all open area, then chronic treated BSA in previous week, else chronic treated BSA in previous week * Weekly reduction in size of open area with chronic wounds treated with B-VEC)
 - (chronic area open in previous week – chronic treated BSA) * Weekly reduction in size of open area with chronic wounds treated with placebo)
 - + if area closed through treatment with B-VEC in previous week is equal to the sum of chronic treated BSA and recurrent treated BSA, then 0, else recurrent treated BSA * (1- Area closed through treatment

with B-VEC in current week)* Probability of B-VEC treated wounds becoming chronic each week
+ the maximum of 0 and (recurrent area open – recurrent treated BSA) * (1- Area closed through treatment with placebo in current week)* Probability of placebo treated wounds becoming chronic each week

- Reopened = The sum of
the minimum of cumulative area closed through treatment with B-VEC in previous week and
(round down of number of B-VEC treated wounds that reopen for the health state in previous week * sample from normal distribution with random number parameter for Size of reopened wounds treated with B-VEC, and mean and SD of average size at which a B-VEC treated wound reopens * (1+ Percentage increase in size of reopened B-VEC treated wounds after initial reopening)
+ if random number for reopening of wounds treated with B-VEC is less than (number of B-VEC treated wounds that reopen for the health state in previous week – round down of number of B-VEC treated wounds that reopen for the health state in previous week), then 1, else 0* sample from normal distribution with random number parameter for Size of reopened wounds treated with B-VEC, and mean and SD of average size at which a B-VEC treated wound reopens * (1+ Percentage increase in size of reopened B-VEC treated wounds after initial reopening))

And the minimum of cumulative area closed through treatment with placebo in previous week and

(round down of number of placebo treated wounds that reopen for the health state in previous week * sample from normal distribution with random number parameter for Size of reopened wounds treated with placebo, and mean and SD of average size at which a placebo treated wound reopens * (1+ Percentage increase in size of reopened placebo treated wounds after initial reopening)

+ if random number for reopening of wounds treated with placebo is less than (number of placebo treated wounds that reopen for the health state in previous week – round down of number of placebo treated wounds that reopen for the health state in previous week), then 1, else 0* sample from normal distribution with random number parameter for Size of reopened wounds treated with placebo, and mean and SD of average size at which a placebo treated wound reopens * (1+ Percentage increase in size of reopened placebo treated wounds after initial reopening))

- Recurrent area open = recurrent area open in previous week
– if treated BSA in previous week is smaller than maximum area open to trigger full closure of all open area, then recurrent treated BSA in previous week, else recurrent treated BSA in previous week * Weekly

- reduction in size of open area with recurrent wounds treated with B-VEC)
- (recurrent area open in previous week – recurrent treated BSA in previous week) * Weekly reduction in size of open area with recurrent wounds treated with placebo
 - if area closed through treatment with B-VEC in previous week is equal to the sum of chronic treated BSA and recurrent treated BSA, then 0, else recurrent treated BSA * (1- Area closed through treatment with B-VEC in current week)* Probability of B-VEC treated wounds becoming chronic each week
 - the maximum of 0 and (recurrent area open – recurrent treated BSA) * (1- Area closed through treatment with placebo in current week)* Probability of placebo treated wounds becoming chronic each week + reopened
 - Total area open = chronic area open + recurrent area open
 - Flag for treatment (Y/N) = (if total area open >0 then 1, else 0) * (if random number for compliance is smaller than or equal to proportion of weeks without B-VEC treatment due to lack of compliance, then 0, else 1)
 - Treated BSA = minimum of total area open and max area to be treated per week * flag for treatment (Y/N)
 - Chronic BSAP open = chronic area open / total BSA of patient
 - Recurrent BSAP open = recurrent area open / total BSA of patient
 - Total BSAP open = Chronic BSAP open + recurrent BSAP open
 - Health state (HS) = if total BSAP open < (Lower bound of area covered in chronic wounds, mild health state + Lower bound of area covered in recurrent wounds, mild health state), then 1, else if total BSAP open < (Lower bound of area covered in chronic wounds, moderate health state + Lower bound of area covered in recurrent wounds, moderate health state), then 2, else if total BSAP open < (Lower bound of area covered in chronic wounds, severe health state + Lower bound of area covered in recurrent wounds, severe health state), then 3, else 4
 - Vials = (Proportion of patient to consider vial sharing for * ceiling((treated BSA/area that can be treated with a syringe) / number of syringes that can be filled with a vial, (1/number of syringes that can be filled with a vial)) + (1- Proportion of patient to consider vial sharing for) * (if treated BSA = 0, then 0, else 1)
 - Chronic treated BSA = minimum of chronic area open and treated BSA
 - Recurrent treated BSA = if recurrent area open if smaller or equal than (treated BSA – chronic treated BSA), then recurrent area open, else treated BSA – chronic treated BSA
 - Area closed through treatment with B-VEC in current week = if treated BSA is smaller or equal than maximum area open to trigger full closure of all open area, then chronic treated BSA + recurrent treated BSA, else (chronic treated BSA * Weekly reduction in size of open area with chronic wounds treated with B-VEC + recurrent treated BSA * Weekly reduction in size of open area with recurrent wounds treated with B-VEC)
 - Cumulative area closed through treatment with B-VEC = maximum of 0 and (cumulative area closed through treatment with B-VEC in previous week

- (round down of number of B-VEC treated wounds that reopen for the health state in previous week * sample from normal distribution with random number parameter for Size of reopened wounds treated with B-VEC, and mean and SD of average size at which a B-VEC treated wound reopens * (1+ Percentage increase in size of reopened B-VEC treated wounds after initial reopening)
 - + if random number for reopening of wounds treated with B-VEC is less than (number of B-VEC treated wounds that reopen for the health state in previous week – round down of number of B-VEC treated wounds that reopen for the health state in previous week), then 1, else 0* sample from normal distribution with random number parameter for Size of reopened wounds treated with B-VEC, and mean and SD of average size at which a B-VEC treated wound reopens * (1+ Percentage increase in size of reopened B-VEC treated wounds after initial reopening)))
- + Area closed through treatment with B-VEC in previous week
 - Area closed through treatment with placebo in current week = (chronic area open – chronic area treated) * Weekly reduction in size of open area with chronic wounds treated with placebo + (recurrent area open – recurrent area treated) * Weekly reduction in size of open area with recurrent wounds treated with placebo
 - Cumulative area closed through treatment with placebo = maximum of 0 and (cumulative area closed through treatment with placebo in previous week
 - (round down of number of placebo treated wounds that reopen for the health state in previous week * sample from normal distribution with random number parameter for Size of reopened wounds treated with placebo, and mean and SD of average size at which a placebo treated wound reopens * (1+ Percentage increase in size of reopened placebo treated wounds after initial reopening)
 - + if random number for reopening of wounds treated with placebo is less than (number of placebo treated wounds that reopen for the health state in previous week – round down of number of placebo treated wounds that reopen for the health state in previous week), then 1, else 0* sample from normal distribution with random number parameter for Size of reopened wounds treated with placebo, and mean and SD of average size at which a placebo treated wound reopens * (1+ Percentage increase in size of reopened placebo treated wounds after initial reopening)))
- + Area closed through treatment with placebo in previous week

Define Week 0 – Placebo arm

- Chronic BSAP open = Area open with chronic wounds defined above for the health state defined above
- Recurrent BSAP open = Area open with recurrent wounds defined above for the health state defined above

- Chronic area open = chronic BSAP open * total BSA
- Recurrent area open = recurrent BSAP open * total BSA
- Total area open = chronic area open + recurrent area open
- Total BSAP open = Chronic BSAP open + recurrent BSAP open
- Health state (HS) = if total BSAP open < (Lower bound of area covered in chronic wounds, mild health state + Lower bound of area covered in recurrent wounds, mild health state), then 1, else if total BSAP open < (Lower bound of area covered in chronic wounds, moderate health state + Lower bound of area covered in recurrent wounds, moderate health state), then 2, else if total BSAP open < (Lower bound of area covered in chronic wounds, severe health state + Lower bound of area covered in recurrent wounds, severe health state), then 3, else 4
- Area closed in current week = recurrent area open * Weekly reduction in size of open area with recurrent wounds + chronic area open * Weekly reduction in size of open area with chronic wounds
- Cumulative area closed = 0

Define weeks 1-156 – Placebo arm

- Define random number parameters for
 - Reopening wounds treated with placebo
 - Size of reopened wounds treated with placebo
- Reopened = the minimum of cumulative area closed in previous week and

(round down of number of placebo treated wounds that reopen for the health state in previous week * sample from normal distribution with random number parameter for Size of reopened wounds treated with placebo, and mean and SD of average size at which a placebo treated wound reopens * (1+ Percentage increase in size of reopened placebo treated wounds after initial reopening)

+ if random number for reopening of wounds treated with placebo is less than (number of placebo treated wounds that reopen for the health state in previous week – round down of number of placebo treated wounds that reopen for the health state in previous week), then 1, else 0* sample from normal distribution with random number parameter for Size of reopened wounds treated with placebo, and mean and SD of average size at which a placebo treated wound reopens * (1+ Percentage increase in size of reopened placebo treated wounds after initial reopening))
- Chronic area open =

(chronic area open in previous week * (1 - Weekly reduction in size of open area with chronic wounds treated with placebo)

+ (recurrent area open in previous week – area closed in previous week) * Probability of placebo treated wounds becoming chronic each week
- Recurrent area open =

(recurrent area open in previous week * (1 - Weekly reduction in size of open area with recurrent wounds treated with placebo)

– (recurrent area open in previous week – area closed in previous recurrent area open in previous week

+ reopened

- Total area open = chronic area open + recurrent area open
- Chronic BSAP open = chronic area open / total BSA of patient
- Recurrent BSAP open = recurrent area open / total BSA of patient
- Total BSAP open = Chronic BSAP open + recurrent BSAP open
- Health state (HS) = if total BSAP open < (Lower bound of area covered in chronic wounds, mild health state + Lower bound of area covered in recurrent wounds, mild health state), then 1, else if total BSAP open < (Lower bound of area covered in chronic wounds, moderate health state + Lower bound of area covered in recurrent wounds, moderate health state), then 2, else if total BSAP open < (Lower bound of area covered in chronic wounds, severe health state + Lower bound of area covered in recurrent wounds, severe health state), then 3, else 4
- Area closed in current week = chronic area open * Weekly reduction in size of open area with chronic wounds treated with placebo + recurrent area open * Weekly reduction in size of open area with recurrent wounds treated with placebo
- Cumulative area closed =
 - maximum of 0 and (cumulative area closed in previous week
 - (round down of number of placebo treated wounds that reopen for the health state in previous week * sample from normal distribution with random number parameter for Size of reopened wounds treated with placebo, and mean and SD of average size at which a placebo treated wound reopens * (1+ Percentage increase in size of reopened placebo treated wounds after initial reopening)
 - + if random number for reopening of wounds treated with placebo is less than (number of placebo treated wounds that reopen for the health state in previous week – round down of number of placebo treated wounds that reopen for the health state in previous week), then 1, else 0* sample from normal distribution with random number parameter for Size of reopened wounds treated with placebo, and mean and SD of average size at which a placebo treated wound reopens * (1+ Percentage increase in size of reopened placebo treated wounds after initial reopening)))

+ Area closed in previous week

B33. b-vec_Markov_v1.0.0 R code, line 849: the presence of conditional statements associated with Sim_max_area_total_closure, appears to be set to a value of 2. Could you please clarify the rationale behind using if statements in this context? It would be helpful to understand the logic or scenario that necessitates this approach and what implications this has for the model outputs.

The value of 2 was used for the assumption that if the total area open is less than or equal to 2cm², it would all be closed with B-VEC treatment. This was a simplifying assumption as otherwise the open area would get smaller and smaller ad Infinium.

B34. Please comment on the limitations of using data from GEM-1 to inform the patient level simulation given that:

- a) the wound size was limited to up to 20 cm² (for all but one patient who was enrolled in the phase 2c where wound size was up to 50cm²,
 - b) no patients with dominant disease were enrolled,
 - c) the dosing was not weekly.
- a) Relative reduction in wound size was used for the model and applied to the entire area of the body that is open with wounds. This means that bigger wounds in the model (although not modelled as such explicitly) will take longer to heal completely than smaller wounds, considering the assumption that if an area of less than 2cm² is treated with B-VEC, it will fully close and smaller wounds will reach this stage earlier than bigger ones. This applies to both wounds treated with B-VEC and with placebo.
- b) While the literature often states that DDEB generally has a milder presentation than RDEB, many DDEB patients suffer from debilitating disease-related outcomes and a subset of patients have severe disease. For example, as reported in Fulchand 2021, DDEB patients suffer from skin lesions/blisters and associated chronic/recurring wounds, and experience many similar symptoms as RDEB patients, including pain, itch, wound infections, anal strictures, difficulty swallowing, dental caries, ocular involvement, anaemia, and failure to thrive (among others).³² As such, a molecularly corrective approach to DEB via COL7 supplementation such as that provided by B-VEC presents a profound and desperately needed treatment option for a patient population with high unmet need, including those with DDEB. Clinical efficacy of B-VEC in treating DDEB-related wounds has been established in the Phase 3 study, where a DDEB patient (Phase 3 Subject 01-07) demonstrated complete wound healing of the B-VEC-treated wound, but not the placebo-treated wound, at month 6 (Table 29). The B-VEC-treated wound met the primary endpoint of complete closure for both Weeks 22 & 24 and Weeks 24 & 26, as well as the more stringent analysis at Weeks 22, 24, & 26; the placebo treated wound failed all these efficacy analyses. Furthermore, this subject enrolled in the US open label extension (OLE) study, and their wound remained closed throughout the 12-month wound observation period (US OLE Subject 01-03). An additional DDEB

patient enrolled in the US OLE study (Subject 05-02) demonstrated benefit from B-VEC treatment at multiple wound sites (Table 29 and Figure 7). Taken together, these data suggest that overexpression of wild-type COL7 mediated by B-VEC application is effective in treating DDEB wounds.

Table 29 Primary wound closure assessment at Month 6 for Subject 01-07

	Week 22	Week 24	Week 26
B-VEC	Closed	Closed	Closed
Placebo	Open	Closed	Open

B-VEC= beremagene geperpavec.

Source: Krystal Biotech, Data on File.

Figure 7 Wound healing in Subject 05-02 in US OLE



OLE=open label extension; US=United States.

Source: Krystal Biotech, Data on File.

- c) The dosing in GEM-1 was more frequent than weekly in the initial period, and less frequent thereafter. As data on wound closure were used from more than only the initial 1-2 weeks where dosing was more frequent and includes mostly time where dosing was less frequent than once weekly, the analysis can be considered conservative.

B35. Model, 'Simulation output' F13:F21: Please comment on the validity of these outputs compared to the trial. In specific, please comment on why patients aged 18

and over are predicted to require fewer vials than patients aged 0 to 6 years in the third year of the model.

Vial consumption was not collected in the GEM-1 and GEM-3 trials of B-VEC, since the trial did not treat all wounds, and was only short term therefore unlikely to be representative of real-world use. The difference is 0.38 vs 0.36. This is due to chance. If changing the random number seed, it will probably be different, but there is no impact on the ICER.

BBE modelling

B36. [Priority] CS, Section 3.3.1.1: Please provide a copy of the replicated model from HST28 so the EAG can verify the company's replication and the implementation of the adjustments described on CS, page 105.

We are providing a copy of the replicated model from HST28. The version shared has a few updates from the one described in the CS Section 3.3.1, namely:

- Time horizon updated from 100 to 50 years (see response to question B37)
- Consideration of caregiver QALYs also after the patient has died (in line with response to question B43)
- Updating the general population utility to that of a person of 43 years old (0.89), in line with the response to question B45
- Updating the mapping between health states as the model had changed slightly based on the three changes discussed above.

Updated conversions, model inputs and transition probabilities are presented in Table 30, Table 31, and Table 32.

Table 30 Updated conversion from health states used in the BBE NICE submission to B-VEC health states

		Current model health state			
		Very Mild	Mild	Moderate	Severe
BBE NICE dossier health state	Health state 1	5%	95%		
	Health state 2		100%		
	Health state 3		3%	97%	
	Health state 4			100%	

	Health state 5			100%	
	Health state 6				100%
NICE=National Institute for Health and Care Excellence					

Table 31 Updated BBE model inputs (mapped to four health states)

Input type	Input	Value
Baseline health state distribution	Very Mild	0.8%
	Mild	33.0%
	Moderate	49.5%
	Severe	16.7%
Transition probabilities	BBE	See Table XX and Table XX
	BSC	
Patient utilities	Very Mild	0.56
	Mild	0.53
	Moderate	0.35
	Severe	0.08
Carer utilities	Very Mild	0.85
	Mild	0.85
	Moderate	0.72
	Severe	0.64
Number of carers	Very Mild	0.5
	Mild	0.51
	Moderate	1.26
	Severe	1.78
Annual costs of monitoring and bandages	Very Mild	£10,614.08
	Mild	£14,644.31
	Moderate	£54,636.70
	Severe	£108,569.11

Table 32 Updated BBE transition probabilities from HST28, mapped to four health states

Day 0-30				
From/to	Very Mild	Mild	Moderate	Severe
Very Mild	0.050	0.950	0.000	0.000
Mild	0.027	0.964	0.009	0.000
Moderate	0.000	0.135	0.865	0.000
Severe	0.000	0.000	1.000	0.000
Day 30-60				
From/to	Very Mild	Mild	Moderate	Severe
Very Mild	0.047	0.953	0.000	0.000
Mild	0.022	0.960	0.018	0.000

Moderate	0.000	0.010	0.999	0.000
Severe	0.000	0.000	0.976	0.024
Day 60-90				
From/to	Very Mild	Mild	Moderate	Severe
Very Mild	0.049	0.951	0.000	0.000
Mild	0.024	0.962	0.015	0.000
Moderate	0.000	0.017	0.983	0.000
Severe	0.000	0.000	0.992	0.008
Day 90+				
From/to	Very Mild	Mild	Moderate	Severe
Very Mild	0.048	0.952	0.000	0.000
Mild	0.024	0.960	0.017	0.000
Moderate	0.000	0.032	0.968	0.000
Severe	0.000	0.000	0.982	0.018

Table 33 Updated BSC transition probabilities from HST28, mapped to four health states

Day 0-30				
From/to	Very Mild	Mild	Moderate	Severe
Very Mild	0.050	0.950	0.000	0.000
Mild	0.025	0.966	0.009	0.000
Moderate	0.000	0.126	0.874	0.000
Severe	0.000	0.000	1.000	0.000
Day 30-60				
From/to	Very Mild	Mild	Moderate	Severe
Very Mild	0.008	0.992	0.000	0.000
Mild	0.004	0.568	0.429	0.000
Moderate	0.000	0.010	0.990	0.000
Severe	0.000	0.000	0.309	0.691
Day 60-90				
From/to	Very Mild	Mild	Moderate	Severe
Very Mild	0.049	0.951	0.000	0.000
Mild	0.023	0.952	0.024	0.000
Moderate	0.000	0.012	0.988	0.000
Severe	0.000	0.000	0.968	0.032
BSC=best supportive care				

B37. CS, Section 3.3.1.1: It appears that the proportion of RDEB-severe patients had to be increased approximately 10-fold (2.43% to 25.16%) to achieve calibration of the total costs in the BSC arm. This suggests that something else is incorrect in the model as the reporting of the % RDEB-severe is unlikely to be incorrect by such a large factor. Please comment on how this issue was explored when calibrating the model and why

changing the % with RDEB-Severe was agreed as the solution to the mismatch in BSC costs.

The replication of the HST28 model as described in the CS was using a lifelong time horizon. Upon further reading the committee papers from HST28 we realised a time horizon of only 50 years was used for the initial company submission. When changing the time horizon in the replicated model to 50 years, we could match the total costs in the CCM arm by using the 2.43% RDEB-S patients as reported in HST28. The updated version of the replicated model therefore considers 2.43% RDEB severe patients

B38. CS, Section 3.3.1.1: Please explain how a calibration of the model from HST28 could be conducted if the costs reported for the BBE arm in the HST28 company submission include the PAS discount and this is not known to the company.

The only cost categories considered in the model from HST28 were health state costs (consisting of monitoring and dressing costs) and BBE acquisition costs. As we were able to replicate the total costs in the BBE arm of the model, we could assume that also the health state costs we modelled for the BBE arm were correct. From that we could conclude that the difference between total costs reported in the CS for HST28, and the health state costs that we modelled, was the total drug acquisition costs for BBE.

We were not able to exactly estimate the PAS discount, as the number of tubes per month was also unknown, but we could estimate the BBE acquisition costs per cycle from dividing the difference between total costs reported in the CS for HST28, and the health state costs that we modelled by the average number of months on treatment.

B39. CS, Section 3.3.1.2: The mapping algorithm provided in Table 3.10 does not align with BSAP coverage for the different health state definitions. For e.g. All of health state 2 patients (BSAP 4-7%) were assumed to belong to the mild health state (2.1-5%). Please comment on the validity of the approach undertaken.

We are aware that the mapping approach does not fully align. When developing the mapping we started with testing an algorithm that aligns with the definitions of the health states in both models, but the only possible solution to making the mapping algorithm converge was with the currently used approach.

B40. CS, Section 3.5.2.3: Please clarify why the average number of BBE tubes of 29.67 per month was used in all health states though the consumption of BBE in the open label phase was reported to be lower than during the double-blind phase of EASE as stated in Section 3.3.1.1. Please explain why a similar back calculation approach was not used in modelling BBE as the one used in the validation exercise.

The assumption of 29.67 tubes per month was needed to be able to do the back-calculation for the HST28 model. There were two unknown parameters, both related to BBE acquisition costs; the number of tubes per month and the PAS applied to the cost per tube. By assuming the number of tubes per month to be 29.67 (the only published mean we were able to identify), we could back-calculate the cost per vial applied.

An alternative approach would be to not explicitly use the number of tubes per month and the PAS applied to the cost per tube, but to instead back-calculate the BBE acquisition costs per month, similar to the response to question B38. This would not make any difference to the outcomes of the replicated model.

B41. CS, Section 3.5.5.2: *"It is assumed that the formal care costs would also account for the administration costs of B-VEC and BBE."* Does BBE need to be administered by health care professional?

BBE does not need to be administered by a health care professional. However, some patients do need professional support with dressing changes. It was assumed that patients who need support with dressing changes may also need support with applying BBE, and that the nurse supporting the patient with the dressing changes would also apply BBE to the wounds.

Quality of life data

B42. [Priority] CS, Section 3.4.5.1.1: Please provide a full study report describing the vignette study used to elicit utility values shown in Table 3.22. The details provided in CS, Section 3.4.5.1.1 are not sufficient for the EAG to critique this study's methods.

Please refer to the attached PDF "[ID3959]_beremagene geperpavec_Vignette Study_Technical Report".

B43. [Priority] Model, Markov engines: The model calculations assume no QALYs are gained by carers after a patient dies which is equivalent to assuming that patient death also results in carer death. Please amend the model to include them QALYs for carers after patient death, or alternatively change the model calculations to account for QALY loss due to caring responsibilities instead of absolute carer QALYs.

We have amended the model engines to consider caregiver QALYs also after the patient has died. For this we have assumed each patient had 1.78 caregivers at the time they die (in line with the number of caregivers as discussed in CS 3.4.5.2) and that the caregivers subsequently die at the rate of that of the general population.

This changed the iNMB in the model base case from £[REDACTED] in the comparison versus BSC and £[REDACTED] in the comparison versus BBE to £[REDACTED] and £[REDACTED] for the respective comparisons.

B44. If choosing to maintain the approach of modelling absolute caregiver QALYs, please explain why caregiver mortality and age-adjusted disutility were not accounted for considering there are differences in mortality for carers between the different treatment arms (as a consequence of the difference in mortality for patients).

In addition to the caregiver mortality introduced in response to question B43, we have also introduced age-adjustment for the caregiver utilities. From the updated results reported in response to question B43, this further changed the iNMB to £[REDACTED] and £[REDACTED] for the comparisons versus BSC and BBE respectively.

B45. Please justify why an average age of 16 was used for caregivers (model, 'QoL data' B66) although Angelis *et al.* states that the average age of caregivers was 43.3 years.

The average age was calibrated to be very low in replicating the HST28 model. However, with the changes to the replicated model discussed in response to question B36, we have realised we can use the average age of caregivers of 43.3 reported by Angelis *et al.*³³ and still match the reported results of that model. Therefore, we have now also updated the executable Excel model to use 43.3 years as the baseline age of caregivers. In addition to the changes to the results reported in response to

questions B43 and B44, this further changed the iNMB to £[REDACTED] and £[REDACTED] for the comparisons versus BSC and BBE respectively.

Cost data

B46. CS, Section 3.5.2.2: From the YHEC report Table 4.3, it seems that the cost for a specialist nurse applying the product was only considered for the first administration. Please justify this assumption.

The SmPC for B-VEC states the following:

A health care professional (HCP) should apply Vyjuvek, either at a healthcare professional setting (e.g., clinic) or the home setting. If deemed appropriate by the healthcare professional, trained patients or caregivers may also apply Vyjuvek.

Based on this we are assuming that the healthcare provider will use the first administration to train the patient or their caregiver(s) and that they can self-administer after that.

B47. CS, Section 3.5.5.1 states that “Administration costs for both B-VEC and BBE treatment arms are assumed to be included in the nurse time associated with dressing changes.” Please explain how this could be possible considering that only 1-36% of patients require professional assistance with dressing changes as mentioned in Table 32 of the BBE CS.

Not all patients require support with dressing changes, and neither B-VEC nor BBE has to strictly be administered by a healthcare professional. The assumption is that patients who do not require professional assistance with dressing changes do not need professional assistance with application of B-VEC or BBE either. The nurse time reported for support with dressing changes (and application of the respective products) is an average across patients who do and those who don't need support from a healthcare professional.

B48. CS, Section 3.5.5 and Table 35 of the BBE CS. Considering that outpatient, bandage and dressing change costs in the current submission relies on the BBE CS, please explain the reasons why there are significant differences in the total costs

estimated. For example, the current model assumes a per-cycle cost (sum of D75, D82, and D89 at the 'Costs' sheet) of £32,985 per patient at the severe state (equivalent to £131,941 annual cost) compared to £108,569 in the BBE CS, Table 35. The costs used in the current model are indeed significantly different from those used in the CS for HST28. However, the nurse cost component of these costs were assuming a cost per hour of £12.50. On page 51 of the response to the clarification questions (HST28 committee papers page 248) it is stated that, as discussed with the ERG, *"the hourly carer cost of £12.50 reported in Pillay et al. (2020) and applied in the submission model 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."*

Section 5.2.5.6.2 of the ERG report for HST28 (committee papers page 364) also discusses the appropriate source for the cost per hour of nurse time is the PSSRU report. Data presented in Table 25 of the ERG report for HST28 (committee papers page 365) are aligned with the costs used in the current model. The differences between the values in that table and the current model are due to correction for inflation and/or use of most up to date data sources for unit costs.

In line with this we have costed the paid care time at £58 per hour, in line with the PSSRU unit cost handbook 2023 (the most recent version at the time of submission).

Executable EXCEL model

B49. 'Mortality' T1291:T1771: The per-cycle death probability for the moderate health state was assumed the same for all patients (equal to values used for the mild state) regardless of age. This seems to contradict the assumptions listed in CS, Table 3.21. Please explain the discrepancy.

As discussed in response to question B8, the parametric curve selected for the curve fitted to RDEB-non-severe data was the exponential curve. As the exponential curve represents a constant hazard, this resulted in the same probability of death being applied regardless of age or time in the model.

In reviewing the model whilst responding to this question, we did realize there was an error in the calculation of mortality in the Moderate health state. As reported in Table

3.21 of the CS, the assumption is that mortality in this health state (for patients entering the model at age ≥ 6) is the average between RDEB-non severe and RDEB-severe. However, the model calculations were setting mortality in the moderate health state equal to that in the Mild health state. We have corrected this in the model, and this changes the iNMB for the original company base case from £[REDACTED] in the comparison versus BSC and £[REDACTED] in the comparison versus BBE to £[REDACTED] and £[REDACTED] for the respective comparisons.

B50. 'Mortality' U1291:U1771: The per-cycle death probability for the severe health state was assumed the same for all patients (equal to parametric estimates from the RDEB-S survival curve) regardless of age. This seems to contradict the assumptions listed in CS, Table 3.21. Please explain the discrepancy.

As discussed in response to question B8, the parametric curve selected for the curve fitted to RDEB-severe data was the exponential curve. As the exponential curve represents a constant hazard, this resulted in the same probability of death being applied regardless of age or time in the model.

B51. Markov engines calculating rates of irreversible clinical manifestations: The equations used seem to be excessively long and erroneous. For example, when calculating the cumulative proportion of children getting BSC and who will acquire SCC in the model, the sum of 'Markov BSC' CA11:CA411 is 7 patients out of a starting cohort of 0.13 children (equal to 5385%). Please amend the formulae used so that the total proportions are in the range of the ones reported in CS, Table 3.18.

We would like to point out to the EAG that the proportions calculated for the irreversible clinical manifestations should not be considered cumulatively, but rather, the calculations consider patients moving between health states (including death). The costs applied are per cycle costs that are applied from when the patient first develops the clinical manifestation, until they die, and they are not considered to be one-off costs.

In investigating this question, we did discover an error in how the calculations for complete or partial mitten deformity of foot and complete mitten deformity of hand were calculated, as they were referring to the number of patients in the previous cycle with squamous cell carcinoma, instead of the respective clinical manifestations. We have corrected this in the model and this changed the iNMB in the model base case from

£[REDACTED] in the comparison versus BSC and £[REDACTED] in the comparison versus BBE to £[REDACTED] and £[REDACTED] for the respective comparisons.

To demonstrate this, we have implemented additional curves in the Markov sheets to calculate the total number of patients with each clinical manifestation. The maximum number during the time horizon is presented in Table 34 below and compared to the proportions reported in Eng et al.¹⁹ These values are in the same ballpark as the values from Eng et al. For complete or partial mitten deformity of the foot, the proportion that ends up with this clinical manifestation is higher in patients treated with BBE than those in the BSC arm. This is because patients treated with BBE are modelled to have longer life expectancy, so there is more time to accrue the clinical manifestation.

Table 34 Rates of irreversible clinical manifestations

Clinical manifestation	Assumption	Proportion calculated from Eng et al			Maximum reached in the model		
	Very Mild	Mild	Moderate	Severe	B-VEC	BSC	BBE
SCC	0%	0%	5%	19%	0.2%	10.3%	6.7%
Complete or partial mitten deformity of foot	0%	45%	48%	81%	1.5%	56.0%	63.2%
Complete mitten deformity of hand	0%	5%	13%	24%	0.3%	17.7%	17.6%

B-VEC= beremagene geperpavec; BBE=birch bark extract; BSC=best supportive care; SCC= Squamous cell carcinoma.

Section C: Textual clarification and additional points

C1. The attachments embedded in Appendices A and J are not accessible. Please provide them in a PDF format.

Please refer to the attached PDFs

- "[ID3959]_beremagene geperpavec_Appendix A_vyjuvek-epar-product-information_en",
- "[ID3959]_beremagene geperpavec_Appendix J_B-VEC_Modeling_Assumptions_Validation_[CON]", and
- "[ID3959]_beremagene geperpavec_Appendix J_B-VEC_Modeling_Assumptions_Validation_[redacted]".

C2. Table 3.27 seems incomplete for the severe state. Please provide an update.

Please see the far-right column in Table 35 below.

Table 35 B-VEC cost per cycle (£) by health state, by year and by age subgroup

Age subgroup	Year	B-VEC cost per cycle (£)			
		Very mild	Mild	Moderate	Severe
0 to <6 years	1				
	2				
	3+				
6 to <18 years	1				
	2				
	3+				
≥18 years	1				
	2				
	3+				

C3. CS, Section 3.5.5.1 states that *“Administration costs for both B-VEC and BBE treatment arms are assumed to be included in the nurse time associated with dressing changes.”* However, Section 4.4 of the YHEC report *“assumes that the first application of B-VEC will be administered by a specialist nurse in a hospital setting, with subsequent applications being administered by patients or their carers in the home setting”*. Please explain the discrepancy.

The sentence in Section 3.5.5.1 should read *“Administration costs for BBE are assumed to be included in the nurse time associated with dressing changes.”* For context, patients are generally self-administering BBE; however, HST28 indicates that up to 36% of patients require professional assistance with dressing changes.²⁹ Therefore, in cases where a healthcare professional is already involved in dressing changes, they can also apply the product during the same visit if needed. See answer to question [B47](#) for further detail.

C4. CS, Section 3.13 states that *“The quality checklist used to assess the cost-effectiveness model of B-VEC in DEB was included in the CEM file in sheet “QC” and it is based on the report produced according to the model review by the York Health Economic Consortium”*. Please provide this sheet as it's missing from the current model version.

The updated model version provided as a separate file includes the model QC checklist.

C5. CS, Section 3.2.2.1.2.2: *“A normal distribution was assumed and the 25th and 75th percentiles were used to provide the lower-bound of the Moderate and Severe health states, respectively, while the average defined the lower-bound of the Moderate health state (Table 3.5)”* This statement appears to give two different definitions for the lower bound of the moderate state and none for the lower bound of the mild state.

Should it say, “A normal distribution was assumed and the 25th and 75th percentiles were used to provide the lower-bound of the **Mild** and Severe health states, respectively, while the average defined the lower-bound of the Moderate health state (Table 3.5)”?

The EAG is correct with the amended statement, the statement should be “A normal distribution was assumed and the 25th and 75th percentiles were used to provide the lower-bound of the Mild and Severe health states, respectively, while the average defined the lower-bound of the Moderate health state (Table 3.5)”

C6. Please clarify what "m_increase_size_PBO" in the R code refers to and how it is used in the simulation. Additionally, the value of [REDACTED] associated with this parameter was not mentioned in the CS. Should this value be [REDACTED] instead?

The value reflects a [REDACTED]% increase in size of the wound relative to the 3.19 cm² at the time of reopening. In the CS Section 3.2.2.1.2.3, this is reported as an increase in size to [REDACTED] cm². [REDACTED] so the wound becomes [REDACTED] times as large, or an increase in size of ([REDACTED]% – 100%) = [REDACTED]%.

C7. CS Section 3.2.2.1.3.2 “baseline size of the reopened wounds previously treated with B-VEC was assumed to be on average [REDACTED] cm² (SE 0.96).” In the corresponding R code, the value [REDACTED] is defined as a standard deviation (SD). Could you please clarify whether [REDACTED] should be interpreted as a standard error (SE) or a standard deviation (SD)?

The value of [REDACTED] is the standard error (SE) based on the data from GEM-1. The standard deviation (SD) was [REDACTED], based on [REDACTED] observations, resulting in an SE of [REDACTED].

C8. CS, Table 3.5 p94: The chronic and recurrent wounds columns seem to be swapped. Please confirm whether this is a typo.

Thank you to the EAG for bringing this to our attention, this is indeed a typo. Please find the corrected table presented below (Table 36), with the corrected labelling highlighted in green.

Table 36 Number of wounds per health state at risk of reopening

Health state	Number of recurrent wounds Range (average)	Number of chronic wounds Range (average)
Very mild	0-4 (2)	0 (0)
Mild	5-10 (7.5)	1-2 (1.5)
Moderate	11-17 (14)	3-4 (3.5)
Severe	≥18 (31.5)	≥5 (7)

References

1. Jafarzadeh A, Pour Mohammad A, Keramati H, et al. Regenerative medicine in the treatment of specific dermatologic disorders: a systematic review of randomized controlled clinical trials. *Stem Cell Res Ther.* 2024;15(1):176.
2. Pabón-Carrasco M, Caceres-Matos R, Roche-Campos M, et al. Management of Skin Lesions in Patients with Epidermolysis Bullosa by Topical Treatment: Systematic Review and Meta-Analysis. *Healthcare (Basel).* 2024;12(2).
3. Welponer T, Christian P, H. KEW, et al. Systematic review on antipruritic therapies for patients with Epidermolysis bullosa. *Journal of Dermatological Treatment.* 2024;35(1):2381762.
4. Cooper C, Varley-Campbell J, Carter P. Established search filters may miss studies when identifying randomized controlled trials. *J Clin Epidemiol.* 2019;112:12-19.
5. Canada's Drug Agency. RCT / CCT - MEDLINE, Embase. In: Canada's Drug Agency Search Filters Database. 2025; <https://searchfilters.cda-amc.ca/link/122>.
6. Harbour J, Fraser C, Lefebvre C, et al. Reporting methodological search filter performance comparisons: a literature review. *Health Info Libr J.* 2014;31(3):176-194.
7. Moreau P, Garfall AL, van de Donk N, et al. Teclistamab in relapsed or refractory multiple myeloma. *N Engl J Med.* 2022;387(6):495-505.
8. Stratenym. Vyjuvek® (beremagene geperpavec) for the treatment of dystrophic epidermolysis bullosa: SLR report 2025.
9. Schwieger-Briel A, Kiritsi D, Schempp C, et al. Betulin-Based Oleogel to Improve Wound Healing in Dystrophic Epidermolysis Bullosa: A Prospective Controlled Proof-of-Concept Study. *Dermatol Res Pract.* 2017:5068969.
10. Niazi M, Parvizi MM, Saki N, et al. Efficacy of a Topical Formulation of Henna (*Lawsonia Inermis* Linnaeus) on the Itch and Wound Healing in Patients With Epidermolysis Bullosa: a Pilot Single-arm Clinical Trial. *Dermatol Pract Concept.* 2022;12(3):e2022115.
11. Woodley DT, Cogan J, Hou Y, et al. Gentamicin induces functional type VII collagen in recessive dystrophic epidermolysis bullosa patients. *J Clin Invest.* 2017;127(8):3028-3038.
12. ClinicalTrials.gov. NCT03012191: Gentamicin for RDEB. <https://clinicaltrials.gov/show/NCT03012191>.
13. National Institute for Health and Care Excellence (NICE). Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template (PMG24).2024.
14. Sterne JAC HM, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JPT. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. *BMJ.* 2016;355.
15. Guide SV, Gonzalez ME, Bağcı IS, et al. Trial of Beremagene Geperpavec (B-VEC) for Dystrophic Epidermolysis Bullosa. *N Engl J Med.* 2022;387(24):2211-2219.

16. Food and Drug Administration. FDA Approves First Topical Gene Therapy for Treatment of Wounds in Patients with Dystrophic Epidermolysis Bullosa. 2023; <https://www.fda.gov/news-events/press-announcements/fda-approves-first-topical-gene-therapy-treatment-wounds-patients-dystrophic-epidermolysis-bullosa>.
17. Krystal Biotech Inc. GEM-1 Clinical Study Report: A Phase 1/2 Study of B-VEC, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB). 24 May 2022.
18. Krystal Biotech Inc. OLE Clinical Study Report: Open label treatment of beremagene geperpavec (B-VEC). B-VEC-EX-02. 18 October 2023 2023.
19. Eng VA, Solis DC, Gorell ES, et al. Patient-reported outcomes and quality of life in recessive dystrophic epidermolysis bullosa: A global cross-sectional survey. *J Am Acad Dermatol*. 2021;85(5):1161-1167.
20. Bruckner AL, Losow M, Wisk J, et al. The challenges of living with and managing epidermolysis bullosa: insights from patients and caregivers. *Orphanet J Rare Dis*. 2020;15(1):1.
21. Fine JD, Johnson LB, Weiner M, et al. Pseudosyndactyly and musculoskeletal contractures in inherited epidermolysis bullosa: experience of the National Epidermolysis Bullosa Registry, 1986-2002. *J Hand Surg Br*. 2005;30(1):14-22.
22. Petrof G, Papanikolaou M, Martinez AE, et al. The epidemiology of epidermolysis bullosa in England and Wales: data from the national epidermolysis bullosa database. *Br J Dermatol*. 2022;186(5):843-848.
23. Fine JD. Inherited epidermolysis bullosa. *Orphanet J Rare Dis*. 2010;5:12.
24. Atanasova VS, Russell RJ, Webster TG, et al. Thrombospondin-1 Is a Major Activator of TGF- β Signaling in Recessive Dystrophic Epidermolysis Bullosa Fibroblasts. *J Invest Dermatol*. 2019;139(7):1497-1505.e1495.
25. Bardhan A, Bruckner-Tuderman L, Chapple ILC, et al. Epidermolysis bullosa. *Nat Rev Dis Primers*. 2020;6(1):78.
26. Guerra L, Odorisio T, Zambruno G, Castiglia D. Stromal microenvironment in type VII collagen-deficient skin: The ground for squamous cell carcinoma development. *Matrix Biol*. 2017;63:1-10.
27. Ara R, Brazier J. Estimating Health State Utility Values for Comorbidities. *Pharmacoeconomics*. 2017;35(Suppl 1):89-94.
28. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making*. 2011;31(6):800-804.
29. National Institute for Health and Care Excellence (NICE). Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]. Committee papers. 20 September 2023.
30. Haute Autorité de Santé. AVIS SUR LES MEDICAMENTS beremagene geperpavec. 2024.
31. Krystal Biotech Inc. GEM-3 Clinical Study Report. A Phase 3 Efficacy and Safety Study of Beremagene Geperpavec (B-VEC, Previously KB103) for the Treatment of Dystrophic Epidermolysis Bullosa (DEB). 24 May 2022.
32. Fulchand S, Harris N, Li S, et al. Patient-reported outcomes and quality of life in dominant dystrophic epidermolysis bullosa: A global cross-sectional survey. *Pediatr Dermatol*. 2021;38(5):1198-1201.

33. Angelis A, Mellerio JE, Kanavos P. Understanding the socioeconomic costs of dystrophic epidermolysis bullosa in Europe: a costing and health-related quality of life study. *Orphanet J Rare Dis.* 2022;17(1):346.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions

May 2025

File name	Version	Contains confidential information	Date
ID3959 Beremagene EAG Clarification letter to company [CON]	1	Yes	22/05/25

Patient level simulation

B15. [Priority] The company's patient level simulation should be sufficiently flexible to generate transition matrices for an alternative set of health states. Please use the patient level simulation to estimate transition matrices for BSC and B-VEC for the 6 health states employed in the HST28 model. Please use these to conduct an indirect comparison (as requested at question A34) between BSC, B-VEC and BBE using the HST28 model structure. The EAG's rationale for requesting this is that it would significantly reduce the number of assumptions required to make the indirect comparison.

Inclusion of B-VEC in the replicated HST28 model

In addition to the response submitted on 21 May 2021, we have taken some further steps to allow for an indirect comparison between B-VEC and BBE. To summarise, we have taken the following steps, which will be discussed in detail below:

- Adjusted the patient-level simulation (PLS) to generate transition matrices for B-VEC and best supportive care (BSC) for 6 health states (using the definitions from HST28) and 1-month cycle length, aligned with the HST28 model;
- Used the generated 6-health state transition matrices for B-VEC and BSC generated to conduct an indirect treatment comparison (ITC) between B-VEC and BBE;
- Included the ITC outputs in the cost-effectiveness model for the current submission to assess the cost effectiveness of B-VEC versus BBE.

Adjusted patient-level simulation

The PLS with 6 health states is included as a separate function in an updated R package. There are three main changes in this PLS function compared to the one used to population the B-VEC CEM:

- Definition of the health states with regards to the BSAP with open wounds. This is aligned with the definitions of health states in HST28. However, as the current PLS

differentiates between chronic and recurrent wounds, and the HST28 model only considered total BSAP, it was assumed that the distribution of wounds between chronic and recurrent in health state 1 was aligned with the average distribution in Very Mild and Mild health states (both <5% BSAP in total, which aligns with HST28 Health state 1), the distribution between recurrent and chronic wounds in Health States 2, 3, 4 and 5 is aligned with the distribution in the Moderate health state, and the distribution between recurrent and chronic wounds in Health State 6 is aligned with the distribution in the Severe health state. This results in health state definitions as presented in Table 1.

Table 1: Health state definitions in 6 health-state patient level simulation

Health state	Total		Recurrent		Chronic	
	Lower	Upper	Lower	Upper	Lower	Upper
HS1	0.0%	5.0%	0.0%	4.4%	0.0%	0.6%
HS2	5.0%	8.0%	4.4%	4.8%	0.6%	3.2%
HS3	8.0%	11.0%	4.8%	6.6%	3.2%	4.4%
HS4	11.0%	18.0%	6.6%	10.8%	4.4%	7.2%
HS5	19.0%	25.0%	10.8%	15.0%	7.2%	10.0%
HS6	25.0%	40.0%	15.0%	20.0%	10.0%	20.0%

- Definitions of the health states with regards to the number of wounds at risk of reopening were estimated using the same approach as was used for the 4 health state model, however, instead of using the 25th, 50th and 75th percentiles (ie quartiles) of the assumed normal distributions, sextiles were used instead (ie, the 16.6th, 33.3th, 50th, 66.6th and 83.3th percentiles). This results in the number of wounds at risk of reopening by health state as presented in Table 2.

Table 2: Number of wounds at risk of reopening by health state, in 6 health-state patient level simulation

	Total		Recurrent		Chronic	
Health state	Lower	Upper	Lower	Upper	Lower	Upper
HS1	0	2	0	1	0	1
HS2	4	8	2	6	2	2
HS3	10	13	7	10	3	3
HS4	14	18	11	15	3	3
HS5	20	24	16	20	4	4
HS6	26	54	21	45	5	9

- The cycle length was adjusted to 4 weeks instead of 3 months. This meant that the output of the simulation consisted of 26 transition matrices per arm, instead of 8, to cover the two years over which patients' health states are tracked in the PLS.

A separate set of six health-state transition matrices was estimated for both B-VEC and BSC, stratified by three age groups: 0–6 years, 6–18 years, and 18 years and older. These matrices were then weighted according to the proportion of the cohort in each age group, as defined in the B-VEC model, to enable a comparison with BBE transition matrices from HST28 model, which were not stratified by age. The final transition matrices for B-VEC and BSC are presented in Table 3 and Table 4.

Table 3: B-VEC transition probabilities based on 6 health-states simulation

Starting health state	Resulting health state					
	HS1	HS2	HS3	HS4	HS6	HS6
Week 0 to 4						
HS1	■	■	■	■	■	■
HS2	■	■	■	■	■	■
HS3	■	■	■	■	■	■
HS4	■	■	■	■	■	■
HS5	■	■	■	■	■	■
HS6	■	■	■	■	■	■
Week 4 to 8						
HS1	■	■	■	■	■	■
HS2	■	■	■	■	■	■
HS3	■	■	■	■	■	■
HS4	■	■	■	■	■	■
HS5	■	■	■	■	■	■
HS6	■	■	■	■	■	■
Week 8 to 12						

HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 12 to 16												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 16 to 20												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 20 to 24												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 24 to 28												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 28 to 32												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 32 to 36												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■

HS5								
HS6								
Week 32 to 40								
HS1								
HS2								
HS3								
HS4								
HS5								
HS6								
Week 40 to 44								
HS1								
HS2								
HS3								
HS4								
HS5								
HS6								
Week 44 to 48								
HS1								
HS2								
HS3								
HS4								
HS5								
HS6								
Week 48 to 52								
HS1								
HS2								
HS3								
HS4								
HS5								
HS6								
Week 52 to 56								
HS1								
HS2								
HS3								
HS4								
HS5								
HS6								
Week 56 to 60								
HS1								
HS2								
HS3								
HS4								
HS5								
HS6								
Week 60 to 64								
HS1								

HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 64 to 68												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 68 to 72												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 72 to 76												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 76 to 80												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 80 to 84												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 84 to 88												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■

HS6						
Week 88 to 92						
HS1						
HS2						
HS3						
HS4						
HS5						
HS6						
Week 92 to 96						
HS1						
HS2						
HS3						
HS4						
HS5						
HS6						
Week 96 to 100						
HS1						
HS2						
HS3						
HS4						
HS5						
HS6						
Week 100 to 104						
HS1						
HS2						
HS3						
HS4						
HS5						
HS6						

Table 4: BSC transition probabilities based on 6 health-states simulation

Starting health state	Resulting health state					
	HS1	HS2	HS3	HS4	HS6	HS6
Week 0 to 4						
HS1						
HS2						
HS3						
HS4						
HS5						
HS6						
Week 4 to 8						
HS1						
HS2						
HS3						

HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 8 to 12												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 12 to 16												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 16 to 20												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 20 to 24												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 24 to 28												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 28 to 32												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 32 to 36												

HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 32 to 40												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 40 to 44												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 44 to 48												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 48 to 52												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 52 to 56												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 56 to 60												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■

HS5						
HS6						
Week 60 to 64						
HS1						
HS2						
HS3						
HS4						
HS5						
HS6						
Week 64 to 68						
HS1						
HS2						
HS3						
HS4						
HS5						
HS6						
Week 68 to 72						
HS1						
HS2						
HS3						
HS4						
HS5						
HS6						
Week 72 to 76						
HS1						
HS2						
HS3						
HS4						
HS5						
HS6						
Week 76 to 80						
HS1						
HS2						
HS3						
HS4						
HS5						
HS6						
Week 80 to 84						
HS1						
HS2						
HS3						
HS4						
HS5						
HS6						
Week 84 to 88						
HS1						

HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 88 to 92												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 92 to 96												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 96 to 100												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■
Week 100 to 104												
HS1		■		■		■		■		■		■
HS2		■		■		■		■		■		■
HS3		■		■		■		■		■		■
HS4		■		■		■		■		■		■
HS5		■		■		■		■		■		■
HS6		■		■		■		■		■		■

Indirect treatment comparison between B-VEC and BBE

To explore the relative efficacy of B-VEC versus BBE, we conducted an ITC using the Bucher method, based on the difference versus BSC in the relative change in the proportion of cohort in each health state over two consecutive model cycles (monthly). The method of this ITC is aligned with the ITC described in the response to question B15 submitted on 21 May 2021. This analysis and incorporated output from the adjusted PLS (See Table 3 and Table 4) and transition probabilities based on the BBE

trial as presented in the company submission for HST28, that inform the modelled distribution across health states.

The ITC was computed for Month 1 until Month 12 versus the previous month respectively. Beyond Month 12, the HST28 model applies a continuity matrix in the BBE arm. To avoid incorporating model-driven extrapolations rather than data-derived transitions, the comparison was therefore limited to the first 12 months of treatment.

The change in patient distribution across health states over time, was calculated for the following arms:

- BBE: Using transition data from the HST28 model, which are based on changes in BSA with open wounds observed in the EASE trial.
- CCM (placebo): Using comparator data from HST28, also informed by the EASE trial.
- B-VEC: Using transition probabilities from the 6 health-states patient-level simulation, based on wound dynamics observed in GEM-1, GEM-3 and the OLE study.
- BSC (placebo): Also based on the 6 health-states patient-level simulation, informed by wound dynamics in the placebo arm of GEM-1 study.

The adjusted indirect comparison was then performed using the Bucher method, with the assumption that CCM and BSC placebo arms are comparable. This Bucher ITC may be considered an improvement compared to a naïve comparison, as it allows for the estimation of the relative efficacy of B-VEC vs BBE, preserving the within-study randomisation.

The relative treatment effect of B-VEC vs BBE was calculated as:

$$\hat{\gamma}_{BB} = \gamma_{BVEC} - \gamma_{BBE}$$

Where:

- γ_{BB} is the estimated difference in the relative change in the proportion of patients in each health state over two consecutive cycles between B-VEC and BBE.

- Y_{BVEC} is the estimated difference vs BSC (placebo) in the relative change in the proportion of patients in each health-state over two consecutive cycles for B-VEC, based on transitions derived from the patient level simulation used in our model (for both B-VEC and BSC).
- Y_{BBE} is the estimated difference vs CCM (placebo) in the relative change in the proportion of patients in each health-state over two consecutive cycles for BBE, based on HST28 model transitions (for both BBE and CCM).

Separate Bucher comparisons were conducted for each of the six health states. The results from each Bucher indirect comparison are presented in Table 5.

Table 5 Bucher adjusted indirect comparison between B-VEC and BBE on the difference in the relative change in proportion of patients in each health-state over time, 6 health states

	Relative change in proportion of patients in health-state over two consecutive model cycles						
	Transitions from PLS based on GEM1, GEM3 and OLE in replicated HST28 model			Transitions from EASE in replicated HST28 model			Bucher ITC
	B-VEC	Placebo (BSC)	B-VEC vs placebo mean, SE ^a (95%CI ^c)	BBE	Placebo (CCM)	BBE vs placebo mean, SE ^a (95%CI ^c)	BBE vs B-VEC mean, SE ^b (95%CI ^c) p-value
Health state 1							
Baseline to Month 1	■	■	■	1.11	1.02	0.09, 0.01 (0.07, 0.1)	■
Month 1 to Month 2	■	■	■	0.93	0.15	0.78, 0.08 (0.63, 0.93)	■
Month 2 to Month 3	■	■	■	0.98	0.98	0.01, 0 (0.01, 0.01)	■
Month 3 to Month 4	■	■	■	0.98	1.00	-0.02, 0 (-0.02, -0.01)	■
Month 4 to Month 5	■	■	■	0.99	1.00	-0.01, 0 (-0.02, -0.01)	■
Month 5 to Month 6	■	■	■	0.99	1.00	-0.01, 0 (-0.01, -0.01)	■
Month 6 to Month 7	■	■	■	0.99	1.00	-0.01, 0 (-0.01, -0.01)	■
Month 7 to Month 8	■	■	■	0.99	1.00	-0.01, 0 (-0.01, -0.01)	■
Month 8 to Month 9	■	■	■	0.99	1.00	-0.01, 0 (-0.01, -0.01)	■
Month 9 to Month 10	■	■	■	0.99	1.00	-0.01, 0 (-0.01, 0)	■
Month 10 to Month 11	■	■	■	1.00	1.00	0, 0 (-0.01, 0)	■
Month 11 to Month 12	■	■	■	1.00	1.00	0, 0 (0, 0)	■
Health state 2							
Baseline to Month 1	■	■	■	1.27	1.34	-0.06, 0.01 (-0.08, -0.05)	■
Month 1 to Month 2	■	■	■	1.05	0.80	0.25, 0.02 (0.2, 0.3)	■
Month 2 to Month 3	■	■	■	1.03	0.99	0.03, 0 (0.03, 0.04)	■
Month 3 to Month 4	■	■	■	1.06	1.00	0.06, 0.01 (0.05, 0.07)	■

Month 4 to Month 5	■	■	■■■■■■■■■■	1.06	1.00	0.06, 0.01 (0.05, 0.07)	■■■■■■■■■■
Month 5 to Month 6	■	■	■■■■■■■■■■	1.06	1.00	0.06, 0.01 (0.05, 0.07)	■■■■■■■■■■
Month 6 to Month 7	■	■	■■■■■■■■■■	1.06	1.00	0.06, 0.01 (0.05, 0.07)	■■■■■■■■■■
Month 7 to Month 8	■	■	■■■■■■■■■■	1.06	1.00	0.06, 0.01 (0.04, 0.07)	■■■■■■■■■■
Month 8 to Month 9	■	■	■■■■■■■■■■	1.05	1.00	0.05, 0.01 (0.04, 0.06)	■■■■■■■■■■
Month 9 to Month 10	■	■	■■■■■■■■■■	1.05	1.00	0.05, 0.01 (0.04, 0.06)	■■■■■■■■■■
Month 10 to Month 11	■	■	■■■■■■■■■■	1.05	1.00	0.05, 0 (0.04, 0.06)	■■■■■■■■■■
Month 11 to Month 12	■	■	■■■■■■■■■■	1.05	1.00	0.05, 0 (0.04, 0.05)	■■■■■■■■■■
Health state 3							
Baseline to Month 1	■	■	■■■■■■■■■■	0.99	0.93	0.06, 0.01 (0.05, 0.07)	■■■■■■■■■■
Month 1 to Month 2	■	■	■■■■■■■■■■	1.01	2.22	-1.21, 0.12 (-1.44, -0.97)	■■■■■■■■■■
Month 2 to Month 3	■	■	■■■■■■■■■■	1.04	1.01	0.03, 0 (0.02, 0.04)	■■■■■■■■■■
Month 3 to Month 4	■	■	■■■■■■■■■■	1.12	1.00	0.12, 0.01 (0.1, 0.14)	■■■■■■■■■■
Month 4 to Month 5	■	■	■■■■	1.09	1.00	0.09, 0.01 (0.07, 0.11)	■■■■■■■■■■
Month 5 to Month 6	■	■	■■■■■■■■■■	1.07	1.00	0.07, 0.01 (0.05, 0.08)	■■■■■■■■■■
Month 6 to Month 7	■	■	■■■■■■■■■■	1.05	1.00	0.05, 0 (0.04, 0.06)	■■■■■■■■■■
Month 7 to Month 8	■	■	■■■■■■■■■■	1.04	1.00	0.04, 0 (0.03, 0.04)	■■■■■■■■■■
Month 8 to Month 9	■	■	■■■■■■■■■■	1.03	1.00	0.03, 0 (0.02, 0.03)	■■■■■■■■■■
Month 9 to Month 10	■	■	■■■■■■■■■■	1.02	1.00	0.02, 0 (0.01, 0.02)	■■■■■■■■■■
Month 10 to Month 11	■	■	■■■■■■■■■■	1.01	1.00	0.01, 0 (0.01, 0.01)	■■■■■■■■■■
Month 11 to Month 12	■	■	■■■■■■■■■■	1.01	1.00	0.01, 0 (0, 0.01)	■■■■■■■■■■
Health state 4							
Baseline to Month 1	■	■	■■■■■■■■■■	1.63	1.72	-0.08, 0.01 (-0.1, -0.07)	■■■■■■■■■■
Month 1 to Month 2	■	■	■■■■■■■■■■	1.50	1.02	0.48, 0.05 (0.39, 0.58)	■■■■■■■■■■

Month 2 to Month 3	■	■	■	1.04	1.45	-0.41, 0.04 (-0.49, -0.33)	■
Month 3 to Month 4	■	■	■	0.93	1.00	-0.07, 0.01 (-0.08, -0.06)	■
Month 4 to Month 5	■	■	■	0.93	1.00	-0.07, 0.01 (-0.09, -0.06)	■
Month 5 to Month 6	■	■	■	0.93	1.00	-0.07, 0.01 (-0.09, -0.06)	■
Month 6 to Month 7	■	■	■	0.93	1.00	-0.07, 0.01 (-0.09, -0.06)	■
Month 7 to Month 8	■	■	■	0.93	1.00	-0.07, 0.01 (-0.09, -0.06)	■
Month 8 to Month 9	■	■	■	0.93	1.00	-0.07, 0.01 (-0.09, -0.06)	■
Month 9 to Month 10	■	■	■	0.93	1.00	-0.07, 0.01 (-0.09, -0.06)	■
Month 10 to Month 11	■	■	■	0.93	1.00	-0.07, 0.01 (-0.09, -0.06)	■
Month 11 to Month 12	■	■	■	0.93	1.00	-0.07, 0.01 (-0.09, -0.06)	■
Health state 5							
Baseline to Month 1	■	■	■	1.00	1.00	0, 0 (0, 0)	■
Month 1 to Month 2	■	■	■	0.18	0.97	-0.79, 0.08 (-0.95, -0.64)	■
Month 2 to Month 3	■	■	■	0.07	0.18	-0.11, 0.01 (-0.13, -0.09)	■
Month 3 to Month 4	■	■	■	0.10	1.00	-0.9, 0.09 (-1.08, -0.72)	■
Month 4 to Month 5	■	■	■	0.10	1.00	-0.9, 0.09 (-1.08, -0.72)	■
Month 5 to Month 6	■	■	■	0.10	1.00	-0.9, 0.09 (-1.08, -0.72)	■
Month 6 to Month 7	■	■	■	0.10	1.00	-0.9, 0.09 (-1.08, -0.72)	■
Month 7 to Month 8	■	■	■	0.10	1.00	-0.9, 0.09 (-1.08, -0.72)	■
Month 8 to Month 9	■	■	■	0.10	1.00	-0.9, 0.09 (-1.08, -0.72)	■
Month 9 to Month 10	■	■	■	0.10	1.00	-0.9, 0.09 (-1.08, -0.72)	■
Month 10 to Month 11	■	■	■	0.10	1.00	-0.9, 0.09 (-1.08, -0.72)	■
Month 11 to Month 12	■	■	■	0.10	1.00	-0.9, 0.09 (-1.08, -0.72)	■
Health state 6							

Baseline to Month 1	■	■	■	0.00	0.00	0, 0 (0, 0)	■
Month 1 to Month 2	■	■	■	0.00	0.00	0, 0 (0, 0)	■
Month 2 to Month 3	■	■	■	0.00	0.00	0, 0 (0, 0)	■
Month 3 to Month 4	■	■	■	0.00	0.00	0, 0 (0, 0)	■
Month 4 to Month 5	■	■	■	0.00	0.00	0, 0 (0, 0)	■
Month 5 to Month 6	■	■	■	0.00	0.00	0, 0 (0, 0)	■
Month 6 to Month 7	■	■	■	0.00	0.00	0, 0 (0, 0)	■
Month 7 to Month 8	■	■	■	0.00	0.00	0, 0 (0, 0)	■
Month 8 to Month 9	■	■	■	0.00	0.00	0, 0 (0, 0)	■
Month 9 to Month 10	■	■	■	0.00	0.00	0, 0 (0, 0)	■
Month 10 to Month 11	■	■	■	0.00	0.00	0, 0 (0, 0)	■
Month 11 to Month 12	■	■	■	0.00	0.00	0, 0 (0, 0)	■

B-VEC=beremagene geperpavec; BBE=birch bark extract; BSC=best supportive care; CCM=current clinical management; CI: confidence interval, ITC=indirect treatment comparison; OLE=open-label extension; SE: standard error.

Notes: Bold p-value indicates statistical significance. a) SE was calculated assuming 10% of mean difference. b) the SE was calculated as square root of the sum of $SE_{B-VEC \text{ vs placebo}}^2$ and $SE_{BBE \text{ vs placebo}}^2$. c) The 95% CI was calculated assuming a normal distribution

Assessing the cost effectiveness of B-VEC versus BBE based on the Bucher ITC on 6 health states transitions

The outputs of the Bucher ITC were used to derive the transitions in the BBE arm implemented within the executable cost-effectiveness model in the current submission to assess the impact on the cost-effectiveness between B-VEC, BBE and BSC:

- The adjusted relative effect between BVEC and BBE obtained from the 6 health-states Bucher ITC (Table 5) was used to estimate the distribution of the cohort across the 6 health-states in the BBE arm (Table 6). The baseline health-state distribution was derived from Bruckner et al., in line with the assumption in the current submission, provided in Table 3.8 of company submission (CS), adjusted to fit the 6 health-states definition.
- The 6 health-states distribution in the BBE arm obtained from the Bucher ITC was then mapped to 4 health-states (i.e. very mild, mild, moderate and severe) and 3-months cycles, as per current submission (Table 7). A continuity matrix was applied for the BBE arm beyond Month 12, as per current model assumptions.
- The cohort distribution across health states in the B-VEC and BSC arms was estimated based on transition probabilities derived from the 4 health-state patient-level simulation, as per current submission (provided in Tables 3.16 and 3.17 of company submission).

Table 6 Distribution of the cohort between the 6 health-states in the BBE arm, estimated from the Bucher ITC

	HS1	HS2	HS3	HS4	HS5	HS6
Baseline	10.4%	10.9%	9.8%	9.8%	9.8%	49.3%
Month 1	■	■	■	■	■	■
Month 2	■	■	■	■	■	■
Month 3	■	■	■	■	■	■
Month 4	■	■	■	■	■	■
Month 5	■	■	■	■	■	■
Month 6	■	■	■	■	■	■
Month 7	■	■	■	■	■	■
Month 8	■	■	■	■	■	■
Month 9	■	■	■	■	■	■

Month 10	■	■	■	■	■	■
Month 11	■	■	■	■	■	■
Month 12	■	■	■	■	■	■

BBE=birch bark extract; HS: health-state; ITC=indirect treatment comparison. Note: the proportion of cohort in each health-state was calculated as: cohort in each health-state at cycle t * (relative change in cohort month t+1 vs t in B-VEC arm – relative effect from Bucher ITC B-VEC vs BBE).

Table 7 Distribution of the cohort between the CS model health-states in the BBE arm

	Very Mild	Mild	Moderate	Severe
Baseline	0.0%	21.6%	29.0%	49.3%
Month 3	■	■	■	■
Month 6	■	■	■	■
Month 9	■	■	■	■
Month 12	■	■	■	■

BBE=birch bark extract. Note:

The resulting cost-effectiveness outcomes are presented in Table 8. These results indicate that the ICER for B-VEC compared to BBE remains dominant, consistent with the results of the base case analysis. The outcomes of the Bucher ITC and its implementation within the cost-effectiveness model included in the CS, support the conclusion that B-VEC is a cost-effective alternative to BBE, regardless of whether transitions from the PLS are modelled using four or six health-states, or whether the cycle duration is set to one month or three months.

Although we conducted the ITC between BVEC and BBE using 6 health-states transitions derived from the PLS, as requested by the EAG, we would like to reiterate that the 6 health-state model structure used in the HST28 is not appropriate for evaluating B-VEC. This is because several key components—critical for accurately assessing the clinical and economic value of B-VEC—are not captured from the HST28 model. These differences are detailed in our responses to Questions B4 and B15, submitted on 21 May 2021.

Table 8: Results of the cost-effectiveness model with BBE arm transitions estimated based on 6 health-states Bucher ITC

						B-VEC vs...					
Technology	Total					Incremental				ICER (£/QALY)	iNMB at £50,000
	Costs	LYs	Patient QALYs	Caregiver QALYs	Total QALYs	Costs	Patient QALYs	caregiver QALYs	Total QALYs		
B-VEC		23.80	12.87	37.58	50.44						
BBE	£1,155,726	23.80	11.10	36.67	47.77		1.77	0.91	2.68		
CCM	£935,208	23.80	9.95	35.65	45.60		2.92	1.93	4.84		

Thank you for your email and for the EAG's further clarification regarding the request related to Clarification Question B15.

We greatly appreciate the EAG's continued engagement and understand the rationale for requesting a full B-VEC model using the 6-state transition matrices within the HST28 model structure. We fully support the objective of facilitating indirect comparisons between B-VEC, BBE, and BSC. However, after careful consideration, we respectfully do not believe it is appropriate to implement B-VEC within the HST28 modelling framework, and therefore will not be providing the requested model. Below we discuss the supporting argumentation for our approach

Rationale for Health States in the B-VEC Model

The de novo model submitted for B-VEC was developed with input from UK clinical experts to capture the clinical value of B-VEC in DEB. The model considers five mutually exclusive and exhaustive health states—Very Mild, Mild, Moderate, Severe, and Death—defined based on the percentage of body surface area (BSA) covered by open recurrent and chronic wounds. These thresholds were derived from structured elicitation with UK clinical experts and align with published clinical literature (e.g., Bruckner et al., Eng et al.). Mapping open wound area to disease severity allowed for the inclusion of reversible and irreversible clinical manifestations, mortality risk, HRQoL impacts, and associated costs across health states. The health state definitions are summarised in Table 3.6 of the submission and reflect a clinically validated understanding of DEB progression and severity.

Importantly, in our model:

- Very Mild is defined as total open wound area <2.1% BSA,
- Mild as 2.1–5.0%,
- Moderate as 5.0–25.0%, and
- Severe as ≥25.0%.

This approach was selected for its clinical relevance, as validated by clinical experts, but it also enables meaningful modelling of B-VEC's clinical value, including reduction in wound burden and downstream complications. By contrast, the clinical rationale supporting the 6-state model in HST28 was not clearly elucidated and does not correspond to the recognised categories of DEB severity used in the published literature or clinical practice.

Moreover, the HST28 model defines the best achievable outcome as body surface area percentage of <5%, which corresponds to the Mild state in our model. Given that B-VEC is a disease-modifying treatment, it addresses the genetic cause of DEB and leads to accelerated wound closure, improved durability of healing, and reduces the likelihood of developing clinical manifestations. These effects required a modelling approach that captured healing of all wounds (i.e., 0% of BSA with open wounds). As such, much of the clinical benefit of B-VEC—particularly achieving and maintaining Very Mild disease (<2.1% BSA percentage [BSAP])—would not be captured using the HST28 structure.

Capturing B-VEC's Long-Term Clinical and Economic Benefits

B-VEC is a topical, redosable gene therapy designed to address the underlying genetic cause of DEB, by delivering functional COL7A1 gene copies and restoring type VII collagen expression at the dermal-epidermal junction. As a result, B-VEC not only accelerates wound closure but also improves the durability of healing, which in turn reduces the likelihood of developing clinical manifestations and deterioration in health-related quality of life (HRQoL). In contrast, the mechanism of action of BBE is not known, and the main goal of treatment is symptom management. To capture the full economic and clinical value of B-VEC, the model needs to account for these differences between B-VEC and BBE.

Our model also accounts for health state-specific mortality risk, capturing increased risk in patients with greater wound burden. This is an important consideration given B-VEC's impact on sustained wound closure and long-term survival. In contrast, the HST28 model applies a uniform mortality risk for all patients and therefore does not account for disease severity.

Key Structural and Input Differences Between B-VEC and HST28 Models

In addition, we would like to point out these key differences between the models (a full list was provided in response to question B15):

- **Utility values:** Derived using EQ-5D-3L via vignette study, per NICE reference case, whereas the HST28 model used alternative utilities, which are less reflective of patient experience.
- **Baseline distribution:** Informed by real-world observational data from RDEB and DDEB patients, resulting in a more representative severity profile compared to the even distribution assumed in HST28.

Justification for Health State Mapping for BBE Arm

We believe our mapping from six to four health states does not materially change the representation of BBE's clinical or economic impact. It's important to note that in the EASE trial, the distribution of BBE patients over wound area (BSAP) categories was relatively stable between the double-blind and OLE baseline (see Table 10 of the HST28 company submission). This is also reflected in the HST28 model's transition matrices, where most patients remain in the same health state, or show modest improvement. The accuracy of the mapping is further supported by the consistency in outcomes with regards to total costs and total QALYs associated with BBE between the replicated HST28 model with six and four health states.

Limitations of the HST28 Transition Matrices for Indirect Comparison

We also wish to highlight two additional important limitations of using the HST28 transition matrices as the basis for comparison:

- The transition probabilities for BBE and CCM used in the company's original HST28 submission were not those used for final decision-making. As such,

comparisons between B-VEC and BBE based on these inputs would not be appropriate.

- In the HST28 transition matrices, all patients exit Health State 6 during the first cycle, and none enter it thereafter, resulting in no patients occupying this state beyond baseline. This is not clinically plausible, particularly in the CCM arm, and would introduce further bias in any indirect comparison using this framework.

Summary of Analyses Submitted in Response to Question B15

We responded to the EAG request by conducting anchored indirect treatment comparisons (ITCs) via Bucher method, based on both 4-state and 6-state transition matrices for BBE, B-VEC and BSC. We also tested several alternative model scenarios based on ITC results to further explore uncertainty. Together, these analyses provide a robust and transparent comparison of B-VEC and BBE using the available evidence. Despite some variation in the ITC outcomes and impact on the ICERs across scenarios tested, all analyses consistently supported the cost-effectiveness of B-VEC compared with BBE.

Conclusions

We therefore believe the health state definitions used in the B-VEC de novo model are clinically more appropriate for capturing B-VEC outcomes. While using the HST28 model framework might appear to facilitate comparison with BBE, it would introduce significant uncertainty regarding overall disease progression in DEB and would not capture B-VEC's true clinical and economic benefits. In our view, using the HST28 model framework is not an appropriate approach for conducting a comparison to BBE.

Given the evidence presented above, we respectfully believe that the EAG's request to adapt the HST28 modelling framework for B-VEC is not appropriate and would not yield a valid assessment of its clinical and economic value. Therefore, we will not be providing the requested model. We are committed to transparency and collaboration and are open to further discussions on alternative approaches that might support the EAG's objectives without compromising the methodological integrity of the B-VEC evaluation.

Single Technology Appraisal
Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]
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	
2. Name of organisation	Cure EB
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	Cure EB was set up and is run by parents of a child with recessive dystrophic epidermolysis bullosa (RDEB). Cure EB is a medical research charity dedicated to finding treatments and cures for all types of epidermolysis bullosa. We do not operate a membership scheme but encourage families to join our Family Forum and research webinars whose purpose is to disseminate research information. We also hold community events such as an annual Family Day at which families can meet each other, the children play whilst parents listen to researchers speak followed by discussions. Cure EB is funded through individual donations, trusts and foundations, corporate donations and sponsorships, appeals, digital campaigns, and money raised through sporting challenges or events such as gala dinners and lunches. Our mission is in our name, to Cure 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 the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	Krystal Biotech, Inc. provided us with £2000 sponsorship towards our annual Butterfly Run and Family Day in September 2024. Chiesi Limited gave us a grant of £1300 in March 2024 and £800 in March 2025 to fund research dissemination activities such as our annual research update meeting printing and research webinars.

Patient organisation submission

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

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We are led by families who have direct experience of the condition, with tight links with families across the UK and the world experiencing it. We used this powerful network to gather information for this submission: 1) UK families – to share their experiences of living with epidermolysis bullosa (EB), unmet needs, current treatments, and their thoughts on the new technology under review. 2) US and European families – to share lived experience views of patients and families who already have access to the treatment. We also obtained an expert opinion from [REDACTED] ([REDACTED]) who has so far treated nine patients on an early access scheme in Europe and would be willing to share her experiences with NICE should you require it.

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 with EB suffer constant and unimaginable pain on a daily basis from blistering and skin loss. Severe types lead to a shortened life through complications of the condition or to a malignant skin cancer which carries a very high mortality (Has, C et al. J Eur Acad Dermatol Venereol 2021 35: 2349-2360). EB patients, and by extension their care givers, have a significantly lower health-related quality of life compared with the general population (Angelis A. et al Eur J Health Econ 2016 17 Suppl 1:S31-S42) <u>Physical Impact</u> With dominant dystrophic EB (DDEB) and RDEB, the lack of or reduced levels of the collagen VII protein in the skin leads to blistering and skin loss leaving raw open wounds that are like severe burns. The blistering and skin loss are apparent at birth and are life-long features of the condition. From birth, management of the condition requires lengthy dressing changes that can take between two and five hours daily. Blisters need to be pricked else they grow larger, and wounds must be dressed. The process is extremely painful and requires powerful pain medication to help. This could be a combination of milder analgesics such as paracetamol and ibuprofen, but often includes opiate drugs and other medications such as gabapentin and amitriptyline, as well as anti-anxiety medication. In addition to wounds externally, the mouth and oesophagus are impacted, leading to issues with nutrition and pain on eating and swallowing. The eye surface is similarly affected, leading to very painful corneal abrasions that can lead to temporary blindness due to the pain and scarring. The condition is progressive, getting worse with age, as the repeated skin damage leads to inflammation and scarring and in turn, increasing disability due to mitten deformities (where the fingers and toes fuse together), limiting hand use and the ability to walk due to increasing chronic pain. The continuous cycle of wounds healing and breaking down leads to a pernicious itch that one patient described as having “a million ants under your skin that you cannot get rid of”; the inability to control the itch leads to further wounding and so the cycle continues. The chronic wounds, inflammation and scar tissue eventually lead to a malignant squamous cell carcinoma (SCC – a type of skin cancer) (Tartaglia G. et al J Mol Sci. 2021 May 12;22(10):5104), causing death in around 80% of RDEB patients by mid-adulthood (Robertson SJ. et al Acta Derm Venereol. 2021; 101: adv00523) DEB is not limited to external skin, internal ‘skin’ is affected too. Internal blistering leads to shortened tongue, microstomia (small mouth), and oesophageal (food pipe) scarring requiring oesophageal dilatation (surgical widening) and in some cases gastrostomy tube placement to maintain adequate nutrition. Because of the multiple body systems involved patients are seen in multidisciplinary clinics to monitor progress and assess the need for interventions. Overseen by dermatologists, paediatricians, and clinical nurse specialists, care is centred around:

	a) Wound care – dressing materials and techniques to optimally protect the skin and manage blistering and infection control b) Nutritional support – the energy needs of constantly wounding skin are vast, coupled with the difficulties associated with eating, so aggressive nutritional support is necessary (dieticians and gastroenterologists) c) Surgical interventions and SCC treatment – for oesophageal dilatation, gastrostomy tube placement, hand surgery, and cancer-related surgery (anaesthetists, surgeons, radiologists, and oncologists) d) Pain management (palliative care pain specialists) e) Eye problems (ophthalmologists, opticians, orthoptists and optometrists) f) Dental care and interventions (dentists, dental hygienists and orthodontists) g) Psychological support (psychologists and psychiatrists) h) Mobility and dexterity (occupational therapists, hand therapists, physiotherapist, podiatrists and orthotists) “EB is a cruel condition. Our son’s skin shears off or blisters at the slightest touch (for example when rubbing his eyes with his hands), which greatly restricts what he is able to do and his independence.” <i>Mum to an ■ year old RDEB patient (UK)</i> “Living with this condition is horrific, it’s very painful, hours and hours of wound care and dressings changes. Then the after-effects is the itching which is nearly as bad as the pain.” <i>Dad to a ■ year old RDEB patient (UK)</i> “Daily dressing changes take hours. They are the worst part of having EB. The pain they experience is unbearable. It involves very strong medication that leaves you feeling drowsy and sick. You are so exhausted afterwards that you just want to sleep, but then the pain can often get worse as new dressings tighten and raw skin begins to sting, so rest becomes impossible. I don’t think my daughter has ever slept a full night in her life.” <i>Mum to a ■ year old RDEB patient (UK)</i> “I have dominant dystrophic epidermolysis bullosa. I have areas of my skin that are particularly vulnerable to injury; my knees, elbows, feet, hands, toes, fingers, mouth and oesophagus. As I am now an adult I have much smaller areas of open skin. However, the toll of repeated injuries, for example to my fingers from everyday tasks using keys, turning knobs, pressing buttons, means I have contractures. I

	have had hand surgery to release these 3 times, however as my skin continues to be damaged the scarring causes contractures again.” ■ year old DDEB patient (UK) <u>Impact on emotional wellbeing</u> The relentless pain and exhausting daily routine of dressing changes is emotionally draining. There is no respite and, with increasing age, the emotional burden can take its toll. Alongside the pain is a desire but inability to do the things that others do so easily. From an early age, those with EB are excluded from sport, physical activity, and rough games leading to feelings of isolation. In the teenage years, these feelings are compounded as their peers achieve greater freedoms leaving them still restricted. As a family, the emotional toll is extreme. Parents who are carers suffer emotional stress at having to constantly hurt their children to care for them, siblings are always second to the child with EB and sometimes feel that their needs are ignored. In some families, siblings may need to start helping with the carer role, and the strain on the parents can result in marriage breakdown. “It’s very traumatic dealing with the wounds, watching your son going through all that pain, it actually gives me anxiety just to think about doing his dressings. The most painful thing I’ve ever seen. The wounds look like raw meat, blisters are sometimes as big as a golf ball.” Dad to a ■ year old RDEB patient (UK) “The impact to their mental health cannot be underestimated. Your life comes with so many limitations that forming friendships, socialising and participating in anything is very restricted. Then there’s the physical appearance of EB. You wear bandages, have sores and scarring. People constantly stare at you because you look different.” Mum to a ■ year old RDEB patient (UK) 70% of EB patients report that EB has a negative impact on their self-confidence, with 50% reporting experiencing bullying or abuse due to their EB (2023 Epidermolysis Bullosa Patient Insights Study) In Europe, where patients have had early access to beremagene geperpavec (B-VEC), one parent expressed the positive impact on family life and reduced worry about long-term effects “Possibility of using the time recovered for other family activities, less preoccupation for the systemic consequences of the pathology

and for the possible degeneration of the wounds (malignant tumor formations etc.)” Parent of a ■ year old RDEB patient (Italy)

Social mobility

Whilst schooling can be a very positive experience for children with EB, where the school and children are supportive, there are many instances reported where children are discriminated against, either because of the special considerations that have to be made by the school to accommodate a child with EB (such as having a carer in class) or because a child feels isolated by activities that they are unable to participate in or feeling isolated by their peers. School attendance can be severely disrupted by hospital appointments and events such as eye abrasions causing additional stress because of children falling behind in their work.

“There's no let up, it is relentless in its ability to impact the simplest aspects of your everyday life. There are no exceptions. You are so fragile that eating, sleeping, mobility, bathing, playing, going outside, socialising all come with consequences that have to be measured and managed closely.” Mum to a ■ year old RDEB patient (UK)

Those who go to university have the initial challenge of having to manage away from home for perhaps the first time in their lives, negotiate explaining their condition, or trying to pretend they are the same as everyone else. They then need to manage their university work around dressings, hospital appointments and interventions such as surgeries. With the increasing disability, finding the ability to work with EB is very difficult. Finding the right flexibility to accommodate the need to manage the condition, and the constraints around travel, requires very understanding work places or suitable self-employment. The reality is that for many, ill health requires sufferers to be homebound.

“It is challenging and painful and very difficult to attain a sense of independence and living life fully.” ■ year old RDEB patient (UK)

Economic Impact

The economic burden of EB is considerable to both the family and the state. It is almost invariably the case that one parent will leave work to become a full-time carer for their child at birth, to learn how to manage the condition and due to the significant number of hours required for wound care, which results in significant informal care expenses ([ISPOR Europe 2023 poster EE395](#)).

“■ also attends frequent hospital appointments and is admitted to hospital due to swallowing difficulties and infection with no notice; this greatly affects our ability to work and focus on our work in

the way we otherwise would; we have both had to take and remain in jobs that allow for our caring responsibilities and the flexibility to be able to stop work to attend and stay in hospital as required."

Mum to an ■ year old RDEB patient (UK)

There are associated costs involved around getting specialist clothing, footwear, furniture (hospital-style beds and lifting chairs), bedding, humidifiers and fans, wheelchairs, blenders and feeding aids (specialist bottles), wheelchairs, sheepskins, bathing aids, and dressings trolleys. Everyday items such as towels and sheets must be replaced frequently because of the extra washing needed and the need to use strong cleaning products to counter the blood and fluid that may invariably mean changing bedding once a day.

For the state, costs are significant when you consider the appointments, interventions, medicines, dressings, hospitalisations, and blood tests, etc. A UK study of 59 RDEB patients, found that severe RDEB patients had median annual costs of £90,000, with wound and skin care (including dressings) accounting for £78,234 ([Jefferis et al Skin Health Dis. 2024; 4\(1\):e314](#)).

Add to this the cost of carers, equipment grants and social support into adulthood and the economic impact is significant. A study in the EU5 countries, found that the average annual cost per DEB patient was estimated at €53,359, significantly higher than those for the overall EB population ([Angelis et al. Orphanet J Rare Dis \(2022\) 17:346](#)). Over three quarters of this was due to direct non-medical costs, which include social health services, professional carer costs, transportation costs and informal care costs. This was borne out by a more recent Spanish study ([Aranda-Reneo et al. Orphanet J Rare Dis \(2024\) 19:352](#)) of 62 EB patients (62% DEB), which demonstrated that direct non-healthcare costs accounted for just over 71.3% of costs (the majority of which was due to informal care) across all EB sub-types, with severe EB patients (which included all the DEB patients) having a higher than average cost.

These studies highlight the importance of including direct non-healthcare costs of informal care and loss of productivity in the economic evaluation of new treatment options.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	There is only one approved wound healing cream (Filsuvez) that is available for EB patients who have junctional EB or DEB available on the NHS. There is nothing that addresses the fundamental lack of the collagen VII protein in patients with dystrophic EB. Treatments are aimed at managing the wounds and pain with various combinations of dressings, creams, topical treatments and oral pain relief. These are provided by the NHS (for the most part) which is extremely valuable, though access across the country is sometimes dependent on GPs acknowledging the needs of EB patients. Patients are often questioned about the necessity of certain dressings and medications because of the costs to primary health providers and a lack of understanding of what the condition involves. “Currently there is one ‘treatment’ available on the NHS... We have found that it is only beneficial on superficial wounds and ... [it] does not address the source of the problem which is the lack of a protein called Collagen VII.” <i>Mum to a ■ year old RDEB patient (UK)</i> “There are no current treatments on the NHS that move the needle in any way.” <i>Mum to a ■ year old RDEB patient (UK)</i> “The current treatments only support some of the symptoms of EB... We are desperate for an effective treatment that will improve the quality of life for these children... Tipping the balance could be huge.” <i>Mum to a ■ year old RDEB patient (UK)</i> “We have yet to come across any treatment with significant benefits.” <i>Dad to a ■ year old RDEB patient (UK)</i>

8. Is there an unmet need for patients with this condition?	There is a huge unmet need for treatments that address the specific protein deficiencies that lead to all types of EB and also for treatments that specifically address the exacerbating symptoms of EB, such as the malignant itch and inflammation, as well as the resulting skin cancer. This consultation is for treatment that addresses defects within the collagen VII gene that gives rise to DEB. There is nothing that significantly improves the condition available as standard of care. Patients are managed on a case-by-case basis. Dressings, creams, and antiseptic washes are chosen according to preference and potential reactions to particular agents. Antibiotics are employed topically or orally depending on levels of infection, and intravenously if infections are severe. Pain medication is tailored to specific individual needs but despite some patients using extremely strong opiates, pain is still an unimaginable burden that impacts heavily on quality of life. 'Off the shelf' antihistamines provide very little help towards itch, and eczema drugs that are available on the NHS, which could have an impact on this symptom of EB, are not licensed for use in EB. "There is most definitely an unmet need for patients with this condition. Patients with this condition currently have no treatments. Patients with dystrophic epidermolysis bullosa are lacking a protein called collagen 7. My son has a severe form of DEB (RDEB-GS) which means he has a complete absence of collagen 7. Patients with this condition desperately need a treatment that can restore the cells' ability to make functional collagen 7 protein and restore anchoring fibrils in the skin/wounds which is what binds the inner and outer layers of the skin together allowing it to heal quickly and more robustly, inevitably reducing pain, reducing the risk of infections and chronic wounds; B-VEC can do all of this, we have seen how well it has worked for children in America and I am desperate to be able to get this treatment for my child. Children with EB also experience a significant amount of inflammation which is extremely important that we address too." <i>Mum to a ■ year old RDEB patient (UK)</i> "Yes; there is currently no treatment beyond wound care; dealing with the effects of the condition. There is currently no treatment that tries to address the genetic cause of the condition itself." <i>Mum to an ■ year old RDEB patient (UK)</i> "Yes; there is currently no other treatment available other than repeated operations to release contractures and hospital appointments to see specialist doctors, nurses, dentists, podiatrists, occupational therapists and ophthalmologists to monitor my condition." <i>■ year old DDEB patient (UK)</i>

	A combination of specific EB treatments is desperately needed to combat this condition and the devastation it causes to sufferers.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients and carers are very keen, if not desperate to use this technology, as it addresses the fundamental lack of or reduced level of collagen VII protein in the skin which leads to the fragility, blistering and wounds. Some EB patients have wounds that have been open for many years, sometimes a lifetime. The expectation is that with B-VEC use their wounds will heal and stay closed for longer. Wound healing will in turn help with pain, inflammation and itch. They hope it might reduce the number of dressings they have to use and reduce the time involved in dressing changes. “If B-VEC improves wound healing, the impact would be incredible. Hopefully less pain, reduced dressing change time, more robust skin and reduced itch. If wounds healed, there would be less chance of infection. The smallest of improvements would have a huge impact on the quality of life. The hope would be that skin with less long-term trauma would slow down the longer-term effects of EB such as cancer.” <i>Mum to a ■ year old RDEB patient (UK)</i> “Firstly, the biggest advantage with this particular treatment is it puts no extra burden on the child and family. B-VEC can fit in with our usual wound care routine and is quick to apply meaning it won’t increase the length of the already timely wound care routine. B-VEC is actually a genetically modified treatment so it is attacking the source of the problem by putting Collagen 7 into the wounds and skin. We also know that it is easy to use and is now being used in the patients’ homes which means that we do not need extra hospital visits which can be quite difficult for us as a family and also costly for the NHS. B-VEC has been tried and tested, it has been approved by the FDA since 2023, we know it works and we know it works well after speaking to families in other countries that have been able to access this treatment.” <i>Mum to a ■ year old RDEB patient (UK)</i> “It would deliver working collagen genes to EB skin wounds and help them to heal more quickly; therefore reducing pain and healing time.” <i>Mum to an ■ year old RDEB patient (UK)</i> “It is life saving. It prevents chronic wounds from occurring leading to fatal skin cancer. [It] gives the skin a break from constantly fighting, reducing chronic inflammation.” <i>Mum to a ■ year old RDEB patient (UK)</i> “From what we have seen, this would be a huge help, and maybe we can get my son walking again because for 6 months he can’t even weight bear.” <i>Dad to a ■ year old RDEB patient (UK)</i> “It offers a painless treatment that can heal wounds more quickly and make the skin more robust therefore reducing the likelihood of further injury. It will therefore reduce pain and avoid pain from injuries avoided from the skin being more robust. Reducing the number of injuries to the skin may also reduce the

risk of skin cancers caused by chronic wounds forming, or could delay the onset of cancer.” ■ year old
DDEB patient (UK)

Any improvement in wound healing would have a huge impact not only on the patient’s quality of life, but on the whole family. In a 2015 clinical trial of intravenous mesenchymal stromal cells in children with RDEB, parents reported whole family quality of life improvements such as better sleep, being able to return to work because of reduced caring needs, and a family being able to plan their first vacation together ([Petrof G, et al 2015 J Invest Derm](#)).

From real world experience of this technology from the United States, where it has been in use since 2023, and Europe where there has been an early access scheme, we have these reports:

"Vyjuvek (B-VEC) is a revolutionary treatment as it is the first that addresses replacing missing or reduced levels of collagen 7 in the skin of patients. It has improved the quality of life for our patients." Prof ■■■■■ (consultant dermatologist who has treated 9 RDEB patients with B-VEC)

“The largest wound we treated was approximately 140cm² and we had complete wound closure... She has an increased amount of hope now that her large chronic painful wounds have healed, which were not healing before treatment. The initial wounds we selected for treatment were large chronic wounds that had not healed in more than 2 years and caused significant pain during our standard of care regime. So overall I would say she has a more positive attitude about the future.” Dad to a ■ year old RDEB patient (USA)

“Our ■-year-old son has been receiving Vyjuvek treatments at home since November 2023. The application and removal process is quick, taking about 10 minutes each. Over the course of treatment, we addressed seven wounds – both chronic and recurring – ranging from 20cm to 2cm in size. All but one chronic wound on his arm fully healed, and even that wound became smaller and shallower. In the first 12 hours after removing Vyjuvek, the treated areas were more sensitive and painful, but as new skin formed, it had greater integrity and elasticity. If reinjury occurred, those areas healed faster than before treatment. One of the most significant changes we noticed was his reduced anxiety around bandage changes. With fewer open wounds, he experienced less pain and emotional distress, making daily activities like getting dressed, bathing, and even socializing with friends much easier. Overall, Vyjuvek has been a positive

	experience, and we plan to continue using it as a resource for wound healing.” Mum to an ■ year old RDEB patient (USA) “Appreciable increase in psychological well-being after five to six months of treatment due to wound closure, pain reduction and itching reduction. In particular it represents the first significant breakthrough in treatment after ■ years of life!” ■ year old RDEB patient (Italy) “The largest wound on the back (since he was born and has never healed) is currently under treatment. The closure percentage is 65% and the open area is less deep if compared with the beginning of treatment...[Emotionally it has had a] positive impact because the progressive healing of the wound induces trust and hope.” Parent of a ■ year old RDEB patient (Italy) “Not time to stop B-VEC now that it’s working” ■ year old female RDEB patient (France)

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	We do not see disadvantages to using the technology, unless the conditions of use require administration in a medical setting which would place a huge additional burden of travel and time on patients and families. Carers see home administration as critical: “B-VEC can fit in with our usual wound care routine and is quick to apply meaning it won’t increase the length of the already timely wound care routine.” <i>Mum to a ■ year old RDEB patient (UK)</i> “The science has proven successful and ■ was part of the clinical trials, so he was eager to later receive treatment at his doctor’s office but ultimately doing the treatment at home proved much more preferable and less stressful.” <i>Mum to a ■ year old RDEB patient (USA)</i> One disadvantage reported by patients and families who already have access to the treatment in the USA and Europe is the limited quantity per week – carers expressed their desire to be able to use it more extensively than the permitted quantity per week, to cover larger areas or more wounds at one time because of the beneficial effects noted by patients. “Our biggest complaint is that the dose is too low. In other words, we don’t get enough of the product weekly to effectively treat all her wounds. We could be making a much larger impact on the symptomology of her disease with a higher dose. Furthermore, a larger dose would lead to a reduction in bandages used, decreased time for proper wound care and bandaging, and a reduction in health care utilization.” <i>Parent to a ■ year old RDEB patient (USA)</i>

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.	It is important here to reiterate that this technology is only for patients with dystrophic EB; that is dominant dystrophic EB patients and recessive dystrophic EB patients, NOT patients with other types of EB. DEB is caused by mutations on the collagen VII gene which leads to a reduction, or complete lack, of collagen VII protein, which this technology addresses. It will only benefit this cohort of patients and will not help patients with other types of EB, such as EB Simplex and Junctional EB, which are caused by different genetic defects (different genes involved) and lead to deficiencies of other proteins which in turn cause differences in depth of skin cleavage and wound characteristics (Has et al, BJD, 2020). The most recent and accurate assessment of prevalence of DEB in England and Wales is 10.7 per million (Petrof G et al BJD 2022 186:765-766). Within the DEB population, all RDEB patients will likely use it because of the severity of the condition and therefore number of open wounds, as well as DDEB patients who have open wounds. “There is currently no treatment available for me on the NHS. I would need to use less of the treatment as the areas of skin that are affected for me are smaller [compared with those of an RDEB patient], but improving my skin’s resilience would reduce the pain I feel in using my hands and walking everyday.” ■ <i>year old DDEB patient (UK)</i>

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	If there was a requirement to travel to the specialist centres for treatment, inequalities could arise because of geographic and socioeconomic circumstances. Those with less resource, both personal and financial, would find the weekly travel burdensome and this could limit ability to access treatment. EB specialist centres are located in Birmingham and London, meaning significant travel for EB patients living in the southwest and north of England, Wales, Scotland, and Northern Ireland. In the 2023 Epidermolysis Bullosa Patient Insights Study, 48% of EB patients found travel to a specialist centre difficult and could cause their EB to flare up, and 28% struggled to afford the travel costs.

Other issues

13. Are there any other issues that you would like the committee to consider?	The ability to administer B-VEC at home is a hugely important component of treatment – feedback from European patients where travel to hospital for weekly application was required showed that this was an important factor in their desire to continue treatment. A UK parent noted that a requirement for B-VEC to administered by a medical professional would be a significant disadvantage “As primary carers, we apply many ointments and creams to our children. We lance blisters, change dressings daily and give an abundance of medication, so applying a gene therapy cream seems straight forward to us. Adding more hospital appointments to your day just becomes another time-consuming task to add to your routine.” <i>Mum to a ■ year old RDEB patient (UK)</i> We believe that home administration by regular care givers is critical for this medication. For the patient, administration could be tailored to their particular dressings schedule and in their normal dressings environment which would reduce the stress for them and for their caregivers. Home administration would also reduce the burden and expense to the NHS which weekly visits for this treatment would necessitate. We would be happy to work with the company, clinicians, patients, and families with training and guidance.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• There is only one approved wound healing cream available on the NHS and there remains a huge unmet need for treatments for patients with Dystrophic EB, and particularly for a treatment that addresses the root cause of the problem i.e. an absence of or reduction of collagen VII protein in the skin. • B-VEC is a first topical treatment that does just this and is transformative as a first gene therapy approved for Dystrophic EB in the US and with a positive response from European Medicines Agency's Committee for Medicinal Products for Human Use. • Lived experience of B-VEC in the US and Europe has been very positive and quality of life changing for patients on it. • The ability to give this treatment in the home setting as part of routine care would be advantageous, as weekly visits to the hospital for administration would be difficult for patients, carers, and hospitals to manage. • DEB is a hugely painful and debilitating condition that places an intolerable burden on the patient and severely impacts families and family life. Healing wounds for longer will have a profound positive impact on pain in daily life, pain at dressing changes, and longer-term consequences such as skin cancer, in turn impacting the emotional health of the patient and reducing stresses on family life as a whole.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES

For more information about how we process your personal data please see our [privacy notice](#).

Single Technology Appraisal
Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]
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	██████████
2. Name of organisation	DEBRA
3. Job title or position	██████████
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are a UK EB charity; a national medical research charity and patient support organisation for anyone in the UK living with an inherited form of EB, their family members, carers, plus healthcare professionals and researchers specialising in epidermolysis bullosa (EB). The charity was established in 1978 by Phyllis Hilton, whose daughter Debra had EB, as the world's first EB patient support organisation. 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 approx. 90 charity shops, individual donations, corporate supporters, trust donations, and money raised by the public through events, runs and challenges. We currently support over 4,000 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	Krystal Biotech provided a grant to support DEBRA's Annual Members Weekend (£3,000), May 2024.

Patient organisation submission

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

companies are listed in the appraisal 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 at 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 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

In addition, DEBRA conducted a 2023 EB Insights Study, aimed to collect data to capture the impact of EB on daily life, including the HRQoL, of patients and their carers/families.

Over 200 people with different types of EB (EB simplex [EBS], dystrophic EB [DEB], junctional EB [JEB], and Kindler EB [KEB]), over 100 carers, 50 dermatologists, and 100 GPs contributed to the study. Hearing the voices of those with and impacted by EB is critical to our understanding of this debilitating condition.

Ref: DEBRA EB Insight Study: <https://www.debra.org.uk/get-involved/members-participation/eb-insights-study/>

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 ■ 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 ■ 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 ■ 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”.

■, one of our members, is ■ 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, ■, 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 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,

Patient organisation submission

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

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. ■■■ 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 gastrostomy 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 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 ■■■ 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, ■■■, 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 before I swallow.”

■■■ is ■■■ and has Recessive Dystrophic Epidermolysis Bullosa (RDEB). EB affects every part of ■■■'s life – the continual blistering causes constant pain and itching as well as severe problems eating and drinking. 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. ■■■ 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 ■■■ 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."

EB Insight Study

This DEBRA study aimed to assess the impact of living with EB on patients and their families/carers through online surveys on wellbeing and daily task performance.

The study had three parts:

1. Qualitative interviews with patients, carers, and EB specialists.
2. A 20-minute online survey of EB patients and carers, covering topics like living with EB, symptom management, daily life impact, healthcare aspirations, and care barriers.
3. A 15-minute online survey of GPs and dermatologists, focusing on their awareness, management, and education regarding EB.

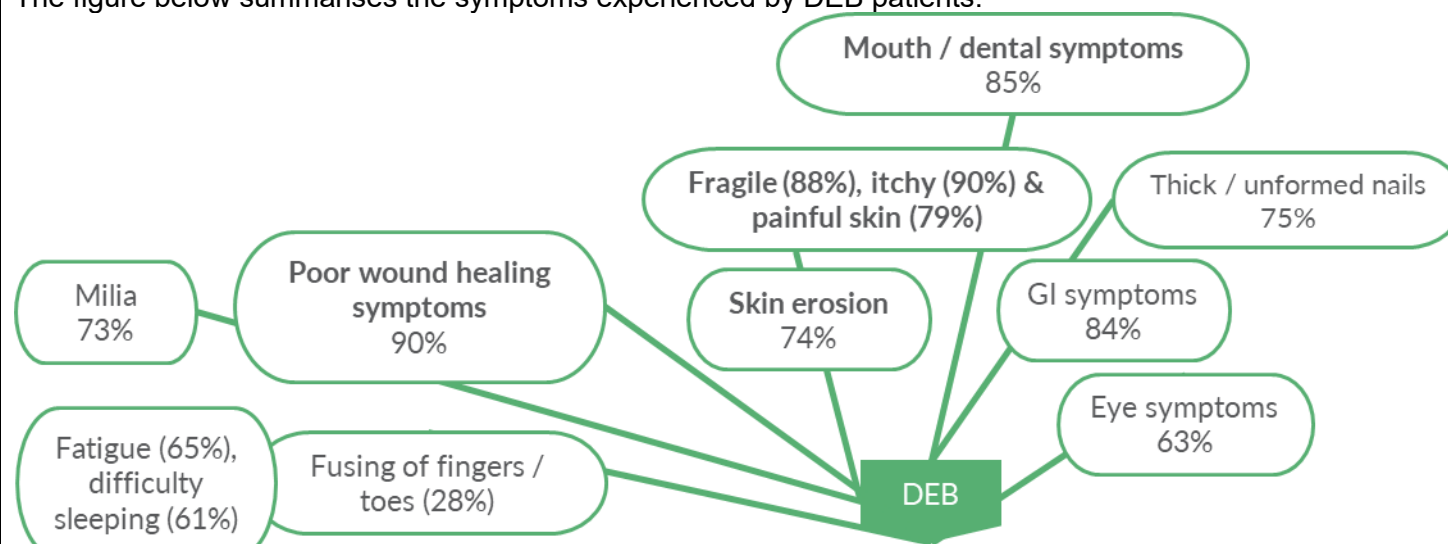
Part 2 also gathered data on EB's impact on daily life, healthcare resource use (HCRU), and the health-related quality of life (HRQoL) for patients and carers and barriers to optimal EB patient care. While Part 3 focused on healthcare professionals' (HCP) awareness, management, and education regarding EB. Part 2 also gathered data on EB's impact on daily life, healthcare resource use (HCRU), and the health-related quality of life (HRQoL) of patients and their families.

A total of 215 patients, 103 carers, 50 dermatologists, and 100 GPs were surveyed, between April and May 2023. All four major subtypes of EB were represented: 61% EBS, 31% DEB, 4% JEB, and 2% KEB.

Results:

Symptoms of EB:

Different EB types are characterised by specific symptoms, though these can vary significantly within each type. The figure below summarises the symptoms experienced by DEB patients.



On a typical day for EB patients...

- 81% of patients spend time on blister / wound care, taking one hour on average
- 85% spend time on personal hygiene e.g. taking an average 1.2 hours
- 67% spend time on resting / recovery, for an average 4.1 hours
- Severe patients spend more time on blister / wound care, personal hygiene, food preparation, getting dressed and resting daily

Patient health-related quality of life

A total of 302 EB patients (across all types) and carers reported HRQoL in surveys. EB significantly impacts daily wellbeing, with a 15% lower HRQoL compared to the average UK population, especially when EB is at its worst. The Insights Study highlighted a substantial HRQoL impact across all five EQ-5D-5L domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) for DEB patients.

Average domain scores (1 = no problems, 5 = severe problems) for 'today'/'at its worst' for DEB were:

- Mobility: **2.2/3.2**
- Self-care: **2.0/3.0**
- Usual activities: **1.9/3.3**
- Pain/discomfort: **2.4/3.8**
- Anxiety/depression: **2.0/3.4**

The EQ-5D VAS score (0 = worst health, 100 = best health imaginable) for DEB was

- **60.9** for 'today'
- **28.7** for when EB was at its worst

The mean EQ-5D utility value (--0.594 = States worse than dead, 1 = full health utility) for DEB was:

- **0.601 (SD: 0.267)** for 'today'
- **0.141 (SD: 0.423)** for when EB was at its worst

	At its worst, DEB patients experience the poorest health and are more likely to experience problems with anxiety/depression <i>Carer health-related quality of life</i> A total of 78% of carers in the study lived with the person with EB. Carers reported moderate to high impacts on various aspects of their lives, with 61% stating it affected their ability to enjoy life, and 59% citing a mental health impact. Additionally, 61% tried to hide the emotional toll of caregiving. 13% strongly agreed they struggled to access mental health support, and 75% felt carers need more emotional support than is currently available. The study highlights that carers receive insufficient emotional and mental health support, indicating carers need more support and respite. In Summary: The Insights Study provides evidence of the substantial impact that DEB has on patients and their carers. Ref: https://www.debra.org.uk/get-involved/members-participation/eb-insights-study/

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?

In August 2023, birch bark extract (Filsuvez® gel) became the first treatment specifically licensed for the treatment of partial-thickness wounds associated with dystrophic epidermolysis bullosa (DEB) and junctional epidermolysis bullosa (JEB) in patients 6 months and older in the UK. NICE recommended Filsuvez through its Highly Specialised Technology evaluation although this comes with a limitation: the number of patients who can be treated with the gel is capped and the controlled access due to its specialised nature.

A 2022 study by Petrof et al. reported an EB prevalence of 34.8 per million and 10.7 per million for DEB, suggesting approximately 730 DEB patients in the UK (census 2021). Most are likely not treated with Filsuvez due to strict inclusion criteria and lack of alternative treatment options. To date, there are no publications on the Filsuvez prescribing pattern, so we are unable to provide any data.

Ref: Petrof et al., *The epidemiology of epidermolysis bullosa in England and Wales: data from the national epidermolysis bullosa database. British Journal of Dermatology (2022) 186, pp843–848*

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. There is only one approved drug for EB, but no treatments specifically designed to significantly reduce pain, wound care, or scarring.

■ 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. The DEBRA Insight study confirmed this, showing only 3% of GPs and 18% of dermatologists had good knowledge of EB. Among GPs, 58% had seen at least one EB patient in the past 5 years, with 52% from suburban practices, 40% from urban, and 8% from rural areas. Dermatologists included 88% consultants and 12% specialist registrars, with 74% working in University Teaching Hospitals and 26% in non-University Teaching Hospitals. None worked at an EB specialist centre, though 82% had seen at least one EB patient in the past 5 years. This limited awareness among healthcare professionals worsens the challenges EB patients and carers face, often requiring them to repeatedly explain the condition and their needs. Ref: https://www.debra.org.uk/get-involved/members-participation/eb-insights-study/
8. Is there an unmet need for patients with this condition?	There is a significant unmet need – In August 2023, NICE approved birch bark extract (Filsuvez® gel) as the first treatment for EB, though its use is limited due to its specialised nature and unclear. Given its recent approval, it is unknown how many patients have been prescribed it. Additionally, there are no NICE guidance or advice or quality standards products for EB. ██████ says <u>“We don’t have treatments. We do have awesome caring medical professionals who help with management of the condition. But that is all.”</u> She goes on to say that the most disappointing element of what is currently available to them is <u>“that nothing helps makes it better. It’s about minimising the damage not improving things.”</u> 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 <u>“son has wounds which have not healed in over three years, and we fear the development of squamous cell carcinoma”</u>.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	To our knowledge, there have been no clinical trials or compassionate use of B-Vec in the UK, so we are unaware of any UK patients with experience using it. <u>However, we are aware of a mother in France whose daughter with Recessive DEB and has been prescribed it. Her experiences are as follows:</u> • <u>The application of B-Vec to the wound site is straightforward and painless.</u> • <u>A wound closed after 6 months of first treatment application.</u> • <u>Both mother and daughter have more energy.</u> • <u>Initially, weekly trips to a national EB centre for 4 months required 8 hours of travel for each appointment, but this has now changed as B-Vec is prescribed locally, reducing travel time to 45 minutes.</u> • <u>The treatment should be brought to patients, rather than requiring patients to travel to it.</u> • <u>The application is simple and could be delegated to the family, rather than relying on healthcare professionals.</u> 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 <u>“quicker healing wounds”</u> and <u>“reduction in healing times for wounds, and potential reduction in pain levels”</u> due to <u>“reducing the pain of dressing changes”</u>. They hope that there may be <u>“fewer areas with wounds”</u>. 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 ■■■ says "<u>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.</u>"

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Depending on where parents/carers and patients live in England, the disadvantage of travel cost and time to EB centres on a weekly basis for each appointment before home delivery and/or local prescription system is implemented.

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. With B-Vec, the travel costs and time required for weekly appointments may create further inequality, limiting access to treatment for those who live far from the centres or lack the financial means to travel.

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.	• 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 EB is 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 help wound closer 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.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

Patient organisation submission

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

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our [privacy notice](#).

Single Technology Appraisal

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

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

- 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 13 pages.

About you

1. Your name	[REDACTED]
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 treatment is to heal dystrophic epidermolysis bullosa (DEB) wounds by generating new functional type VII collagen, which is missing or is reduced in these patients. It is considered a re-dosable gene therapy - it is not a cure because it needs reapplication if wound reopens. Closing wounds leads to reduced pain and itch, as well as a reduced likelihood of scarring with a consequent improvement in mobility, as well as reduced incidence of skin and wound infections, a major issue in DEB patients. In the long-term, reducing the wound burden on the body and generating new type VII collagen should <i>theoretically</i> lead to reduced incidence of squamous cell carcinoma (SCC) (https://doi.org/10.1111/bjd.14104; https://doi.org/10.1016/j.humimm.2024.110805) – the major reason patients with severe recessive DEB die in early adulthood.
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.)	A clinically significant treatment response would be durable complete closure of >50% of wounds to which the treatment is applied.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a huge unmet need in the DEB population. Severe DEB is an intractable condition, recognised as conferring high levels of morbidity and necessitating extensive multidisciplinary input with daily time-consuming dressings and a broad array of medications to treat both skin and extra cutaneous complications arising due to chronic and recurrent wounds. Due to the complexity of DEB care, coordinating the processes involved can be challenging for healthcare professionals. Affected individuals experience severe disability and are unable to reach their full potential. The impact on their families, particularly siblings, is often under-recognised, under-appreciated and neglected, but is highly significant. Moreover, care for DEB patients often requires training all family members. This will necessitate additional nursing staff and, potentially, more medical and pharmacy time.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Currently, the treatment of DEB within the NHS focuses on managing symptoms, preventing complications, and improving the quality of life for patients, as there is no cure for the condition. Severe DEB affects every aspect of an individual's life. Treatment is tailored to the individual and requires the involvement of a multidisciplinary healthcare team, including dermatologists, dietitians, specialist nurses, ophthalmologists, gastroenterologists, surgeons, physiotherapists, occupational therapists, interventional radiologists, pain management experts and psychologists. Key aspects are: 1. Wound care • Specialised and costly silicone-based dressings: These soft, non-stick bandages or dressings are important to protect the skin, manage blisters, and promote healing. However, dressing changes are time-consuming, taking hours, and are extremely painful. For children, parents are usually responsible for this care, although some families may also require professional care too, adult patients may rely on family members, nurses and professional carers for this. • Infection: Since open wounds can easily become infected, antibiotics and antiseptic treatments are used. In severe cases, infection may require hospitalisation and intravenous antibiotics. Frequent wound infections are common and cause worsening of pain and itch. Birch bark extract (Filsuvez®) topical gel is an approved topical treatment which has an anti-inflammatory effect in around 50% of patients. 2. Pain management • People with DEB often experience chronic pain due to multiple wounds, contractures and oesophageal strictures. Pain management includes topical and systemic medications and often strong analgesics such as morphine, ketamine, methadone and/or fentanyl.

	3. Nutritional support • DEB can interfere with the body's ability to absorb nutrients due to the skin and mouth involvement. In addition, the metabolic requirements from having open wounds, and bacterial colonisation and infection are increased in DEB. Nutritional support is needed from birth, and multiple vitamin and micronutrient deficiencies need monitoring and replacement. Reduced absorption poses a huge challenge how to deliver these best. Mouth and oesophageal contractures make chewing and swallowing very slow and painful and impact on feeding. Several patients require gastrostomies to meet their basic nutritional needs. • Frequent oesophageal dilatations are needed to maintain swallowing. 4. Physical and emotional support • Physical therapy is needed to maintain joint mobility and flexibility, as scarring and contractures (tightening of the skin) limit movement. • Psychological support: DEB affects every aspect of a person's quality of life due to the visible nature of the condition, chronic pain, and frequent medical interventions. Psychological and counselling support is integral part of care. • Expert care: In the UK, individuals with DEB are often referred to specialised dermatology centres which are centrally commissioned. These centres offer a coordinated approach to care.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are numerous guidelines for treating all aspects of DEB. EB health care - Clinical Practice Guidelines DEBRA International
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.)	The pathway of care is well defined, with all four EB centres working collaboratively and with NHSE. There are virtually no differences in opinions among healthcare professionals.

9c. What impact would the technology have on the current pathway of care?	The technology will significantly impact in how we care for DEB. In a condition with limited meaningful and effective treatment options, the availability of this product will be an extremely valuable addition to the multidisciplinary care provided for DEB patients.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This is a new technology so will be used alongside current care for DEB, rather than as a replacement.
10a. How does healthcare resource use differ between the technology and current care?	Current care focuses upon symptom control and management of complications arising from the underlying pathology of type VII collagen deficiency. This new technology differs in being the first topical disease-modifying therapy addressing the underlying pathomechanism. The technology reduces: • burden of disease by diminishing symptoms such as pain and itch • burden of wound management including dressing and antimicrobial therapy • fibrosis, scarring and risk of aggressive carcinogenesis This is an additional resource, but the vision is that in the long term will lead to fewer symptoms, less pain so therefore less need for medications, less need for dressing, antibiotics and hopefully long term reduce incidence of SCC.
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	It should be initiated in specialised centres who look after DEB patients and then application can continue at home by trained carers/parents/nurses. At present, this can only be dispensed by hospital pharmacy and 2 healthcare professionals have to administer it in a hospital setting, taking 2-4 hours per week per patient. Unless the stability of the drug changes and the rules that families can administer at home the 4 centres will need a large number of additional pharmacies, nurses and day care beds to administer this weekly for patients
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Investment is needed in medical, pharmacy, administrative and nursing staff and likely physical space depending on where the treatment will be delivered. This is a large piece of work that will depend on stability data to determine several important factors. These include:

	• whether the drug can be prepared and stored in a standard refrigerator, • whether caregivers can safely administer the treatment at home and dispose of it at home; • whether homecare services can handle deliveries, and whether vials can be shared to reduce waste. In particular, for children under 3 years old, there is a risk of wasting half a vial (1.6 ml). which needs to be taken into consideration.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. As delineated above, this is the first disease modifying therapy for this cohort, targeting the underlying pathomechanism by increasing expression of functional type VII collagen within the skin. By doing this, restoration of dermo-epidermal integrity will reduce the need for the current standard of care which essentially is supportive: time-consuming and costly dressings, recurrent antibiotics and analgesia, frequent hospital visits. Ultimately there will likely be improved longevity and global wellbeing, as well as wider benefits for affected families and society.
11a. Do you expect the technology to increase length of life more than current care?	Yes
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals	The technology is anticipated to be straightforward to administer, provided the healthcare teams are adequately supported with the necessary staff. No concomitant medications are required, and the

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.)	treatment can be administered on an outpatient basis. The staff required include pharmacy to defrost and prepare the treatment under aseptic conditions, dispense it, and support homecare delivery. During the first hospital application or until families or carers are trained, two healthcare professionals, including EB Clinical Nurse Specialists (CNS) will need to prepare and apply the treatment to wounds. This process can take 2-4 hours in adults and significantly longer in children. As such, additional nurses or HCPs may be necessary, and patients may need day-case or admission for the first application. In some cases, patients must visit the specialised centre each week.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment will begin after genetic confirmation. The criteria for stopping treatment include treatment intolerance or lack of efficacy.
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?	
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	Yes, the technology is innovative.

way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	Yes.
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, the technology addresses skin fragility and wound healing, the fundamental characteristics of DEB.
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?	There are no known significant side effects. However, as wounds reopen, weekly treatment is required to manage the condition effectively

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?	The most important outcomes include wound closure, time to wound closure, duration of wound healing, and reduction of pain and itch.

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 trials but have come to light subsequently?	Not to our knowledge
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No. However, as the technology has been in use in the US for several years, both in and outside of clinical trials, updated evidence on its long-term benefits would be valuable.
20. How do data on real-world experience compare with the trial data?	The data from real-world experience closely align with the trial data.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	If the technology is provided only at specialised centres, this may create inequalities to access. Patients living far away may face difficulties in starting and continuing the treatment due to travel distance and time, disproportionately affecting people of low income. Additionally, language barriers may further pose challenges to communication with patients and their carers. This can result in increased demands on their time, including the need to take additional time off work for appointments, exacerbating existing socioeconomic inequalities.
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.	• Beremagene geperpavec is the first topical gene therapy treatment for DEB, now approved in the EU. • By generating new type VII collagen, the technology can potentially reduce the likelihood of wound reopening, and scarring; it may also help reduce the incidence of skin and wound infections and squamous cell carcinomas. • Stability data is needed, along with information on who will prepare the drug and where it can be administered. • Clarification is needed on whether the vials can be shared. • It is important to determine who will administer the treatment, especially if it is in the hospital, as staff requirements will need to be factored in.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our [privacy notice](#).



**Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]
A Single Technology Appraisal**

Produced by	Sheffield Centre for Health and Related Research (SCHARR), The University of Sheffield
Authors	Andrew Metry, Research Fellow, SCHARR, University of Sheffield, Sheffield, UK Sarah Davis, Senior Research Fellow, SCHARR, University of Sheffield, Sheffield, UK Christopher Carroll, Reader, SCHARR, University of Sheffield, Sheffield, UK Kate Ren, Professor, SCHARR, University of Sheffield, Sheffield, UK Sunhong Kwon, Research Associate, SCHARR, University of Sheffield, Sheffield, UK Emily Pulsford, Research Assistant, SCHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Andrew Metry, Research Fellow, SCHARR, University of Sheffield, Sheffield, UK
Date completed	11 th July 2025

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR175574.

Declared competing interests of the authors

None of the other authors have any conflicts of interest to declare.

Acknowledgements

We would like to thank Professor John McGrath for clinical advice relating to this project. We would also like to thank Matt Stevenson, SCHARR, for providing comments on the draft report and Gill Rooney, Programme Manager, SCHARR, for providing administrative support and in preparing and formatting the report.

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.

This report should be referenced as follows:

Metry A., Davis S., Carroll C., Ren K., Kwon S., Pulsford E. Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]. A Single Technology Appraisal. Sheffield Centre for Health and Related Research (SCHARR), 2025.

Contributions of authors

Andrew Metry was project lead. Emily Pulsford critiqued the company's search strategy. Chris Carroll summarised and critiqued the clinical effectiveness data reported within the company's submission. Kate Ren critiqued the statistical aspects of the submission. Andrew Metry, Sarah Davis and Sunhong Kwon critiqued the health economic analysis submitted by the company. All authors were involved in drafting and commenting on the final report.

Copyright belongs to The University of Sheffield

Copyright is retained by Krystal Biotech for Tables 4-10, 12-13, 19, 36-37, 51-52 and figures 1, 3-4, 6-9, 22.

TABLE OF CONTENTS

ABBREVIATIONS	1
1. EXECUTIVE SUMMARY	3
1.1 Overview of the EAG's key issues	4
1.2 Overview of key model outcomes	6
1.3 The decision problem: summary of the EAG's key issues	7
1.4 The clinical effectiveness evidence: summary of the EAG's key issues	8
1.5 The cost-effectiveness evidence: summary of the EAG's key issues	10
1.6 Other key issues: summary of the EAG's key issues.....	20
1.7 Summary of EAG's preferred exploratory analyses	21
2. BACKGROUND	24
2.1 Critique of company's description of underlying health problem	24
2.2 Critique of company's overview of current service provision.....	26
2.3 Company's definition of the decision problem.....	29
3. CLINICAL EFFECTIVENESS	41
3.1 Critique of the methods of review(s)	41
3.2 Results of the company's SLR.....	47
3.3 Baseline characteristics	59
3.4 Quality Assessment.....	67
3.5 Clinical effectiveness	71
3.6 Safety	81
3.7 Ongoing studies	87
3.8 Meta-analysis	87
3.9 Indirect treatment comparison (ITC)	87
3.10 Additional work on clinical effectiveness undertaken by the EAG.....	89
3.11 Conclusions of the clinical effectiveness section.....	89
4. COST EFFECTIVENESS	92
4.1 EAG's comment on company's review of cost-effectiveness evidence	92
4.2 Summary of the company's submitted economic analysis	94
4.3 Critique of company's submitted economic evaluation by the EAG.....	133
4.4 Exploratory analyses undertaken by the EAG	166
4.5 Discussion.....	178
5. OVERALL CONCLUSIONS	180
6. REFERENCES	182

LIST OF TABLES

Table 1:	Overview of the EAG’s key issues.....	5
Table 2:	Results of the EAG’s exploratory analyses.....	21
Table 3:	Decision problem (adapted from Table 1 of the CS)	30
Table 4:	Inclusion and exclusion criteria for the SLR (adapted from CS Appendix B, Table 15)	44
Table 5:	Summary of the trial design of GEM-3 (adapted from CS, Section B.2.3.1, Table 2.3)	48
Table 6:	Summary of the trial design of GEM-1 (adapted from CS, Section B.2.3.1, Table 2.4)	51
Table 7:	Summary of eligibility criteria and treatment randomisation for GEM-1 (reproduced from CS, Section B.2.3.3.3, Table 2.7)	53
Table 8:	Summary of the trial design of EASE (adapted from CS, Section B.2.3.1, Table 2.5)	54
Table 9:	GEM-3: Demographic and baseline characteristics (ITT population) (reproduced from CS, Section B.2.3.2.3, Table 2.6).....	60
Table 10:	GEM-1: Demographic and baseline characteristics (ITT population) (reproduced from CS, Section B.2.3.3.3, Table 2.8).....	61
Table 11:	Characteristics of participants in EASE across treatment groups at DBP baseline ^{10, 27}	62
Table 12:	Analysis of primary and secondary endpoints in GEM-3 (reproduced from CS, B.2.4.1.3, Table 2.9)	65
Table 13:	Analysis of primary and secondary endpoints in GEM-1 (modified from CS, Section B.2.4.2.3, Table 2.10)	66
Table 14:	Quality assessment results for GEM-3 (modified from CS, Section B.2.5, Table 2.12)	68
Table 15:	Quality assessment results for GEM-1 (modified from CS, Section B.2.5, Table 2.13)	70
Table 16:	Quality assessment results for EASE (modified from CS, Section B.2.5, Table 2.14).....	71
Table 17:	GEM-3: Primary and key secondary endpoint analyses (imputed data) (modified from CS, Section B.2.6.1, Table 2.15).....	72
Table 18:	GEM-3: Primary endpoint analyses (imputed data) (modified from Clarification response, A19) ³¹	73
Table 19:	GEM-3: Secondary endpoint analysis for pain severity during wound dressing changes (reproduced from CS, Section B.2.6.1.5, Table 2.17).....	74
Table 20:	GEM-3: Supplementary analyses for durability of wound closure (imputed data) (modified from CS, Section B.2.6.1, Table 2.16 and Guide et al 2022, Table S4 ²²)..	75

Table 21:	GEM-1: Primary endpoint analysis for wound closure at 3 months (observed data) (modified from CS, Section B.2.6.2.1, Table 2.18).....	76
Table 22:	GEM-1: Primary endpoint analysis for time to and durability of wound closure (observed data) (modified from CS, Section B.2.6.2.2, Table 2.19).	77
Table 23:	EASE: Primary and key secondary endpoint analyses	78
Table 24:	GEM-3: Summary of AEs (modified from CS, Section B.2.10, Table 2.20)	82
Table 25:	GEM-3 OLE: Summary of AEs (modified from CS, Section B.2.10, Tables 2.22 and 2.23)	83
Table 26:	GEM-1: Summary of AEs (modified from CS, Section B.2.10, Table 2.21)	85
Table 27:	Summary of safety and tolerability outcomes from EASE (DBP and OLP).....	86
Table 28:	EAG's additional analysis results	89
Table 29:	Results of the replicated HST28 model for the 6-state versus 4-state structures	96
Table 30:	The mapping algorithm used to convert from 6-state to 4-state structure.....	96
Table 31:	Summary of evidence sources used to inform the model parameters for the company's base-case	99
Table 32:	Age stratified BSA estimates for RDEB and DDEB	104
Table 33:	Summary of parameters for sampling patients.....	105
Table 34:	Summary of parameters for modelling wound dynamics.....	106
Table 35:	Assumed wound counts and expected reopened wounds by health state and treatment arm	107
Table 36:	Sources of mortality according to health state, DEB subtype, and model start age (replicated from CS, Table 3.21)	115
Table 37:	Patient utility values by health states as applied in the company's base-case and scenario analysis (adapted from CS, Table 3.22).....	120
Table 38:	Data used to incorporate carer QALYs	121
Table 39:	Summary of health state costs per cycle	125
Table 40:	QALY shortfall calculation when using either BSC or BBE as comparator for the company's base case and their scenario analysis using HST28 utility values (estimated by the EAG from the company's post clarification model)	126
Table 41:	Company's base-case results (generated by the EAG based on the company's post clarification model).....	126
Table 42:	Company's base-case results (generated by the EAG based on the company's post clarification model).....	127
Table 43:	Base case disaggregated outcomes for the post-clarification company's deterministic model	129
Table 44:	Company's scenario analyses, deterministic versus BSC (adapted from clarification response, Table 13).....	131

Table 45:	Company's scenario analyses, deterministic versus BBE (adapted from clarification response, Table 13)	132
Table 46:	Adherence of the company's economic analyses to the NICE Reference Case.....	133
Table 47:	Summary of severity levels in the adult and child vignettes*	140
Table 48:	Summary of responders with complete wound closure for primary wounds previously treated with B-VEC during GEM-3 (adapted from OLE CSR).....	145
Table 49:	B-VEC vial consumption per 13 week model cycle as predicted by the PLS.....	147
Table 50:	Health state occupancy at baseline and month 3 according to the TP matrices estimated from the PLS average weighted by the split of patient population across the three age groups	151
Table 51:	Bucher adjusted indirect comparison between B-VEC and BBE on the difference in the relative change in proportion of patients in each health-state over time using the adapted HST28 model with 4 health states (adapted from response to clarification question B15)	152
Table 52:	Bucher adjusted indirect comparison between B-VEC and BBE on the difference in the relative change in proportion of patients in each health-state over time using the replicated HST28 model with 6 health states (adapted from response to clarification question B15).....	153
Table 53:	Patient flow for B-VEC as estimated from ITC (calculations provided here are for Month 3, same calculations carry forward)	159
Table 54:	Patient flow for BBE as estimated from ITC (calculations provided here are for Month 3, same calculations carry forward).....	159
Table 55:	Patient flow for B-VEC and BBE with and without using the ITC relative treatment effect estimates	160
Table 56:	Baseline distribution of the cohort at model start by BSAP.....	166
Table 57:	Comparison of the modelling approaches employed by the company and the EAG against those preferred by the committee in HST28.....	168
Table 58:	Changes applied to the EAG adaptation of the HST28 replicated model and their individual impact on the cost-effectiveness results for BBE vs BSC compared to the adapted model (without any PAS for BBE).....	171
Table 59:	Vial usage predicted by the PLS for the six-health states used in HST28	173
Table 60:	EAG exploratory analysis results.....	176
Table 61:	Transition probabilities associated with BBE used at the CS of the HST.....	189
Table 62:	Transition probabilities associated with BSC used at the CS of the HST.....	189
Table 63:	Estimated patient utility by model health state in the HST28 company's base case.	191
Table 64:	Estimated carer utility by model health state in the HST28 company's base case ...	191

Table 65:	Annual costs associated with dressing changes and outpatient visits in the HST28 company's base case.....	192

LIST OF FIGURES

Figure 1:	Anticipated clinical pathway of care for patients with DEB in the UK (reproduced from CS, Figure 1.9)	27
Figure 3:	Overview of trial design and participant of GEM-3 (reproduced from CS, Section B.2.3.2.2, Figure 2.1)	57
Figure 4:	Overview of trial design and participant flow of GEM-1 (reproduced from CS, Section B.2.3.3.2, Figure 2.2)	58
Figure 5:	Overview of trial design of EASE (reproduced Kern 2022, Figure S3 ²⁷)	59
Figure 6:	Proportion of patients with first complete closure of EB wound by visit (reproduced from CS, Section B.2.6.3.1, Figure 2.6)	79
Figure 7:	Subgroup analyses for complete wound closure at 6 months in GEM-3 (reproduced from CS, Section B.2.7, Figure 2.8).....	80
Figure 8:	Subgroup analyses of the primary efficacy endpoint in EASE (reproduced from CS, Section B.2.7, Figure 2.9)	81
Figure 9:	The company's model structure (reproduced from Figure 3.1 of the CS)	95
Figure 10:	Cycle-based simulation of wound dynamics and health state reclassification (EAG interpretation of the PLS R code).....	102
Figure 11	Normal distributions with identical mean (■■■■) and different SD	109
Figure 12:	Health state occupancy in the first two years of the company's base case model for B-VEC and BSC	113
Figure 13:	Health state occupancy in the first two years of the company's base case model for BBE	114
Figure 14	Vignette estimates of utility for the company's four health states and the BSAP range they apply across	119
Figure 15:	Cost-effectiveness plane, B-VEC versus BSC	127
Figure 16:	Cost-effectiveness plane, B-VEC versus BBE.....	128
Figure 17:	Tornado diagram for deterministic sensitivity analyses (B-VEC versus BSC).....	130
Figure 18:	Tornado diagram for deterministic sensitivity analyses (B-VEC versus BBE)	130
Figure 19:	Utility values for the four health states in the company's vignette and the 6 health states in HST28 estimated from the EASE OLE.....	137
Figure 20	Utility values from EASE OLE and the mapped values applied as a scenario analysis in the company's four health state model.....	138
Figure 21:	Comparison of utility values in the company's base case and those provided by the company in HST28.....	139
Figure 22:	Kaplan-Meier plot for time to reopening in GEM-1 (replicated from Figure 2 of the clarification response)	143

Figure 23:	Modelled BSA opened by recurrent and chronic wounds (PLS outputs)	145
Figure 24:	Markov trace of the 6-state and 4-state structures in the HST28 replicated model – BBE arm.....	149
Figure 25:	Markov trace of the 6-state and 4-state structures in the HST28 replicated model – BSC arm.....	149
Figure 26:	Prevalence of SCC in the modelled children group in the BBE arm	162
Figure 27:	Prevalence of SCC in for the different age groups in the BBE arm.....	162
Figure 28:	The HST28 model structure (reproduced from Figure 14 of the HST28 CS).....	188

LIST OF BOXES

Box 1	Summary of the main issues identified within the company’s health economic model..	135

ABBREVIATIONS

AE	adverse event
AESI	adverse Events of Special Interest
AIC	akaike Information Criterion
ASA	additional sensitivity analysis
BBE	birch bark extract
BIC	bayesian Information Criterion
BNF	British National Formulary
BSA	body surface area
BSAP	body surface area percentage (covered with wounds)
BSC	Best supportive care
B-VEC	beremagene geperpavec
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
COL7A1	collagen type VII alpha 1 chain
CS	Company submission
CSR	Clinical Study Report
DBP	double blind period
DDEB	dominant dystrophic epidermolysis bullosa
DEB	dystrophic epidermolysis bullosa
EA	exploratory analysis
EAG	External Assessment Group
EB	epidermolysis bullosa
EBDASI	Epidermolysis Bullosa Disease Activity and Scarring Index
EQ-5D	EuroQol 5-Dimensions
EQ-5D-Y	EuroQol 5-Dimensions Youth
FDA	Food and Drug Administration
FLACC-R	Faces, Legs, Activity, Cry, Consolability Revised
QOLEB	epidermolysis Bullosa Quality of Life Instrument
HCRU	healthcare resource use
HRQoL	health-related quality of life
HST	Highly Specialised Technology
HSV-1	herpes simplex virus type 1
ICER	incremental cost-effectiveness ratio
IGA	Investigator global assessment
INMB	incremental net monetary benefit

ITC	indirect treatment comparison
JEB	junctional epidermolysis bullosa
KEB	Kindler epidermolysis bullosa
LYs	Life years
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	net monetary benefit
OLE	open label extension
PAS	Patient Access Scheme
PFU	plaque-forming unit
PICOS	Population, Intervention, Comparator, Outcome, Study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PSA	Probabilistic sensitivity analyses
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RDEB	recessive dystrophic epidermolysis bullosa
RR	relative risk
SAE	serious adverse event
SCC	squamous cell carcinoma
SD	standard deviation
Skindex-29	29-Item Skindex instrument
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMC	Scottish Medicines Consortium
SSRI	selective serotonin reuptake inhibitors
STA	Single Technology Appraisal
TEAE	Treatment emergent adverse event
TTO	time trade-off
VAS	Visual analogue scale
WTP	Willingness-to-pay
YHEC	York Health Economics Consortium

1. EXECUTIVE SUMMARY

This External Assessment Group (EAG) report assesses beremagene geperpavec (B-VEC) for treating skin wounds associated with dystrophic epidermolysis bullosa (DEB). The company submission (CS) provides a comparison of B-VEC against birch bark extract (BBE), which was recommended as a treatment for partial thickness wounds associated with DEB in NICE's Highly Specialised Technology Evaluation 28 (HST28). (HST28 also recommends BBE for junctional epidermolysis bullosa [JEB], but this population is distinct from DEB and falls outside of the scope of this appraisal). The CS also provides a comparison against best supportive care (BSC), which includes treatments which can help ease and control infections, pain and other aspects of DEB. The EAG considers that both B-VEC and BBE would be given in addition to BSC and therefore BSC constitutes current clinical management in patients not receiving either BBE or B-VEC. It should be noted that although BBE was evaluated by NICE through its Highly Specialised Technologies Evaluation process, this appraisal of B-VEC is being conducted via NICE's Single Technology Appraisal (STA) process.

The key clinical evidence for B-VEC presented in the CS are the phase 1/2 GEM-1 trial and the phase 3 GEM-3 trial. Both of these trials were placebo controlled. However, they both used an intra-patient randomisation design, whereby individual wounds on the same patient were randomised to either B-VEC or placebo. Therefore, no studies are available in which patients were randomised to receive B-VEC or placebo across all eligible wounds. The company provided a cost-effectiveness analysis comparing B-VEC against BSC. However, this analysis relied on using a patient-level simulation (PLS) to simulate the clinical outcomes that would be expected if patients received either B-VEC or BSC across all eligible wounds.

The key clinical evidence for treatment with BBE identified in the CS was the EASE study, which was a phase 3 randomised controlled trial (RCT) of BBE compared with placebo. This study used a standard interpatient randomisation design with patients randomised to receive either BBE or placebo across all eligible wounds. No studies were identified which provided a direct head-to-head comparison of B-VEC versus BBE. In addition, the CS states that it was not feasible to conduct an indirect treatment comparison (ITC) using the data from the GEM-3 and EASE studies to provide an estimate of the relative treatment effect for B-VEC versus BBE. Instead the company estimated a mapping algorithm to allow transition probabilities to be estimated for BBE for its preferred four-state model structure from the transition probabilities reported in the committee papers for HST28. This mapping algorithm was necessary as the cost-effectiveness model for HST28 employed a six-state structure, meaning that the health states were defined differently to those in the company's four-state cost-effectiveness model for B-VEC. By taking this approach, the company was able to provide a cost-effectiveness analysis comparing B-VEC against BBE. However, this comparison was not informed by comparison of trial

outcomes between the EASE and GEM-3 trials. Instead it relied on the PLS of outcomes for patients receiving B-VEC across all eligible wounds, and the mapping algorithm to estimate outcomes for BBE which matched the company's preferred model structure.

This executive summary provides a brief overview of the key issues identified by the EAG as being potentially important to decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs) which are specified in terms of the cost per quality-adjusted life-year (QALY). In situations where one treatment has a higher cost but lower QALYs than the alternative treatment, it is said to dominate the alternative treatment. In these situations, ICERs can be difficult to interpret and therefore incremental net monetary benefit (INMB) is reported instead. The company has not submitted a patient access scheme (PAS) for B-VEC and therefore its analyses use the list price for B-VEC. There is a PAS discount in place for BBE. The analyses presented in the CS and this EAG report include the list price for BBE, as the PAS price for BBE is confidential and cannot be shared with the company. The cost-effectiveness results when using confidential comparator PAS price for BBE are included in a separate confidential appendix.

The company has provided an assessment of the proportional and absolute QALY shortfall, which is used to determine the appropriate severity modifier for decision making. The company's base-case analysis assessment of QALY shortfall supported a QALY weighting of 1.7 when using either BBE or BSC to represent the current standard of care. The EAG has presented a QALY shortfall calculation for its own preferred base case scenario which supports a QALY weighting of 1.2. The company has taken the QALY weighting into account when estimating INMBs but has not included the QALY weighting when calculating ICERs.

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 impact on the ICER. Sections 1.3 to 1.6 explain these key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main report (Sections 2 to 5).

All issues identified represent the view of the EAG, and do not necessarily reflect the opinion of NICE.

1.1 Overview of the EAG's key issues

Key issues identified by the EAG that impact on the incremental costs and QALYs are summarised in Table 1. A fuller description of each issue, together with potential alternative approaches, the expected impact on the ICER of such approaches and additional evidence that would resolve the issue are contained in Sections 1.3 to 1.5.

Table 1: Overview of the EAG's key issues

ID 6256	Summary of issue (More detail is provided in Section 1.3, 1.4 and 1.5)
Issue 1	Limited data available on clinical effectiveness of B-VEC in patients with dominant DEB
Issue 2	An ITC between B-VEC and BBE based on a comparison of trial outcomes from the GEM-3 and EASE studies has not been provided
Issue 3	Utility values are based on a vignette study despite there being EQ-5D estimates available
Issue 4	Validity of the company's patient level simulation as a source of effectiveness estimates
Issue 5	Estimation of vial usage from the patient level simulation
Issue 6	The company's preferred four-state model structure is dependent on a mapping algorithm which the EAG considers lacks face validity
Issue 7	The plausibility of reduced clinical manifestations and mortality in patients with reduced wound burden
Issue 8	Patients discontinuing treatment are assumed to stay in the state they occupy when discontinuing
Issue 9	Uncertainty regarding the feasibility of vial sharing

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The EAG prefers to use the utility values from the EASE trial obtained from HST28 instead of the utility values obtained from the vignette study which were preferred by the company
- The EAG prefers to use the six-state model structure from HST28, as this avoids the need to rely on the company's mapping algorithm to estimate outcomes for BBE for the company's preferred four-state model structure
- The EAG prefers to use estimate the effectiveness of B-VEC in the modelling by conducting an ITC between the data reported for complete wound closure in the GEM-3 and EASE studies and applying the estimated RRs to the transition probabilities for BBE from HST28; this avoids the need to rely on the PLS to estimate transition probabilities for B-VEC
- The EAG prefers to make alternative assumptions to the company regarding the risk of mortality for patients with differing levels of wound burden to reflects it belief that not all of the excess risk of mortality associated with more severe forms of RDEB can be removed by achieving a lower wound burden
- The EAG preferred analysis does not include a decreased risk of clinical manifestations associated with DEB in patients achieving a lower wound burden as it did not believe the company's assumption clinical manifestations would not occur in patients achieving a very low wound burden and it was unable to implement a more plausible assumption for clinical manifestations within its preferred model structure

- The EAG prefers to assume that patients who discontinue B-VEC treatment are redistributed across the health states according to the state-state distribution of patients receiving BSC whereas the company preferred to assume that they remained in the health state they occupied at the time of treatment discontinuation.

1.2 Overview of key model outcomes

NICE technology appraisals estimate how much a new technology improves length of life, overall survival (OS), and quality of life, using QALYs. In the company's model, B-VEC increases QALYs compared with both BSC and BBE by increasing expected OS by moving patients to less severe health states which are modelled to have lower mortality. Moving patients to less severe health states also results in QALY gains due to these milder states having higher health utilities patients. No adverse effects of treatment are included in the model to offset these QALY gains from treatment. Although the increase in survival increases the duration of time over which carers experience a utility loss associated with caregiving, the higher carer utilities in the less severe health states means that treatment with B-VEC results in caregiver QALY gains versus both BSC and BBE. The company's model estimates that B-VEC will result in additional drug acquisition costs relative to BSC, but lower drug acquisition costs relative to BBE. There is also an additional administration cost versus both BSC and B-VEC. However, the company's model also estimates cost savings relative to both BBE and BSC for bandages, monitoring, and the management of clinical manifestations. Overall, the company's model estimates that B-VEC will result in substantial cost savings, relative to both BBE and B-VEC. However, it should be noted that the comparison against BBE does not include the confidential PAS for BBE.

The modelling assumptions that have the greatest effect on the ICER are:

- The choice of data source for the patient utility values
- The assumption that because patients with the most severe forms of DEB have both a higher wound burden and a higher risk of mortality it is possible for patients to achieve a lower risk of mortality by achieving a lower wound burden through treatment
- The assumption that patients with a lower wound burden with have a lower risk of clinical manifestations, including non-cutaneous manifestations of DEB
- The assumption that patients withdrawing from treatment remain in the health state they occupied at the time they withdrew from treatment

The assumptions within the company's base case modelling that the EAG believes are either incorrect, or uncertain, and that impact most on the INMB, are discussed in more detail in Sections 1.3 to 1.5.

1.3 The decision problem: summary of the EAG's key issues

The key issues related to the decision problem are described here, with other issues discussed in Section 2.3. The EAG's only key issue relating to the decision problem, was the fact that the company did not provide a subgroup analysis for patients with dominant DEB (DDEB) and recessive DEB (RDEB) as specified in the final NICE scope. The EAG considers this to be particularly problematic given that the GEM-1 and GEM-3 studies contained very few patients with DDEB making the effectiveness of B-VEC in this group uncertain.

Issue 1. Limited data available on clinical effectiveness of B-VEC in patients with dominant DEB

Report section	2.3.1
Description of issue and why the EAG has identified it as important	The GEM-1 and GEM-3 trials included only one patient with DDEB, with a further one treatment naïve patient with DDEB being recruited to the GEM-3 open label extension (OLE) study. Therefore the clinical effectiveness evidence reflects a cohort of patients who have almost exclusively RDEB. However, both DDEB and RDEB have been included in the cost-effectiveness analysis with no subgroup analysis provided for these groups separately.
What alternative approach has the EAG suggested?	The EAG would prefer to see a subgroup analysis in which the population of the model is restricted solely to patients with RDEB as it considers that there is not sufficient evidence from the GEM-1 and GEM-3 trials to determine if the treatment effectiveness would be equivalent across these two types of DEB, but it can be fairly confident that the treatment effectiveness estimates from the GEM-1 and GEM-3 trials would relate closely to those expected for an exclusively RDEB population.
What is the expected effect on the cost-effectiveness estimates?	The EAG conducted a subgroup analysis for its preferred base-case scenario to determine the cost-effectiveness for the RDEB population which is better represented in the GEM-3 studies. This was implemented by setting the proportion of DDEB patients to 0% with no other changes to model inputs. This resulted in minimal change to the ICER for the EAG's preferred base-case scenario. This is because the main difference between DDEB and RDEB in the model is the potential for improved mortality in the

	RDEB group, which is limited in the EAG's base-case to patients with the most severe wound burden at baseline (see Key Issue 8). However, the impact on the cost-effectiveness of B-VEC across the whole licensed population is uncertain as it would depend on whether it is correct to assume that the treatment effectiveness from the almost exclusively RDEB population in the GEM-3 study would be generalisable to patients with DDEB.
What additional evidence or analyses might help to resolve this key issue?	The company could provide real world evidence to support its assumption that the clinical effectiveness of B-VEC observed in the GEM-3 trials can be replicated when B-VEC is used in patients with DDEB.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The key issues related to the clinical effectiveness evidence are described here, with other issues discussed in Section 3.

Issue 2. An ITC between B-VEC and BBE based on a comparison of trial outcomes from the GEM-3 and EASE studies has not been provided

Report section	3.9 and 3.10
Description of issue and why the EAG has identified it as important	The company did not conduct an indirect treatment comparison using the outcomes reported for the GEM-3 and EASE studies as they determined that such a comparison was not feasible. They stated that this was infeasible based on differences in study design, patient population and definitions of outcomes across these studies. Instead, the company provided a model-based ITC using the health state occupancy predicted for each treatment. This was done both for a replicated version of the HST28 model, which has six health states, and for an adapted version of the HST28 model which used the four health states incorporated in the company's own cost-effectiveness analysis. The company's model-based ITC used a comparison of changes in health state occupancy for each cycle versus the previous cycle and analysed this for each health state and each model cycle without accounting for the fact that there is correlation between the

	occupancies of each health state. The EAG had serious concerns about the model-based ITC conducted by the company. The reported relative effect in terms of health state occupancy does not provide a meaningful indication of treatment effect as it does not account for whether patients are moving into the health state from a more or less severe state. A more meaningful measure would be the estimation of relative risk based on transition probability matrices. In addition, the company's ITC relied on simulated transition matrices for B-VEC (i.e. not directly derived from clinical evidence). The EAG did not have confidence in these matrices predicted by the patient-level simulation as discussed in Issue 4.
What alternative approach has the EAG suggested?	The EAG used the estimates of complete wound healing from the GEM-3 and EASE studies to estimate a relative risk of achieving complete wound healing between B-VEC and BBE. Whilst the EAG acknowledges that there are some limitations to this approach, due to heterogeneity across the two trials, the EAG considered this to provide more meaningful estimates than the company's model-based ITC which: a) relied on the PLS outputs for the comparison between B-VEC and placebo and b) treated each health state as an independent variable without accounting for the correlation between occupancy which should exist via the transition matrix.
What is the expected effect on the cost-effectiveness estimates?	The EAG's preferred analysis which uses an adapted version of the company's replicated HST28 model, incorporates the EAG's preferred ITC method. However, the EAG has not implemented the company's model-based ITC within its adapted version of the replicated HST28 model to determine the impact of this alternative approach as it did not consider this to be a valid alternative.
What additional evidence or analyses might help to resolve this key issue?	Real world evidence could be provided to demonstrate the impact of B-VEC on wound outcomes in patients who are treated with B-VEC across all eligible wounds. This evidence could be used to assess the external validity of the model predictions for wounds outcomes from both the company and the EAG's preferred analyses.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

The key issues related to the cost-effectiveness evidence are summarised in this section. Due to the large number of issues of concern related to the cost-effectiveness analysis identified by the EAG (see Box 1), only key issues likely to affect decision making are summarised in detail here. The remaining issues of concern are discussed in more detail in Section 4.3.3. In addition to these key issues, the EAG also identified and corrected some errors in the model which are not described in detail here (see Section 4.3.3.1). However, the EAG notes that the correction of carer utilities to account for ageing did have a moderate impact on the estimates of incremental carer QALYs as demonstrated in the EAG's exploratory analyses (see Section 1.7).

Issue 3. Utility values are based on a vignette study despite there being EQ-5D estimates available from a relevant trial population

Report section	4.3.3.2
Description of issue and why the EAG has identified it as important	The company has used utility estimates obtained from a vignette study despite there being relevant EQ-5D data measured in patients with DEB available from the EASE clinical trial. The hierarchy in the NICE methods guide and the supporting NICE DSU report by Rowen <i>et al.</i> clearly states that vignettes studies should only be used in situations where suitable EQ-5D estimates obtained from a relevant patient sample are not available or the EQ-5D is not suitable. The company is not making the case that the EQ-5D is unsuitable and it has in fact used the EQ-5D in its vignette study. Using a vignette may have been appropriate if EQ-5D data reported in a suitable cohort of patients were not available, or if the data available were insufficient for the purposes of the modelling. The company argues that the vignette study provides utility values for a set of health states aligned to the health states in the company's model. However, the availability of a regression analysis for utility versus body surface area percentage (BSAP) affected by wounds allows the EQ-5D data from the EASE trial to be used to estimate utility values for any set of health states defined by BSAP. Therefore, it cannot be argued that the data from the EASE study are insufficient simply because the company has

	chosen a set of health states defined by a different set of BSAP boundaries to those used in HST28.
What alternative approach has the EAG suggested?	The EAG prefers to use the EQ-5D data available from the EASE clinical trial which informed the committee's preferred analysis in HST28.
What is the expected effect on the cost-effectiveness estimates?	This has a large impact on the cost-effectiveness estimates. When the company used the data from the EASE study in a scenario analysis it reduced the incremental QALYs gained versus BSC from 22.47 to 14.27. The incremental QALYs gained versus BBE reduced from 16.43 to 7.24.
What additional evidence or analyses might help to resolve this key issue?	No additional data or analyses are required as the data available from the EASE study are appropriate.

Issue 4. Validity of the company's patient level simulation as a source of effectiveness estimates

Report section	4.3.3.5
Description of issue and why the EAG has identified it as important	Due to the intra-patient design of the GEM-1 and GEM-3 trials, there were no data available on wound outcomes in patients where all eligible wounds were treated with either B-VEC or BSC. Therefore the company had to use a PLS to predict the BSAP affected by wounds in patients treated with either B-VEC or BSC across all eligible wounds. This PLS was mainly parameterised using wound closure data from the GEM-1 study. A notable exception was the data on durability of closure, where data for the B-VEC arm were obtained from the GEM-3 study and its OLE, whereas data from the GEM-1 study were used to inform this outcome for BSC. The EAG had many concerns regarding the appropriateness of the model inputs and assumptions that informed the PLS (see Sections 4.3.3.4 and 4.3.3.5). These included the fact that the GEM-1 study did not use a dosing regimen that matched the dosing regimen used in the GEM-3 RCT or that described in the European Medicine Agency's (EMA's) Summary of Product Characteristics (SmPC). In addition, when using GEM-3 data to estimate the duration

	wound of closure for B-VEC treated patients, the company made assumptions about what happened to wounds between the GEM-3 and OLE studies which led to an unrealistically high estimate of the duration of wound closure which does not reflect the anticipated half-life of COL7 within skin. Furthermore, the PLS distinguishes between recurrent and chronic wounds and makes differing assumptions for B-VEC and BSC with regards to the evolution of chronic wounds. This leads to chronic wounds dominating the wound healing dynamics for BSC treated patients. Overall, the EAG did not have confidence in the transition matrices predicted by the PLS for these reasons.
What alternative approach has the EAG suggested?	The EAG prefers to use the ITC conducted by the EAG on the outcome of complete wound closure to estimate a RR for wound closure for B-VEC versus BBE and to then estimate transition probabilities for patients treated using B-VEC by applying the RR to the transition probabilities reported for the BBE arm of the EASE study. This avoids the need to rely on the company's PLS of clinical outcomes for B-VEC or BSC. It also means that the effectiveness of B-VEC in the model is based on outcomes from the GEM-3 study, which used a dosing regimen that matches the EMA's SmPC, rather than data from the GEM-1 study which used several different dosing regimens across the various trial phases. As transition probabilities are only available for BBE based on the six-state HST28 model structure, this approach could only be implemented when using the model structure from HST28. The company's preference for a four-state model structure over the six-state structure used in HST28 is further discussed in Key Issue 6.
What is the expected effect on the cost-effectiveness estimates?	The EAG were unable to incorporate a scenario analysis exploring the impact of using the outputs from the PLS directly in their adapted version of the replicated HST28 model due to the limited time available. This was also not considered a priority due to the EAG's concerns regarding the validity of the PLS described above. However, the cost-effectiveness of B-VEC was much less favourable in the EAG's preferred analysis which incorporated the RRs from the EAG's ITC.

What additional evidence or analyses might help to resolve this key issue?	The company could provide real world evidence showing the impact of treatment on BSAP in patients treated in clinical practice where B-VEC would be used across all eligible wounds. These data could then be used to externally validate the predictions from both the company's and the EAG's preferred model.

Issue 5. Estimation of vial usage from the patient level simulation

Report section	4.3.3.5
Description of issue and why the EAG has identified it as important	The company has estimated vial usage within its PLS simulation of wound burden for patients treated with B-VEC. The EAG considers that this results in an estimate of vial usage per model cycle which lacks clinical face validity. Each vial can be used to prepare four syringes of mixed product with each syringe being able to treat up to 50 cm² of open wounds. Patients will therefore require a minimum of 0.25 vials of treatment per week if they have any treatable open wounds. This would equate to a vial usage of ~3.25 vials per 3-month (13-week) model cycle. The vial usage predicted for the very mild health states in the company's PLS is between [REDACTED] and [REDACTED] vials per 3-month cycle in children (aged 0 to 6 years). This means that the company's simulation is estimating that no treatment is required for children with very mild disease for the vast majority of weeks. The EAG does not consider that this is likely to be realistic given that repeat treatment will be needed to maintain skin integrity in areas where wounds were previously present due to the half-life of COL7 being estimated at 2 months in addition to cell turn-over being estimated at 4-8 weeks. The expected rate of skin breakdown associated with the finite lifespan of COL7 and cell turn-over rates does not appear to have been captured in the company's PLS. As discussed in Key Issue 4, the company's duration of wound closure for B-VEC treated patients, which drives the transition matrices and estimates of vial usage in the PLS, relies on assumptions being made regarding wound closure between the GEM-3 and OLE studies and the EAG considers

	that the resulting estimate lack face validity. The EAG notes that the company's estimates of vial usage also appear not to correlate with the rate of dosing reported in the company's OLE study.
What alternative approach has the EAG suggested?	The EAG's preferred analysis uses the estimate of vial usage from the company's PLS which has been adapted to estimate outputs for the six states used in HST28. The EAG corrected the parameterisation of wound area for reopened wounds within the PLS. As the estimates of vial usage from the corrected six-state PLS appeared more plausible, the EAG implemented these in their adaptation of the company's replicated HST28 model. However, it also explored an alternative assumption requiring a minimum of 1 syringe per week.
What is the expected effect on the cost-effectiveness estimates?	The EAG has used the company's prediction of vial usage from the PLS simulation adapted to output estimate for the six-states included in the HST28 model in its basecase analysis. A scenario analysis exploring the impact of assuming a minimum usage of 1 syringe per week shows that this further increases the ICERs for B-VEC versus BBE from [REDACTED] to [REDACTED] and for B-VEC versus BSC from [REDACTED] to [REDACTED].
What additional evidence or analyses might help to resolve this key issue?	Evidence on vial usage from real world studies would help reduce this key uncertainty.

Issue 6. The company's preferred four-state model structure is dependent on a mapping algorithm which the EAG considers lacks face validity

Report section	4.3.3.6
Description of issue and why the EAG has identified it as important	The company's preferred model structure uses four health states defined by BSAP affected by wounds. These differ from the states defined by BSAP which were employed in the six-state model structure used in HST28. Many of the model inputs used by the company, such as the resource use estimates and caregiver utility values, have been taken from HST28 and are defined for the six health states used in HST28. The company has built a replicated version the HST28 model including these data

	sources. It has then estimated a mapping algorithm between the six states from the HST28 model and the four states in their preferred model structure. The mapping algorithm has been estimated by trial and error to give similar costs and QALYs for the six-state model structure. However, the mapping lacks face validity as groups which should overlap based on the BSAP definition of the health states do not overlap. The mapping algorithm has then been used to estimate the transition probabilities for BBE when using the company's preferred four state model structure. It has also been used to convert other data inputs obtained from the HST28 model into the inputs required for the four health states used in the company's model. The EAG is concerned that the mapping algorithm is a source of considerable uncertainty. The EAG asked the company to provide a cost-effectiveness model which compares B-VEC to BBE and BSC using the six-health state structure from HST28, but the company declined to do so.
What alternative approach has the EAG suggested?	The EAG prefers to use the original six-state model structure from HST28 as this means that the indirect comparison between B-VEC and BBE no longer depends on the mapping algorithm which it considers to be lacking face validity. Some of the features of the company's model such as changes in mortality and non-cutaneous manifestations across health states were not included in the HST28 model. This means that these features are lacking when using the HST28 model as a starting point. However, the EAG considers that these additional benefits of B-VEC treatment modelled by the company are themselves uncertain. It has therefore made alternative assumptions to model these aspects of DEB within the six-state HST28 model structure (see Key Issue 7).
What is the expected effect on the cost-effectiveness estimates?	It is not possible to determine the impact of choosing the six-state model structure from HST28 over the four-state model structure in isolation from the other changes that are necessary to implement the six-state model structure.

What additional evidence or analyses might help to resolve this key issue?	The company could provide an analysis of the cost-effectiveness of B-VEC versus BBE using the model structure from HST28 and its preferred assumptions for additional benefits such as mortality and non-cutaneous manifestations.

Issue 7. The plausibility of reduced clinical manifestations and mortality in patients with reduced wound burden

Report section	4.3.3.8
Description of issue and why the EAG has identified it as important	The company's model assumes that the association observed in cross-sectional studies between rates of clinical manifestations and severity of wound burden means that lower clinical manifestations will be achieved in patients who achieve a lower wound burden through treatment. The EAG is not convinced that non-cutaneous clinical manifestations can be reduced through treatment with B-VEC (or BBE) and this was supported by comments made by two of the three clinicians consulted by the company in their model validation. It also notes that the data on clinical manifestations was not taken from a study that measured wound burden explicitly using BSAP. This means that the association between clinical manifestations and wound burden assumed by the company cannot be derived directly from the cited source. Instead the company had to make assumptions about wound burden for patient self-declared skin disease severity levels. The company makes a similar assumption for mortality, whereby patients who have severe RDEB, which is associated with both a higher risk of death and a higher wound burden, will have their mortality risk reduced by achieving a lower wound burden through treatment. The EAG considers that some of the excess mortality related to severe RDEB may be related to non-cutaneous manifestations such as anaemia and poor nutrition associated with mucosal wounds and gastrointestinal strictures. These non-cutaneous manifestations are unlikely to be affected by reducing the wound burden through treatment with B-VEC (or BBE). The EAG therefore considers that it is unlikely that

	patients with severe RDEB will be able to achieve a risk of mortality that is similar to patients with less severe forms of DEB through a non-systemic localised treatment of wounds. In addition, the company had to make assumptions about which health states correlated to the disease severity levels in the study reporting mortality data. This adds a further degree of uncertainty to the correlation between health state occupancy and mortality applied in the company's model.
What alternative approach has the EAG suggested?	The EAG does recognise that the risk of death from squamous cell carcinoma (SCC) is particularly high in more severe forms of RDEB and that it is clinically plausible that the SCC risk will be reduced in patients whose wound burden is lowered with treatment as chronic wounds are known to have an increased risk of SCC in other disease areas. The EAG therefore prefers to assume that mortality can be reduced by moving patients out of the health states with the highest wound burden. In its adaptation of the HST28 model, the EAG has applied the mortality risk from severe RDEB patients to those in the two most severe health states and the mortality risk from non-severe RDEB to all other RDEB patients residing in health states with lower wound burden. (Both the EAG and the company apply general population mortality risks to patients with DDEB). Although the EAG notes that there is still considerable uncertainty regarding whether any modification of the SCC risk can be achieved in practice as there are as yet no long-term data to demonstrate a lower risk in patients achieving a lower wound burden through treatment. The EAG prefers to assume no difference in other clinical manifestations associated with DEB and has therefore not included any clinical manifestations within its adaptation of the replicated HST28 model.
What is the expected effect on the cost-effectiveness estimates?	The EAG's exploratory analyses demonstrate that switching from the mortality assumptions applied in HST28, in which there was mortality gain associated with lower wound burden, to the EAG's preferred assumptions had a small impact on the cost-effectiveness estimates. For example, incremental QALYs

	(patient and carer combined) for B-VEC versus BSC increased from 4.94 to 5.07. However, the EAG has not been able to implement the company's preferred mortality assumptions within its adapted replication of the HST28 model as the company assumptions for mortality were aligned with its preferred four states and also varied by the age of the patient.
What additional evidence or analyses might help to resolve this key issue?	Long-term real world evidence studies could examine whether life-expectancy improves in patients offered B-VEC relative to historical controls.

Issue 8. Patients discontinuing treatment are assumed to stay in the state they occupy when discontinuing

Report section	4.3.3.12
Description of issue and why the EAG has identified it as important	Patients who discontinue treatment with either B-VEC or BBE are assumed to follow the transitions for patients receiving BSC. However, the model assumes that patients receiving BSC remain in the same health state from 90 days. This means that patients discontinuing treatment with B-VEC after 90 days will remain in the health state they occupied when they discontinued treatment. The EAG considers that this assumption lacks clinical face validity as it means patients who have achieved a lower wound burden through treatment will maintain that benefit indefinitely after discontinuing treatment.
What alternative approach has the EAG suggested?	The EAG prefers to redistribute patients who discontinue treatment according to the steady state distribution of BSC patients over time.
What is the expected effect on the cost-effectiveness estimates?	When the EAG implemented this change in their adaptation of the company's replicated HST28 model, it had a fairly minimal impact on costs, but it reduced incremental patient QALYs from 1.53 to 1.31 for B-VEC versus BBE and from 2.71 to 2.25 for B-VEC versus BSC. There was a similar impact on carer incremental QALYs.
What additional evidence or analyses might help to resolve this key issue?	Additional real-world evidence could provide information on the rates of discontinuation in clinical practice and the impact of treatment discontinuation on wound outcomes.

Issue 9. Uncertainty regarding the feasibility of vial sharing

Report section	4.3.3.10
Description of issue and why the EAG has identified it as important	The company is assuming that vial sharing occurs for 80% of patients receiving B-VEC. However, the EAG is unclear as to whether vial sharing is feasible for B-VEC due to: a) the need for B-VEC to be used within 7 days if mixed under aseptic conditions, and within 24 hours otherwise; b) the need for mixed syringes to be stored and transported under refrigeration; c)

	uncertainty regarding whether the treatment will be administered at specialist centres, local hospital or at home. The EAG notes that administration at specialist centres would make vial sharing more feasible but would place a large travel burden on patients. However, administration at local hospitals or in patients' own homes would require the coordination of refrigerated transport of syringes to multiple sites if assuming that the syringes are mixed at the specialist centres to facilitate vial sharing.
What alternative approach has the EAG suggested?	The EAG considers that the feasibility of vial sharing is currently very uncertain as it depends on many factors being clarified either by the company or by the clinicians who will be involved in delivering the treatment in practice. It has therefore kept the company's assumption of 80% vial sharing in its base case analysis, but has explored alternative assumptions including 50% and 0% vial sharing to determine how sensitive the cost-effectiveness estimates are to this uncertainty.
What is the expected effect on the cost-effectiveness estimates?	Assuming that reduced vial sharing is feasible in clinical practice had a substantial impact on the cost-effectiveness of B-VEC in the EAG's additional scenario analyses (ASAs). For example, reducing the vial sharing from 80% to 50% increased the ICERs from [REDACTED] to [REDACTED] and for B-VEC versus BSC from [REDACTED] to [REDACTED] (ASA2). Eliminating vial sharing entirely resulted in ICERs of [REDACTED] and [REDACTED] for B-VEC versus BBE and BSC respectively (ASA3).
What additional evidence or analyses might help to resolve this key issue?	Further information would be useful from the company on whether the treatment can be delivered in a home environment and what implications this would have for transportation and disposal of the product. Further information would be useful from the clinicians (prescribers, pharmacists, nurses etc) likely to be involved in delivering B-VEC in the NHS regarding who would be involved in prescribing, preparing, and administered B-VEC, where these processes would occur, and what implications this would have for vial sharing.

1.6 Other key issues: summary of the EAG's key issues

No other key issues were identified.

1.7 Summary of EAG's preferred exploratory analyses

Table 2 provides a summary of the results from the EAG's exploratory analyses. The ICERs substantially increased upon using the EAG-adapted HST28 replicated model compared to the CS model, where B-VEC shifted from being [REDACTED] to generating ICERs around [REDACTED] and [REDACTED] versus BBE and BSC respectively. Large changes in the ICER were seen when correcting model errors and when patients were redistributed according to the steady state associated with BSC after B-VEC/BBE discontinuation. The implementation of the EAG's preferred mortality assumptions had marginal impact on the ICERs. Using the baseline distribution from EASE decreased both incremental costs and incremental QALYs but as these both decreased to a similar extent, the impact on the ICERs was not significant. Implementing the utility values estimated from applying a GLM model to the 24-month HRQoL data from the EASE OLE instead of the utility values fitted to 12-month data from the EASE OLE notably decreased the ICERs to approximately [REDACTED] and [REDACTED] versus BBE and BSC respectively.

When including all the changes preferred by the EAG, the deterministic ICERs were [REDACTED] and [REDACTED] versus BBE and BSC respectively. Making more conservative assumptions regarding B-VEC efficacy or assuming higher B-VEC vial consumption per patient further increase the ICERs.

Table 2: Results of the EAG's exploratory analyses

Option	Absolute outcomes by treatment arm			Incremental			ICER of B-VEC versus comparator (£/QALY)
	Costs (£)	QALYs (patients)	QALYs (carers)	Costs (£)	QALYs (patients)	QALYs (carers)	
Company’s base case – post-clarification (Deterministic)							
B-VEC		10.97	40.37				
BBE	3,042,222	-2.07	36.98		13.04	3.39	Dominant
BSC	2,011,845	-4.87	33.74		15.84	6.63	Dominant
The EAG-adapted HST28 replicated model (Table 59) including EA3 and EA5 to incorporate B-VEC arm							
B-VEC		12.95	40.74				
BBE	2,711,026	11.42	39.54		1.53	1.19	
BSC	1,135,638	10.24	38.50		2.71	2.23	
EAG EA1: Correction of model errors							
B-VEC		12.95	37.44				

Option	Absolute outcomes by treatment arm			Incremental			ICER of B-VEC versus comparator (£/QALY)
	Costs (£)	QALYs (patients)	QALYs (carers)	Costs (£)	QALYs (patients)	QALYs (carers)	
BBE	2,711,026	11.42	36.36	████████	1.53	1.08	████████
BSC	1,135,638	10.24	35.41	████████	2.71	2.03	████████
EAG EA2: Using the HST28 utility values estimated from applying a GLM model to the 24-month HRQoL data from the EASE trial							
B-VEC	████████	13.14	40.74	████████	████████	████████	████████
BBE	2,711,026	10.62	39.54	████████	2.52	1.19	████████
BSC	1,135,638	8.96	38.50	████████	4.18	2.23	████████
EAG EA4: Mortality assumptions preferred by the EAG							
B-VEC	████████	12.97	40.81	████████	████████	████████	████████
BBE	2,713,374	11.44	39.61	████████	1.53	1.19	████████
BSC	1,109,188	10.19	38.51	████████	2.78	2.29	████████
EAG EA6: Patients redistributed according to the steady state associated with BSC after B-VEC/BBE discontinuation							
B-VEC	████████	12.48	40.34	████████	████████	████████	████████
BBE	2,776,919	11.18	39.30	████████	1.31	1.03	████████
BSC	1,135,638	10.24	38.50	████████	2.25	1.83	████████
EAG EA7: Assuming the same baseline distribution from EASE							
B-VEC	████████	13.07	40.79	████████	████████	████████	████████
BBE	2,611,036	11.80	39.87	████████	1.27	0.92	████████
BSC	1,034,384	10.67	38.72	████████	2.40	2.07	████████
EAG base case applying EAs 1+2+4+6+7							
B-VEC	████████	12.74	37.24	████████	████████	████████	████████
BBE	2,674,622	10.81	36.49	████████	1.93	0.75	████████
BSC	1,013,844	9.40	35.63	████████	3.35	1.60	████████
EAG ASA1: EAG base case + estimating the transitions for B-VEC by applying the RR value for complete wound closure only to the transitions to HS1							
B-VEC	████████	11.92	36.77	████████	████████	████████	████████
BBE	2,674,622	10.81	36.49	████████	1.11	0.28	████████
BSC	1,013,844	9.40	35.63	████████	2.53	1.13	████████
EAG ASA2: EAG base case + assuming vial optimisation for B-VEC of 50%							
B-VEC	████████	12.74	37.24	████████	████████	████████	████████
BBE	2,674,622	10.81	36.49	████████	1.93	0.75	████████
BSC	1,013,844	9.40	35.63	████████	3.35	1.60	████████
EAG ASA3: EAG base case + assuming vial optimisation for B-VEC of 0%							

Option	Absolute outcomes by treatment arm			Incremental			ICER of B-VEC versus comparator (£/QALY)
	Costs (£)	QALYs (patients)	QALYs (carers)	Costs (£)	QALYs (patients)	QALYs (carers)	
B-VEC		12.74	37.24				
BBE	2,674,622	10.81	36.49		1.93	0.75	
BSC	1,013,844	9.40	35.63		3.35	1.60	
EAG ASA4: EAG base case + assuming a minimum of one vial per cycle							
B-VEC		12.74	37.24				
BBE	2,674,622	10.81	36.49		1.93	0.75	
BSC	1,013,844	9.40	35.63		3.35	1.60	
EAG base case: Subgroup analysis of RDEB population							
B-VEC		12.64	37.17				
BBE	2,652,436	10.73	36.43		1.91	0.74	
BSC	1,000,255	9.31	35.59		3.33	1.58	

2. BACKGROUND

2.1 Critique of company's description of underlying health problem

The CS describes dystrophic epidermolysis bullosa (DEB) as a chronic, lifelong skin fragility disorder that is caused by mutations in the collagen type VII alpha 1 chain (*COL7A1*) gene.¹ This gene encodes COL7 which is the main component of anchoring fibrils, which are necessary to maintain adequate adhesion between the dermal and epidermal layers of the skin. Absent or reduced COL7 leads to skin fragility, with blisters forming spontaneously or from minimal friction. Wound healing is disrupted in patients with DEB, meaning that wounds remain unhealed for long periods, which is associated with inflammation, an increased risk of wound infection and scarring. Patients with DEB typically either present with symptoms at birth or within the first year, with morbidity accumulating over time from repeated cycles of blistering, healing and scarring. In severe forms, fibrosis and scarring from chronic wounds can lead to joint contractures and webbing of the fingers and toes that limit joint function and mobility.

Although skin manifestations are the hallmark of DEB, patients can also experience significant morbidity from extra-cutaneous complications. These include blistering of the mucous membranes and oesophageal strictures, which together can contribute to impaired nutrition and growth retardation and blistering of the cornea which can lead to blindness. Chronic inflammation and iron loss due to extensive blistering and mucosal involvement also results in chronic anaemia in many patients, which further hinders wound healing.

DEB can be inherited in either an autosomal recessive or autosomal dominant pattern. Whilst recessive DEB (RDEB) is typically more severe than dominant DEB (DDEB), with a higher rate of mortality, there is a range of severity for both RDEB and DDEB and considerable phenotypic overlap.² According to a recent International Consensus statement, the most common subtypes of DDEB are intermediate DDEB (previously known as generalised DDEB) and localised DDEB.² The most common subtypes of RDEB are severe and intermediate RDEB, with rarer forms of RDEB including RDEB-Inversa.² This nomenclature replaces previous naming conventions in which severe RDEB was referred to as Hallopeau-Siemens (HS) type RDEB and intermediate RDEB was referred to as non-HS RDEB.²

The CS states that there is no objective measure of disease severity in DEB, with severity in burden of disease studies typically being based on patient or clinician perception.¹ However, many of the data on rates of complications presented in the CS background section (e.g., Table 1.4 and Table 1.5) are described as being estimates for patients with 'severe DEB' without this being further defined. The EAG is concerned that the description of disease burden presented in the CS is biased towards data that represent the severe form of RDEB and that the CS does not present a balanced picture of disease

severity across all groups covered by the marketing authorisation for B-VEC which includes DDEB and non-severe RDEB. The lack of transparency regarding data sources makes it difficult for the EAG to ascertain if the estimates presented in the background section are relevant to the whole population covered by the CS or whether they are specific to subgroups such as severe RDEB. However, from cross checking a subset of the data reported, the EAG suspects that the data presented mainly relate to patients with severe RDEB, with many estimates appearing to come from a review by Tang *et al.* This review only included studies reporting disease burden in patients with RDEB (studies had to comprise $\geq 80\%$ RDEB) and the proportion with severe RDEB ranged from 26% to 100% in the included studies.³ In some cases, the risks of complications are reported in the cited studies for groups other than severe RDEB, but the CS does not cite these data. For example, the risk of blindness presented in CS, Table 1.5, appears to correspond to the risk of blindness of 6.47% for HS-RDEB (i.e. severe RDEB) reported by Fine *et al.*⁴ However, the CS does not present data on the risk of blindness for patients with non-severe RDEB (1.15%) or DDEB (0.95%) which are also available from Fine *et al.*⁴ As the data presented in CS, Tables 1.4 and 1.5 are not used directly within the company's cost-effectiveness analyses, the EAG has not invested time in checking and validating the source for each of the estimates presented in Table 1.4 and 1.5. However, from the checks it has made, the EAG is not confident that the CS presents a balanced description of the complications of DEB across the whole population relevant to the submission, as the data presented appear to be skewed towards the more severe forms of RDEB.

The CS describes how patients with severe DEB have an increased risk of early death, with squamous cell carcinoma (SCC) being a frequent cause of premature death. The CS states, “*Rates of occurrence of SCC are 47% by age 65 in less severe forms of DEB and in excess of 90% by age 55 in more severe forms of DEB.*”¹ Whilst no specific citation is given for these data points, the EAG identified that the 2009 paper by Fine *et al.* cited elsewhere in the CS, reported cumulative incidences of 47.51% by age 65 for patients with non-HS RDEB and 90.12% by age 55 for patients with HS-RDEB, which appear to be data consistent with this statement.⁵ However, the EAG notes that in the same study, the risk of SCC was lower in patients with RDEB-Inversa (23% at 55 years) and patients with DDEB (4.8% by age 65).⁵ Similarly, when discussing the risk of death from metastatic SCC, the company cites a risk of 60% by age 65 years for patients with ‘less severe forms of DEB,’ and 87% by age 45 for patients with “*more severe forms of DEB.*”¹ These data appear to correspond to data from Fine *et al.* for the cumulative risk of mortality for patients with a SCC diagnosis for the non-HS-RDEB and HS-RDEB subgroups respectively. The CS does not describe risks of mortality from SCC in patients with RDEB-Inversa (50% by age 55) or DDEB (0%) which are available from the same source.⁵ SCC in patients with DEB is described as also being more aggressive and difficult to treat than SCC occurring in the general population and the CS states that 21% to 42% of individuals with SCC associated with DEB require amputation of the affected limb to prevent spread of the disease.¹ Again, these figures appear to correlate to data reported by Fine *et al.* for non-HS RDEB and HS-RDEB respectively.⁵ Patients are

also at risk of death from infections and their complications which include renal failure and cardiomyopathy, although the EAG notes that the data quoted in the CS appears to relate specifically to the RDEB subgroup.⁶

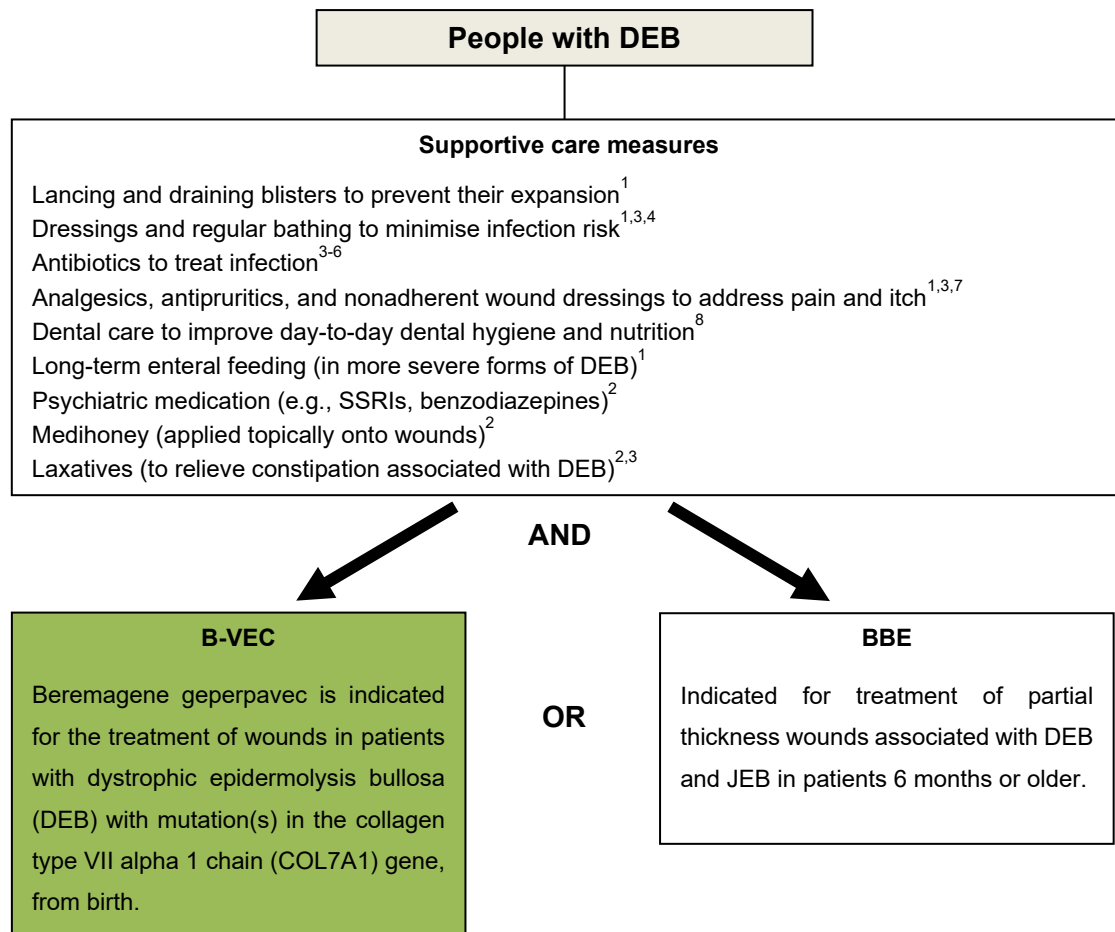
The EAG notes that the data on mortality applied in the company's economic model are taken from a Registry of EB cases in England and Wales, which estimated mortality for DDEB, severe RDEB and non-severe RDEB.⁷ Severe RDEB was described in this study as being that previously referred to as HS-RDEB.⁷ The higher mortality observed for severe-RDEB (see CS, Figure 3.2) suggests that data for this severe RDEB subgroup cannot be seen as representative of data for all patients with DEB as mortality is much lower for DDEB and less severe forms of RDEB. Given that the marketing authorisation for B-VEC is not restricted to severe RDEB, the EAG would have preferred the company to have presented a more balanced set of data on complications and mortality that cover severe RDEB, intermediate RDEB and DDEB.

In terms of the day-to-day burden of DEB, the CS describes the key symptoms as being chronic and acute wound pain and pruritus (itching), with widespread use of painkillers, including opioids in some cases, to manage pain. There is also considerable burden for both patients and carers associated with wound care which is both time consuming and distressing. DEB has a wide impact on activities of daily living and health-related quality of life for both patients and carers. In a survey of patients with epidermolysis bullosa and their carers by DEBRA UK (a patient support organisation for people affected by epidermolysis bullosa), the subgroup with DEB reported EuroQol 5-Dimension 5-Level questionnaire (EQ-5D-5L) utility values of 0.601 on the day of the survey and 0.141 when asked to recall a day when the disease was at its worst.⁸

2.2 Critique of company's overview of current service provision

The CS describes the current care pathway as consisting of management of symptoms and secondary complications. Best supportive care (BSC) is described as including dressing, regular bathing, antibiotics, analgesics, antipruritic, dental care and enteral feeding (CS, page 33).¹ BSC is also summarised within the company's clinical pathway diagram in CS, Figure 1.9 (reproduced here as Figure 1).¹ The EAG notes that the formatting of Figure 1.9 within the CS led to the following elements of BSC being omitted from the visible area of the figure: dental care to improve day-to-day dental hygiene and nutrition; long-term enteral feeding (in more severe forms of DEB); psychiatric medication (e.g., selective serotonin reuptake inhibitors [SSRIs], benzodiazepines); Medi honey (applied topically onto wounds); and laxatives (to relieve constipation associated with DEB). The EAG reproduced that here as Figure 1 and notes that dental care and enteral feeding are mentioned as forming part of usual care in CS, Section 1.3.6.2, and laxatives, Medi honey and psychiatric medications are described as part of BSC in CS, Section 3.2.3.2. In addition to the aspects of BSC covered in the CS, the submission from

the British Association of Dermatologists (BAD) describes the need for physical therapy to maintain joint mobility, monitoring for vitamin deficiencies and vitamin replacement and psychological and counselling support.⁹



BBE=birch bark extract; B-VEC=beremagene geperpavec; DEB=dystrophic epidermolysis bullosa; DDEB=dominant dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; JEB=junctional epidermolysis bullosa; RDEB=recessive dystrophic epidermolysis bullosa; SSRI=selective serotonin reuptake inhibitors.

Figure 1: Anticipated clinical pathway of care for patients with DEB in the UK (reproduced from CS, Figure 1.9)

Highly Specialised Technology Evaluation 28 (HST28) recommended birch bark extract (BBE) for the treatment of partial thickness wounds in patients with DEB.¹⁰ The CS states that the NICE committee concluded that BBE, “*is not disease modifying or curative,*” citing the committee papers for HST28.¹ However, the EAG were unable to identify statements to this effect in the final appraisal document (FAD) for HST28. At the factual accuracy check, the company clarified that its statement was based on a statement made during Technical Engagement, however, the EAG notes that the statement was made by the British Association of Dermatologists and not by the Committee. The EAG notes that the guidance for HST28 states, “*The committee considered the primary outcome of the trial and concluded that birch bark extract was a clinically effective treatment for treating skin wounds associated with*

junctional and dystrophic epidermolysis bullosa.”¹⁰ The CS highlights that the precise mechanism of action for BBE is unknown and states that according to the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use it has only demonstrated modest clinical efficacy.¹

¹² The company’s figure showing the anticipated pathway of care (Figure 1) suggests that BBE is currently offered in addition to BSC.

The CS proposes that B-VEC therapy be given in addition to BSC, and that B-VEC is intended to replace BBE rather than to be used in combination with BBE, as shown in Figure 1.¹ This is consistent with the company’s decision problem, as discussed later in Section 2.3.

When describing the burden of DEB (CS, Section 1.3.5.1), the CS describes the need for multiple surgeries to manage the complications of DEB. This includes surgical management for pseudosyndactyly, which is a joint deformity involving fusion of the fingers and toes, oesophageal dilation and gastrostomy tube placement in some patients to support nutrition and surgical management of SCC where this occurs.¹

The CS states that DEB requires long-term specialist management across a patient’s lifetime (CS, Table 3.3) and describes the burden of DEB care as including dermatologist visits and visits to other specialist to manage the complications of DEB.¹ However, the CS does not describe current service provision for DEB within the NHS. The FAD for HST28 describes care for patients with EB as being provided by multidisciplinary teams across four specialist UK centres, with specialist care being described as essential to manage the condition. It also describes patients having access to local dermatologists between visits to the specialist centres and day-to-day care being provided at home with the help of carers.¹⁰ The EAG’s clinical expert noted that the management of DEB involves multidisciplinary care with involvement from various specialities including plastic surgeons, dentists, gastroenterologists, interventional radiologists, ophthalmologists, pain teams, physiotherapists and psychologists.

The CS does not explicitly state whether B-VEC will be provided at specialist centres, at local hospitals, within primary care settings or within the patient’s own home. Reference is made in the cost-effectiveness section to ‘home delivery’ as part of the costs of administration, suggesting that the intention is for B-VEC to be administered at home but this is not explicitly stated in the CS.¹ When describing outpatient costs in the model, the CS states that B-VEC is to be applied by a healthcare professional and that administration costs can be assumed to be included in the nurse time associated with dressing changes.¹ However, the need for dressing changes to be done by a healthcare professional is not consistent with the CS stating that wound care is often performed by patients and carers in addition to specialised nurses, and it is unclear to the EAG whether patients routinely receive weekly dressing changes by nurses in current practice.¹ The company stated in response to clarification (questions B46

and B47), that they assume that patients (or their caregivers) who do not require assistance with dressing changes will be trained to self-administer B-VEC during administration of the first dose by a healthcare professional. The company assumes that those requiring assistance with dressing changes will have B-VEC administered during dressing changes but that this will not require any additional healthcare professional time.

The EAG's clinical expert noted that they treat patients within one of the four specialist centres and their patients have access to specialist nurses who coordinate care between the hospital and community services and also visit patients at home. However, they thought that weekly nurse delivered treatment in the home environment would require additional resources relative to the current care. The submission from the BAD states that B-VEC treatment *"should be initiated in specialised centres who look after DEB patients and then application can continue at home by trained carers/parents/nurses."*⁹ However, the BAD submission goes on to comment that at present B-VEC can only be dispensed by a hospital pharmacy and it requires 2 healthcare professionals to administer it in a hospital setting, taking 2- 4 hours per week per patient. It notes that weekly hospital administration would require substantial additional resources for pharmacy, nurses, and day care beds.⁹ It notes that hospital delivery of B-VEC would therefore require investment to increase these resources and that if home delivery of B-VEC were to become an option, this would require additional work around preparation, refrigerated storage and delivery, and disposal, in addition to determining if caregivers can safely administer the treatment at home.⁹ The EAG's clinical expert also noted that B-VEC administration is routinely being undertaken by patients or their caregivers in the USA where it has been approved since May 2023.

2.3 Company's definition of the decision problem

A summary of the company's adherence to the decision problem set out in the final NICE scope is provided in Table 3. The EAG's critique of the company's deviations from the final NICE scope are discussed in Section 2.3.

Table 3: Decision problem (adapted from Table 1 of the CS)

	Final scope issued by NICE¹³	Decision problem addressed in the company submission and company's rationale if different from the final NICE scope	EAG comments
Population	People with dystrophic epidermolysis bullosa (DEB)	As per final scope issued by NICE	None.
Intervention	Beremagene geperpavec	Vyjuvek® (beremagene geperpavec [B-VEC]) Throughout this submission, the intervention is abbreviated to B-VEC.	CS, Section 3.2.3 describes the intervention as B-VEC in combination with best supportive care (BSC). ¹
Comparators	Established clinical management without B-VEC including, but not limited to: • treatments that can help ease and control infections, pain, and other aspects of DEB • Birch bark extract (BBE)	As recommended by NICE, comparisons were made between B-VEC and BSC, and between B-VEC with BBE gel. Comparators align with the recommendations from NICE. The company states that there was substantial heterogeneity between studies for B-VEC and BBE in terms of study design and patient population that would likely bias results and cannot be corrected for through an ITC approach. In particular, frequency of the application of placebo treatment differed between trials (which precludes the use of the placebo arms as a common comparator), and concomitant topical	CS, Section 3.2.3 describes the comparators as: • BSC alone • BBE alone.¹ The EAG considers that the relevant comparators according to the final NICE scope are: • BBE with BSC • BSC alone in those ineligible for BBE. This is because the EAG considers that BBE would be given in addition to BSC, which is described in HST28 as including wound management, topical steroid and antimicrobial creams, pharmacological and non-pharmacological forms of pain management and surgical procedures where necessary to manage complications. ¹⁰

	Final scope issued by NICE ¹³	Decision problem addressed in the company submission and company's rationale if different from the final NICE scope	EAG comments
		medications were permitted in at least one BBE study. This is further described in CS, Section 2.9.	In addition, CS section 3.2.3.3 states, " <i>BBE is, similarly to B-VEC, considered an add-on to BSC, so it should be administrated in combination with concomitant medication.</i> " Therefore, the EAG assumes that BSC will continue to be offered to patients receiving either BBE or B-VEC although the intensity of BSC required may be lower in patients responding to either BBE or B-VEC.
Outcomes	The outcome measures to be considered include: • Proportion of complete wound closure • Time to wound closure • Duration of wound closure • Percentage of BSA with wounds • Pain • Change in itching • Incidence of squamous cell carcinoma • Mortality	• Percentage of the surface area of wound healed • Change in total body wound burden • Time to wound closure • Duration of wound closure • Percentage of body surface area with wounds • Pain • Change in itching • Incidence of SCC • Mortality (surrogate) • Adverse effects of treatment • HRQoL	The EAG notes that the following outcomes were not pre-specified trial outcomes in GEM-3: • Percentage of the surface area of wound healed • Change in total body wound burden • Time to wound closure • Duration of wound closure • Percentage of body surface area with wounds The primary outcome in GEM-3 was the proportion of patients with complete wound closure at 6 months that is persistent over a 2 week period (22 to 24 weeks or 24 to 26 weeks) but this is not included in the company's list of outcomes in CS, Table 1.¹ Durability of response (complete response at both 3 and 6 months) was reported in GEM-3 but this was not a pre-specified trial outcome.

	Final scope issued by NICE ¹³	Decision problem addressed in the company submission and company's rationale if different from the final NICE scope	EAG comments
	• Adverse effects of treatment • Health-related quality of life	The company states that NICE suggested that <i>"Percentage of the surface area of wound healed"</i> and <i>"change in total body wound burden"</i> should be merged into a single outcome, <i>"percentage of body surface area with wounds."</i> The rationale for separating these outcomes is that the first outcome (interpreted as a change in wound size over time) is less relevant as the treatment aims to promote durable wound closure). The company states that the mortality outcome will be assessed through surrogate endpoints, given the long timeframe needed to collect direct evidence on mortality. The EAG is unclear what the company means by this statement.	In addition, itching (reported as pruritus), SCC and mortality were only reported as adverse events in GEM-3 Proportion with complete wound closure, time to complete wound closure and duration of wound closure were efficacy endpoints in the phase 2 of GEM-1 However, percentage of body surface area with wounds was not assessed in either GEM-3 or GEM-1. Whilst CS, Table 1, states that this is an outcome covered in the CS,¹ this outcome has been estimated for B-VEC using simulation methods (see Section 4.2.5.1). The EAG is unsure where change to total body wound burden has been presented within the CS, other than in the trial data for the comparator BBE. Change from baseline in EQ-5D-5L and Skindex-29 are described as patient reported outcomes (PROs) for GEM-3, but these are not listed as efficacy outcomes and are not reported as comparative measures.

	Final scope issued by NICE ¹³	Decision problem addressed in the company submission and company's rationale if different from the final NICE scope	EAG comments
Subgroups to be considered	If evidence allows, the following subgroups will be considered: • Dominant dystrophic epidermolysis bullosa (DDEB) • Recessive dystrophic epidermolysis bullosa (RDEB)	Aligning with the final scope issued by NICE, subgroup data are reported for: • Dominant DEB (DDEB), • Recessive DEB (RDEB), and additionally, • Paediatric patients with DEB, • Adult patients with dystrophic epidermolysis bullosa. Given that B-VEC is indicated for all patients with DEB, starting at birth,¹⁴ paediatric and adult patient subgroups should additionally be considered. Treatment of newborns can potentially prevent the devastating sequelae of DEB (such as fibrosis and scarring, deformities like mitten hands and feet, SCC, and reduce the risk for early mortality).	Whilst CS, Table 1.1 states that the company submission will report subgroup data for the DDEB and RDEB subgroups and for adult and paediatric patients,¹ the EAG notes that subgroup analyses by type of DEB (DDEB vs RDEB) were not preplanned in the GEM-3 trial, with preplanned subgroups specified only for age, sex and race (as stated in CS, Table 2.3).¹ In addition, only one patient with DDEB was recruited to the GEM-3 trial, and one additional treatment naïve subject with DDEB was recruited to the GEM-3 OLE. The GEM-1 trial only included REB patients and no subgroup analysis was planned or performed. Therefore, across the GEM-1, GEM-3 and GEM-3 OLE, only 2 DDEB patients were recruited making subgroup analysis by DEB type unfeasible. Subgroup analyses for EB sub-type (RDEB, DDEB and JEB) were reported for the EASE trial of BBE. The company's economic analysis is conducted assuming a mixed population of DDEB and RDEB, and a distribution of patients across age categories (under 6 years, 6 to 18 years and over 18 years), but subgroup

	Final scope issued by NICE¹³	Decision problem addressed in the company submission and company's rationale if different from the final NICE scope	EAG comments
			analyses by DEB subtype or age category are not reported for the cost-effectiveness analysis.
Special considerations including issues related to equity or equality	• Guidance will only be issued in accordance with the marketing authorisation. • Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	NA	Whilst no discussion of equality issues was included in CS, Table 1.1, the EAG notes that CS, Section 1.4, discusses equality considerations. ¹ These are discussed further in Section 2.3.6.
Abbreviations: BBE, birch bark extract; B-VEC; BSC, best supportive care; beremagene geperpavec; DDEB, dominant dystrophic epidermolysis bullosa; DEB, dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; ITC, indirect treatment comparison; JEB, junctional epidermolysis bullosa; NA, not applicable; OLE, open label extension; PRO, patient reported outcomes; RDEB, recessive dystrophic epidermolysis bullosa; SCC, squamous cell carcinoma;			

2.3.1 Population

The population addressed in the CS is people with DEB,¹ which is consistent with the population specified in the final NICE scope.¹³ According to the Summary of Product Characteristics (SmPC) approved by the European Medicines Agency (EMA), B-VEC is indicated, “*for the treatment of wounds in patients with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene, from birth.*”¹⁴ Although all DEB is caused by mutations in the *COL7A1* gene, the EMA’s marketing authorisation requires the use of genetic testing to confirm mutations in the *COL7A1* gene before treatment initiation.¹⁵ However, the EAG’s clinical advisor, confirmed that genetic testing is routine within the NHS as part of the diagnosis of DEB. The EAG is therefore satisfied that the population is consistent with the marketing authorisation and that no additional tests are required to identify the eligible population over and above those already provided routinely in clinical practice.

2.3.2 Intervention

The intervention is B-VEC. B-VEC is, “*a replication-defective Herpes Simplex Type-1 HSV-1-based gene therapy vector that has been genetically modified to express the human type VII collagen (COL7) protein under the control of the human cytomegalovirus (hCMV) promoter.*”¹⁴ It is a topical and redosable gene therapy engineered to deliver functional *COL7A1* gene to restore COL7 production and normalise anchoring fibril formation.¹ The CS describes B-VEC as having received a positive opinion from the EMA’s Committee for Medicinal Products for Human Use (CHMP) in February 2025. It then went on to receive an EU Marketing Authorisation in April 2025. However, its marketing authorisation status within the UK is not described in the CS, and much of the company’s description of the intervention in the CS appears to rely on its EMA approved SmPC. The EAG notes that the MHRA approval is expected in May 2026.

As B-VEC contains genetically modified organisms, special precautions should be taking when preparing, handling and disposing of B-VEC.¹⁴ The EMA’s SmPC states that a health care profession (HCP) should apply B-VEC, but that trained patients or carer givers may also apply B-VEC if deemed appropriate by the HCP.¹⁴ B-VEC is applied cutaneously to wounds once a week in small droplets from a syringe in a grid-like pattern approximately 1-cm by 1-cm apart with only the droplet and not the syringe touching the wound.¹⁴ See the EMA’s SmPC for specific guidance on the dose required for wounds according to size.¹⁴ As there is a total maximum weekly dose that can be applied across all wounds (1 mL in patients aged up to 3 years old and 2 mL for older patients), it may not be possible to treat all wounds at each visit. B-VEC should be applied weekly to a wound until it is closed before selecting new wounds to treat and treatment of previously treated wounds should be prioritised if they re-open.¹⁴ B-VEC should not be administered if no wounds are present.¹⁴ B-VEC should not be applied to wounds with a confirmed or suspected diagnosis of SCC but can be applied to other wounds not affected by SCC in patients who develop SCC.¹⁴

Each carton of product contains one vial of B-VEC suspension (1 mL extractable volume containing 5 billion [5×10^9] plaque forming units [PFU]) and one vial of excipient gel (1.5mL).¹⁴ Pharmacy preparation of B-VEC involves thawing the product and mixing the suspension with the excipient gel, preferably under validated aseptic conditions, with the medicinal product having a concentration of 2×10^9 PFU/mL after mixing.¹⁴ The product should then be transferred to syringes containing 0.5mL of medicinal product.¹⁴ Mixed product should be refrigerated during storage and transport and syringes can be stored at room temperature for only up to 8 hours (see the EMA's SmPC for specific guidance on storage).¹⁴ Although chemical and physical in-use stability for refrigerated mixed product has been demonstrated for 7 days, the EMA's SmPC states that from a microbiological point of view the product should be used immediately, and that refrigerated storage times would not normally be longer than 24 hours unless mixing has taken place in controlled and validated aseptic conditions.¹⁴

The list price per 1 mL vial containing 5×10^9 PFU is £21,500,¹ which when mixed with the excipient gel provides 5×10^9 PFU in 2.5mL, with an extractable volume of 2.0 mL containing 4×10^9 PFU.¹⁴ When assuming that only the extractable volume is available for treatment, the maximum number of vials that can be applied per week is one vial in patients aged over 3 years (4×10^9 PFU) and half a vial in patients aged up to 3 years old (2×10^9 PFU). The maximum annual treatment cost per patient aged over 3 years old is £1.1 million. The EAG notes that not all patients will have a wound area sufficient to require the maximum weekly dose (200 cm²), although vial sharing would be required to realise any cost savings associated with patients requiring less than one vial per week. No patient access scheme discount has been proposed by the company.

2.3.3 Comparators

The comparator listed in the final NICE scope is "*established clinical management without beremagene geperpavec*" including, but not limited to: a) treatments which can help ease and control infections, pain and other aspects of DEB, and b) BBE.¹³ The EAG considers that the former constitutes BSC. As the CS indicates that both BBE and B-VEC should be given in addition to BSC, the EAG considers that the relevant comparators are a) BBE with BSC (hereafter referred to simply as BBE) and b) BSC alone, with the latter only being relevant for those patients ineligible for BBE.

BBE was recommended, in HST28, as an option for treating partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa in people aged 6 months and over.¹⁰ Only the group of patients with DEB overlap with population addressed in the CS. Patients with DEB who are ineligible for BBE under HST28 would include those aged under 6 months and those whose wounds are not considered to be partial thickness wounds. However, the clinical advisor to the EAG considered that by nature all wounds caused by DEB would be classified as 'partial thickness' because they occur at or

close to the dermal-epidermal junction, although this terminology is more relevant to burn wounds and it is not generally used in the context of DEB. Therefore, the EAG considers that there would be a high degree of overlap between DEB patients with wounds eligible for treatment with B-VEC and DEB patients with wounds eligible for treatment with BBE, with the exception of patients under 6 months old.

BBE is marketed as a gel where 1 g of gel contains 100 mg of extract, “(as dry extract, refined) from *Betula pendula* Roth, *Betula pubescens* Ehrh. as well as hybrids of both species, cortex (equivalent to 0.5 l.0 g birch bark), including 84 95 mg triterpenes calculated as the sum of betulin, betulinic acid, erythrodiol, lupeol and oleanolic acid. Extraction solvent: *n*-Heptane.”¹⁶ The EMA’s SmPC states that it is available in tube sizes of 9.4g or 23.4g,¹⁶ although only the 23.4g tube is listed within the BNF.¹⁷ The NHS indicative price for BBE is £275.33 per 23.4g tube.¹⁷ BBE should be applied cutaneously to the wound surface. “at a thickness of approximately 1 mm and covered by a sterile non-adhesive wound dressing or applied to the dressing so that the gel is in direct contact with the wound.”¹⁶ It should not be applied sparingly or rubbed into the wound and it should be reapplied at each wound dressing change.¹⁶ Each tube is for single use and should be discarded after use.¹⁶ BBE should not be applied to wounds affected by SCC.¹⁶

2.3.4 Outcomes

The key outcome addressed in the CS is the proportion of patients with complete wound closure at 6 months as this was the primary outcome in the GEM-3 trial,¹⁸ the main comparative randomised controlled evidence presented for B-VEC. Wound closure was specified as skin reepithelialisation without drainage, as determined by the investigator.¹⁸ Complete wound closure at 6 months was defined as 100% wound closure from the exact wound area selected at baseline and wounds were required to remain closed over a 2-week period (22 to 24 weeks or 24 to 26 weeks).¹⁸ Complete wound closure at 3 months (8 to 10 weeks or 10 to 12 weeks) was a key secondary endpoint.¹⁸ Durability of response, defined as complete wound closure at both 3 and 6 months, was also reported in GEM-3 but this was not a pre-specified outcome.¹⁸

Whilst time to wound closure and duration of wound closure were included in the final NICE scope these were only addressed as endpoints in the GEM-1 trial (a phase 1/2 trial) and not in GEM-3.^{18, 19} It should also be noted that wound closure in GEM-1 required only $\geq 90\%$ reduction in wound surface from baseline, which differs from the 100% reduction required in GEM-3.^{18, 19}

Although it would have been necessary to measure the percentage of the surface area of wound healed in both GEM-1 and GEM-3 in order to determine when patients met the criteria for complete wound closure, this outcome does not appear to have been a pre-specified outcome in either trial. The CS does

present data on mean percent change from baseline in the area of all target wounds in patients from GEM-1 in CS, Figure 2.4c, however, it is not clear if this was a pre-specified trial outcome. Wound burden does not appear to be an outcome in either GEM-1 or GEM-3.

The outcome used to drive the cost-effectiveness analysis in HST28 was body surface area percentage (BSAP) with wounds.¹⁰ This outcome was not addressed in either the GEM-1 or GEM-3 trials,^{18, 19} but does form the basis of the company's cost-effectiveness comparison against BBE. To facilitate this comparison the company has conducted a patient-level simulation to estimate what the BSAP would be in patients treated with either B-VEC or BSC using other wound related outcomes from the GEM-1 and GEM-3 trials and epidemiological data on the expected number and size of wounds. The company's approach to estimating BSAP for patients treated with B-VEC or BSC is discussed further in Section 4.2.4.

The outcome of pain was measured in both GEM-1 and GEM-3, albeit using differing methods across these trials. GEM-3 measured pain during wound dressing changes and used a visual analogue scale (VAS) pain score in patients aged 6 years and over, and the FLACC-R (Faces, Legs, Activity, Cry, Consolability Revised) scale for younger patients, whereas GEM-1 used a "*patient reported outcome pain scale*," with no further details provided on the scale used.

Incidence of SCC, mortality and itch for B-VEC treated patients are addressed in the CS only via adverse event (AE) reporting in the GEM-1 and GEM-3 trials. Adverse event reporting is non-comparative due to each patient being treated with both B-VEC and placebo. Although health-related quality of life was measured in GEM-3, using both the EQ-5D-5L and Skindex-29 measures, these could not be reported comparatively according to a specific wound treated as these measures capture global quality of life which both wounds contribute towards. The EAG's clinical expert also noted that it is unlikely that global measures of itch, pain and quality of life would be affected in a trial where only one wound was randomised to receive active treatment and the patient's other wounds received placebo or BSC.

For the EASE trial comparing BBE to placebo, complete wound closure was assessed as the proportion of patients with first complete closure of the target EB wound within 45 days (+/-7 days), which was the primary outcome in the EASE trial.²⁰ The EASE trial also reported the proportion with complete wound closure at 90 days, time to complete target wound closure, BSAP affected by wounds, total body wound burden measured using the Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) tool, background pain, procedural pain and itch.

2.3.5 Subgroups

Whilst CS, Table 1.1 states that the company submission will report subgroup data for the DDEB and RDEB subgroups and for adult and paediatric patients,¹ the EAG notes that subgroup analyses by type of DEB (DDEB vs RDEB) were not preplanned in the GEM-3 trial, with preplanned subgroups specified only for age, sex and race (as stated in CS, Table 2.3).¹ In addition, only one patient with DDEB was recruited to the GEM-3 trial, and one additional treatment naïve subject with DDEB was recruited to the GEM-3 open label extension (OLE). The GEM-1 trial only included RDEB patients and no subgroup analysis was planned or performed. Therefore, across the GEM-1, GEM-3 and GEM-OLE, only 2 DDEB patients were recruited making subgroup analysis by DEB type unfeasible. Subgroup analyses by age category are reported for the primary outcome in GEM-3 and for adverse events in the GEM-3 OLE.

Subgroup analyses for EB sub-type (RDEB, DDEB and JEB) were reported for the EASE trial of BBE. These were conducted for the primary outcome (proportion with complete wound closure at 45 days) and the key secondary outcome (median time to wound closure). Data for the RDEB and DDEB subgroups combined (i.e., excluding only the JEB subgroup) are not available, meaning that data for a population matching the licensed indication for B-VEC is not available. However, it should be noted that the data available for B-VEC have limited patients with DDEB. Subgroup analyses from EASE were also available by age category, and whilst these are discussed in the CS (page 76), these data are not presented.

The company's economic analysis is conducted assuming a mixed population of DDEB and RDEB, and a distribution of patients across age categories (under 6 years, 6 to 18 years and over 18 years), but subgroup analyses by DEB subtype or age category are not reported for the cost-effectiveness analysis.

Overall, the EAG considers that the subgroups specified in the final NICE scope are not adequately addressed in the CS because the data on the use of B-VEC in patients with DDEB are too limited to support subgroup analyses, and also because the company has not presented economic analyses separately for the adult and paediatric subgroups. The EAG's clinical expert also noted that there is a good biological rationale to expect treatment effectiveness might differ in DDEB compared with RDEB due to patients with DDEB having one non-mutated copy of the *COL7A1* gene. Therefore, it may not be appropriate to assume equivalent effectiveness in patients with DDEB, although anecdotal evidence from the USA suggests DDEB patients do experience some benefit.

2.3.6 *Special considerations*

Whilst no discussion of equality issues was included in CS, Table 1.1, which summarises the decision problem, the EAG notes that CS, Section 1.4, discusses equality considerations.¹ It states that a substantial proportion of people with DEB would meet the criteria for disability under the Equality Act 2010. It also notes the high cost of raising disabled children, and barriers that may exist in accessing health and social care, and financial support provided for disabled family members, particularly in families from minority ethnic communities.

The EAG notes comments from the patient organisation, DEBRA, that travel costs and time associated with receiving weekly treatment in an outpatient setting may further exacerbate the inequalities facing those who live further from treatment centres or who lack the financial means to travel.²¹ This was echoed in comments from the BAD, which stated that providing the technology only at specialist centres may create inequalities in access which disproportionately effect those on low income and those experiencing language barriers which can increase the time required to interact with health services.⁹

3. CLINICAL EFFECTIVENESS

The clinical evidence contained in the CS is comprised of:

- A systematic literature review (SLR) of clinical evidence on the efficacy, safety, and HRQoL modulation effect for B-VEC for treating wounds associated with DEB.
- Summary and results for the GEM-3 and GEM-1 trials for B-VEC and EASE trial for BBE.

This chapter summarises and critiques the company's review methods and clinical effectiveness data. Full details are presented in the Section B.2 of the CS and CS Appendix B.

3.1 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 B-VEC for treating wounds associated with the DEB (CS, Section B.2 and Appendix B). The primary clinical evidence detailed in the CS for B-VEC comes from the GEM-3 and GEM-1 trials.

GEM-3 (B-VEC-03; NCT04491604) was a national phase III, multi-centre, double-blind, intra-patient (i.e., each patient served as their own control), randomised controlled trial (RCT) with a 7-month follow-up. Four published and unpublished reports and protocols relating to this trial were identified by the SLR and their data reported in the CS.^{18, 22-24} This includes a 112-week OLE to GEM-3 to assess the long-term safety and tolerability of B-VEC (NCT04917874).²³

GEM-1 (KB-103-001; NCT03536143) was a phase I/II, single-centre, open-label, intra-patient (i.e., each patient served as their own control), randomised controlled trial (RCT) with an unclear follow-up. Three published and unpublished reports and protocols relating to this trial were identified by the SLR and their data reported in the CS.^{19, 25, 26} The data reported in the CS for B-VEC were extracted from the main trial publications for GEM-3²² and GEM-1²⁵ and the Clinical Study Reports (CSRs) for both trials (GEM-3 and GEM-1).^{18, 19, 23}

The current clinical management of DEB is heterogeneous and includes but is not limited to treatments which can help ease and control infections, pain and other aspects of EB. The GEM-3 and GEM-1 trials used a placebo control gel as a comparator. Clinical advice to the EAG suggests that this approach represented a reasonable comparator for B-VEC. The final NICE Scope specified BBE as a comparator for B-VEC, as it is the only NICE recommended therapy for treating wounds of patients with DEB (NICE HST28).¹⁰ For this reason, the SLR also included the key clinical evidence available for this intervention, an RCT comparing BBE with a placebo control gel (the

EASE trial: BEB-13; NCT03068780; EudraCT2016-002066-32). It is an international phase III, multi-centre, double-blind, RCT with a 24-month open-label, single-arm follow-up phase.²⁷ This study forms the key evidence for clinical effectiveness and safety of BBE within the CS. The data reported in the CS were extracted from the main trial publications.²⁷

The CS did not perform a meta-analysis. This was reasonable given the presence of only two small, placebo-controlled and related RCTs (GEM-1 and GEM-3) with some patient overlap.^{18, 19, 22} There was one additional trial of a relevant comparator (BBE), which was also placebo-controlled (the EASE trial).²⁷ The CS argues that an indirect treatment comparison (ITC) and network meta-analysis comparing B-VEC with BBE was not appropriate due to population, comparator, outcome and study design differences between the B-VEC and BBE trials (CS, Sections B.2.9). This assessment is discussed in detail in Section 3.9.

The safety evidence reported in the CS comprised a narrative summary of data from the GEM-3, GEM-1 and EASE trials (CS, Sections B.2.10).

3.1.1 Searches

CS Appendix B presents the search strategy for the SLR conducted to identify clinical trials reporting on the efficacy and safety of B-VEC and comparators (most notably BBE) for the treatment of DEB. The literature search was conducted in November 2024 and was designed to maximise sensitivity by searching for population terms and eligible study designs but not intervention terms. There were also no limits on publication language or date.

A comprehensive range of bibliographic databases was searched: MEDLINE (ALL); Embase; Allied and Complementary Medicine Database; Cumulative Index to Nursing and Allied Health Literature (CINAHL); PsycINFO; Retraction Watch via INAHTA; Cochrane Central Register of Controlled Trials (CENTRAL). The Cochrane Database of Systematic Reviews (CDSR) was searched simultaneously with CENTRAL, but the results were excluded from the review as systematic reviews were not eligible for inclusion (CS, Appendix B, Table 15, confirmed in clarification response A3).

Clarification was sought on why systematic reviews had been excluded, when the 'Additional Searching' section of Appendix B of the CS stated that the bibliographies of systematic reviews were hand-searched to identify further relevant studies. Clarification response A3 indicated that some systematic reviews were identified through the database searching that were eligible based on the population, intervention and outcomes of the PICOS criteria. It remains unclear why some systematic reviews were excluded based on study type alone, and some were taken forward for hand searching. However, the company states in A3 that records identified from the bibliographies of the included

reviews were then compared to results already found, and no new studies were identified. This suggests that there is little chance of missing key evidence from the methods employed in the SLR.

Supplementary searching also included the trial registries ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP), relevant conference proceedings from 2023-2025 and a comprehensive range of HTA websites.

The CS comprehensively reports the search strings used for database searches, including line-by-line result numbers for each database. The search string for the MEDLINE search, presented in Table 3, also includes annotations explaining the rationale behind each part of the search. This is a welcome level of detail in the reporting, especially where the narrative states the source of the study design filter used and specifies the changes that have been made to it. However, the CS does not specify whether a published, validated filter for the relevant study design has been used, in either unmodified or modified form, in the searches of the other databases (e.g., Embase, for which such filters are available). This was addressed in clarification response A4, which explained that the MEDLINE search used an adaptation of the Canada's Drug Agency (CDA-AMC) RCT/CCT filter from Cooper *et al.* (2018),²⁸ and that these amendments were applied in a similar fashion in the other database searches. While it is best practice not to make modifications to validated search filters, reporting where changes have been made and why (in this case to make the search more sensitive, and therefore unlikely to miss key evidence) is an acceptable pragmatic approach in the opinion of the EAG.

The supplementary searches have also been reported transparently, in line with the methods set out by Stansfield *et al.* (2016) for conducting and reporting the searches of websites and other online sources systematically.²⁹

The EAG noted that the CINAHL search (Appendix B, Table 6) did not include the available subject heading "Epidermolysis Bullosa" alongside the free-text terms in lines S1-S5. Clarification response A5 explains that CINAHL was searched in order to complement the essential databases of MEDLINE, Embase and the Cochrane databases, as per Cochrane Handbook for Systematic Reviews of Interventions (Cochrane, 2024), and to identify any studies with a nursing focus.³⁰ The EAG agrees with the response that CINAHL's inclusion adds to the comprehensiveness of the overall search strategy, and that not including the subject heading would have a minimal effect on retrieval. It is likely that any study indexed under the heading "Epidermolysis Bullosa" would contain these words in the title and abstract, or other words that were searched for in the free-text search lines (S1-S5).

Overall, the sensitive approach taken with the search strategy, and the comprehensive range of databases and supplementary sources searched, means that the EAG is confident that the relevant evidence from the literature for the clinical SLR informing this submission would have been retrieved.

3.1.2 Inclusion criteria

The inclusion and exclusion criteria for the SLR are reported in Table 4. These criteria were largely consistent with the final NICE scope (CS, Section B.1.1 Table 1.1).

The SLR criteria included the key effectiveness outcomes from the final NICE scope. These included: proportion of complete closure of target wounds; time to wound closure and duration of wound closure (in GEM-1 trial only); incidence and severity of wound infection; pain; adverse effects of treatment and health-related quality of life (for patients and carers) (CS, Section B.1.1 Table 1.1). The CS noted that the NICE Scope outcome of mortality was not included in the GEM-3 and GEM-1 trials given their duration. The company's description of the outcomes addressed in the decision problem (CS, Table 1.1) it states, "*The mortality outcome will be assessed through surrogate endpoints, given the long timeframe needed to collect direct evidence on mortality.*" However, it is unclear to the EAG what is meant by this statement. The final NICE scope also included the outcomes considering wound burden and affected body surface area, as well as 'change in itching', and the EAG noted that no specific assessment of these outcomes was included in the GEM-3 or GEM-1 trials.

Table 4: Inclusion and exclusion criteria for the SLR (adapted from CS Appendix B, Table 15)

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	- Children, adolescents, and adults diagnosed with DEB (RDEB or DDEB) - Mixed population of adults, adolescents, and children with other forms of EB if results for patients with DEB are reported separately or if DEB patients make up $\geq 85\%$ of the total population	Patients without DEB, including those with other forms of EB
Intervention and comparators	Interventions - B-VEC - BBE (Oleogel-S10) - Current clinical management without B-VEC (including, but not limited to, treatments that can help ease and control infections, pain and other aspects of DEB) Comparators - Current clinical management without B-VEC (including, but not limited to,	Interventions Studies not investigating a relevant intervention (e.g., bone marrow transplant, autologous fibroblast therapy) Comparators Non-pharmacologic therapies (e.g.,

Clinical effectiveness	Inclusion criteria	Exclusion criteria
	treatments that can help ease and control infections, pain and other aspects of DEB) • Placebo • Any comparator (i.e., head-to-head trials) • No comparator (i.e., single-arm trials)	physiotherapy, hydrotherapy)
Outcomes	Efficacy: • Closures of unhealed target wounds • Time to wound closure • Duration of wound closure • Incidence of wound infection • Severity of wound infection • Percentage of surface area of wound healed • Change in total body wound burden (EBDASI, etc) • Change in itching Safety: • Overall AEs • Treatment-emergent AEs • Serious AEs • Discontinuation due to AEs • AEs due to wound complications • Mortality (all-cause; treatment related. SCC-related; sepsis-related) HRQoL: • EQ-5D and EQ-5D-Y • PedsQL • SF-36 • DFIQ • IT-DQL Skin specific • DLQI and CDLQI • Skindex-29 Pain specific • FLACC-R • VAS • Pharmacodynamic/ pharmacokinetic outcomes • Non-clinical outcomes (e.g., gene or protein expression outcomes) • Studies not reporting any relevant outcome Itch specific: • LIS • Itch Man Assessment DEB specific: • BEBSS • QOLEB • IscorEB Caregiver: • ZARIT Burden Interview Sleep disturbance: • PSQI • SDC • PROMIS	

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Study design and publication type	Study design • RCTs (phases I–IV) • Randomised crossover trials • Randomised cluster trials • Head-to-head comparisons • Single-arm interventional trials • Long-term follow-up studies (e.g., open-label extensions) Publication type • Journal articles • Research letters reporting data • HTA manufacturer submissions • Conference abstracts	Study design • Observational studies (retrospective and prospective), including studies comparing outcomes in groups / individuals receiving different interventions and real-world studies • Pre-clinical studies • Animal studies • Cell model studies • Case studies/case series • Studies reporting pooled data from >1 trial • Patient registries and natural history studies • Prognostic studies • Meta-analyses of aggregated and individual participant data Publication types • Editorials • Commentaries • Replies • Narrative reviews • Opinions • Dissertations and theses • Book chapters • Systematic reviews* • Consensus reports
Limits	No date or language limits applied	None
Abbreviations: AE=adverse event; BEBS=Birmingham Epidermolysis Bullosa Severity Score; BSAP=body surface area percentage; BVEC=beremagene geperpavec; CDLQI=Children's Dermatology Life Quality Index; DEB=dominant dystrophic epidermolysis bullosa; DEB=dystrophic epidermolysis bullosa; DFIQ=Dystrophic Epidermolysis Bullosa Family Impact Questionnaire; DLQI=Dermatology Life Quality Index; EBDASI=Epidermolysis Bullosa Disease Activity and Scarring Index; QOLEB=Quality of Life in Epidermolysis Bullosa questionnaire; EQ-5D-Y=EQ-5D Youth version; FLACC-R=Face Legs Activity Cry Consolability – Revised; HCRU=health care resource use; HUI=Health Utilities Index; IT-DQL=Infants and Toddlers Dermatology Quality of Life; iscorEB=Instrument for Scoring Clinical Outcomes of Research for EB; LIS=Leuven Itch Scale; PedsQL=Pediatric Quality of Life Inventory; PROMIS=Patient-Reported Outcomes Measurement Information System; PSQI=Pittsburgh Sleep Quality Index; RDEB=recessive dystrophic epidermolysis bullosa; RCT=randomised controlled trial; RWE=real world evidence; SAE=serious adverse event; SDC=Sleep Disturbance Scale; SF-36=Short Form Health Survey with 36 items; Skindex-29=29-Item version of Skindex scale; SLR=systematic literature review; VAS=visual analog scale; WHO=World Health Organization		

3.1.3 Critique of study selection, data extraction and quality assessment

CS Appendix B 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 resolved by discussion or by a third independent reviewer, if necessary. 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 Appendix B, Figure 1).

Data extracted from the included studies are presented in Sections B.2.2-2.10 of the CS. Details of the data extraction process were reported in CS Appendix B. The process was undertaken by one reviewer, and a second reviewer independently audited the extraction, cell by cell, for accuracy and completeness, and any discrepancies were resolved by consensus or by discussion with by a third independent reviewer, if necessary. The EAG considers complete independent data extraction by two or more reviewers to be best practice in systematic reviewing but accepts that the stated approach is adequately robust.

CS Appendix B 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, A9).³¹ The response stated that 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.

3.2 Results of the company's SLR

The clinical SLR presented in the CS identified for inclusion 32 reports covering seven RCTs and four non-RCTs (CS, Appendix B, page18, Figure 1 and Table 16). However, only evidence from four trials was presented in the clinical effectiveness section of the CS and details of the exclusions were not provided. The four included trials were: two B-VEC trials (the phase I/II GEM-1¹⁹ and phase III GEM-3²² plus its expanded open label extension study [B-VEC-OLE²³]) and two BBE trials (the phase II BEB-10³², and the phase III EASE and its open label phase (OLP)^{20, 27}). The phase II BEB-10 trial³² was only mentioned in relation to the ITC (CS, Section B.2.9).

The EAG believes that no relevant published phase III trials of B-VEC in DEB patients have been omitted from the CS that could have provided additional data on safety and efficacy.

Characteristics of the GEM-3, GEM-1 and EASE trials

3.2.1 Study design: GEM-3

GEM-3 is a phase III, randomised, multi-centre, double-blinded, RCT initiated in August 2020 and conducted in three centres, all in the USA. There were no UK centres or patients (NCT04491604).²⁴

Details of study location, treatments, trial inclusion and exclusion criteria, permitted and prohibited concomitant medications and relevant outcomes are reported in Table 5. The primary completion date was 29 October 2021, and the actual completion date is listed as 14th January 2022 (NCT04491604).²⁴ Overall, 31 patients and wound pairs satisfied all eligibility criteria and were randomised. The full eligibility criteria of the GEM-3 study are listed in Table 5.

The GEM-3 trial comprised patients aged ≥ 6 months with a clinical diagnosis of DEB confirmed by genetic testing, including *COL7A1* mutations. Eligible patients had to have two cutaneous wounds similar in size, anatomical region, and appearance (i.e., clean with adequate granulation tissue, excellent vascularisation, and no appearance of infection). Wounds were randomly assigned in a 1:1 ratio to be treated with B-VEC or placebo; therefore, each patient served as their own control. The EAG noted that wound duration was not considered as a factor in wound selection, but might represent a confounding factor given that so-called ‘recurrent’ wounds might satisfy these criteria but close without treatment (CS, Section B.1.3.5, Table 1.3, Eng *et al.* and Solis *et al.*^{33,34}). In response to an EAG request, the company confirmed that the GEM-3 trial likely included both recurrent and chronic wounds, but these details were not recorded (Clarification response, A1 and A2).³¹

Table 5: Summary of the trial design of GEM-3 (adapted from CS, Section B.2.3.1, Table 2.3)

Study name	B-VEC-03 (NCT04491604) GEM-3: Phase 3 Efficacy and Safety Study of Beremagene Geperpavec (B-VEC, Previously KB103) for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)
Objectives	To determine whether topical administration of B-VEC in addition to standard of care improved wound closure as compared to placebo in children, adolescents, and adults with DEB.
Location	Three study centres in the United States
Design	Multicentre, double-blind, placebo-controlled, randomised, intra-patient, efficacy, and safety study (i.e., each patient served as their own control)
Eligibility criteria	Inclusion criteria: • Age ≥ 6 months with clinical diagnosis of DEB • Confirmation of DEB diagnosis (either dominant [DDEB] or recessive [RDEB]) by genetic testing including <i>COL7A1</i> • Two cutaneous wounds meeting the following criteria: – Location: similar in size, located in similar anatomical regions, and similar in appearance – Appearance: clean with adequate granulation tissue, excellent vascularisation, and did not appear infected • Use of reliable birth control throughout the duration of the study and for 3 months after the last dose of B-VEC, if of childbearing potential • Negative pregnancy test at Visit 1 (Week 1), if applicable • Willing to comply with study requirements; written informed consent from patient or legal representative Exclusion criteria: • Medical instability limiting ability to travel to the investigative centre • Diseases or conditions that could have interfered with the assessment of safety and efficacy of the study treatment and compliance of the subject

	with study visits/procedures, as determined by the investigator • Current evidence or a history of squamous cell carcinoma in the area that would undergo treatment • Actively receiving chemotherapy or immunotherapy at Visit 1 (Week 1) • Active drug or alcohol addiction as determined by the investigator • Hypersensitivity to local anaesthesia (lidocaine/prilocaine cream) • Participated in an interventional clinical trial within the past 3 months (not including B-VEC administration) • Receipt of a skin graft in the past 3 months • Pregnant or nursing
Method of randomisation	Using a pre-generated randomisation schedule, the matched primary wounds were randomised to receive either B-VEC or placebo gel. The randomisation schedule was generated using a block size of 6 for 7 sites with a maximum of 72 randomisations per site. The randomisations were not stratified. The randomisation schedule was generated by an independent statistician and validated by an independent statistical programmer.
Method of blinding	Trial participants (including their carers) and investigator as well as sub investigator conducting outcome-related assessments and procedures were blinded to the identity of treatment for the primary wounds. The unblinded staff, including the pharmacist or authorised designee, and the monitor remained separate from the primary study team and were not involved in any study conduct outside of their functions of managing the receipt, storage, preparation, dispensing, and reconciliation of all study products. No unblinding occurred during the study.¹⁸
Intervention(s) and comparator(s)	The wounds within each pair were randomly assigned in a 1:1 ratio to receive once-weekly application of either B-VEC or placebo for 26 weeks until wound closure. B-VEC (N=31): • Thawed cryopreserved drug product mixed with excipient gel (Methocel) • Topical dose ranging from 4×10^8 to 1.2×10^9 PFU depending on the baseline wound size Placebo (N=31): • Normal saline mixed with excipient gel, at a matched volume to B-VEC drug product Additional secondary wounds were selected for open-label B-VEC treatment.
Permitted and disallowed concomitant medication	• Topical administration of any medication (other than B-VEC and placebo) to a study target wound was prohibited throughout the study period up to Week 26 unless approved in advance by the medical monitor/sponsor. • Topical concomitant medications or treatments deemed necessary to provide adequate supportive care to nontarget wounds were permitted (and documented). Although prescription of tacrolimus, clobetasol, or becaplermin was permitted per protocol, none was applied during the study. • Women of childbearing potential using oral contraception must have consistently been taking their birth control for 3 months prior to Visit 1 (Week 1) and must have committed to continue using contraception throughout the study and for up to 3 months following the last dose of B-VEC.
Duration of follow-up, lost to follow-up information	Study period: August 2020 to April 2021 7-month follow-up (6-month double-blind period, 30-day safety follow-up) Treatment discontinuation: n=0 Study withdrawal: n=3 • One patient was lost to follow-up at Week 6 • One patient relocated at Week 12 • One patient withdrew at Week 24 because of travel constraints due to COVID-19

Primary outcomes (including scoring methods and timings of assessments)	Proportion of primary wounds with complete wound closure at 6 months (Week 22+24 or Week 24+26). - Only wounds that were healed for at least 2 consecutive weeks were counted as having had a response. - Complete wound closure was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin reepithelialisation without drainage, as determined by the investigator.
Other outcomes used in the economic model/specified in the final NICE scope	Key secondary endpoint: - Primary wounds with complete closure at 3 months (Week 8+10 or Week 10+12). Other secondary end points: - Change from baseline to Week 22, 24, and 26 in pain severity during changes in wound dressing. Assessed with the use of: - VAS (scores range from 0–10, with higher scores indicating greater pain) for patients aged ≥6 years - FLACC-R scale for patients aged <6 years. Exploratory endpoints: - Change from baseline to Week 26 in general HRQoL assessed using the EQ-5D-5L. - Change from baseline to Week 26 in skin-specific HRQoL assessed using the Skindex-29 questionnaire.
Preplanned subgroups	Subgroup analyses for the primary endpoint were prespecified on the basis of sex, age, and race.
B-VEC=beremagene geperpavec; DDEB=dominant dystrophic epidermolysis bullosa; DEB=dystrophic epidermolysis bullosa; COL7=type VII collagen; EQ-5D-5L=EuroQol 5-Dimension 5-Level questionnaire; FLACC-R=Face, Legs, Activity, Cry, and Consolability–Revised; HRQoL=health-related quality of life; HSV=herpes simplex virus; ITT=intent-to-treat; mITT=modified intent-to-treat; RDEB=recessive dystrophic epidermolysis bullosa; Skindex-29=29-Item Skindex instrument; VAS=visual analogue scale Source: Section B.2.3.1, Table 2.3 and GEM-3 CSR¹⁸	

3.2.2 Study design: GEM-1

GEM-1 is a phase I/II, randomised, single-centre, open-label, RCT initiated in May 2018 and conducted in a single centre in the USA. There were no UK centres or patients (NCT03536143).²⁶ Details of study location, treatments, trial inclusion and exclusion criteria for each phase of the GEM-1 study, permitted and prohibited concomitant medications and relevant outcomes are reported in Table 6. The primary and actual completion date was 1st November 2019 (NCT03536143).²⁶ Overall, 9 patients and 12 wound pairs (across phase I and II) satisfied all eligibility criteria and were randomised to receive either B-VEC or a control gel. GEM-1 comprised patients with a clinical diagnosis of RDEB, with a genetic mutation in the *COL7A1* gene confirmed by genetic testing, immunofluorescence, and immunoelectron microscopy. Eligible patients had to have two cutaneous wounds satisfying the criteria outlined in Table 7. Wounds were randomly assigned in a 1:1 (phase 1 and 2c) or 2:1 (phase 2a and 2b) ratio to be treated with B-VEC or placebo; therefore, each patient served as their own control.

Table 6: Summary of the trial design of GEM-1 (adapted from CS, Section B.2.3.1, Table 2.4)

Study name	KB103-001, NCT03536143 GEM-1: A Phase 1/2 Study of B-VEC, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)
Objectives	Phase 1: • To preliminarily assess the safety of topical B-VEC compared with placebo and to demonstrate evidence of molecular correction, that is, functional COL7 expression and anchoring fibrils, associated with B-VEC after treatment. • To preliminarily assess the effect of B-VEC on wound closure compared with placebo (wound surface area reduction, duration of wound closure). • To assess changes in laboratory values and the condition of the patients (HSV and COL7 antibodies, vital signs, physical examination). Phase 2: • To further assess the effect of B-VEC on wound closure compared with placebo (wound surface area reduction, duration of wound closure, time to wound closure). • To demonstrate evidence of molecular correction (functional COL7 expression) associated with B-VEC after treatment.
Location	One study centre in the United States
Design	Interventional, single centre, open-label, randomised, intra-patient, placebo-controlled study (i.e., each patient served as their own control)
Eligibility criteria	Inclusion criteria: • Age: – Phase 1: aged ≥ 18 years – Phase 2a: aged ≥ 5 years – Phase 2b: aged ≥ 2 years – Phase 2c: aged ≥ 2 years • Clinical diagnosis of RDEB confirmed by genetic testing, immunofluorescence, and immunoelectron microscopy • Confirmed RDEB <i>COL7A1</i> mutations • LH24 antibody negative (NC2-negative and NC1-positive). (This criterion is applicable to the first 2 adults on the study (phase 1). Subsequent patients could be NC1-positive or NC1-negative) • Wounds meeting the wound size/surface area entry criteria: – Phase 1: 2 wounds up to 10 cm²; 1 randomised to B-VEC and 1 randomised to placebo – Phase 2a and 2b: At least 3 wounds up to 20 cm²; 2 wounds randomised to B-VEC and 1 randomised to placebo – Phase 2c: At least 2 wounds up to 50 cm²; at least 1 randomised to B-VEC and 1 randomised to placebo • Willing to comply with study requirements; written informed consent from patient or legal representative Exclusion criteria: • Medical instability limiting ability to travel to the investigative centre • Presence of medical illness (e.g., HIV, hepatitis B, or hepatitis C) expected to complicate participation and/or compromise the safety of the technique • Serum antibodies to COL7 (patients with negative results within 12 months of screening are eligible) • Active infection in the area that will undergo administration • Evidence of systemic infection • Known allergy to any of the constituents of the product • Current evidence or a history of squamous cell carcinoma in the area that

	will undergo treatment • Active drug or alcohol addiction • Hypersensitivity to local anaesthesia (lidocaine/prilocaine cream) • Receipt of chemical or biological study product for the specific treatment of RDEB in the past 3 months • Specific wounds that have previously been administered investigational gene or cell therapy • Use of systemic antibiotics within 7 days • Positive pregnancy test or breast-feeding • Clinically significant abnormalities as determined by the investigator
Method of randomisation	A complete randomised-block design, with each patient designated as a block to receive all conditions, was used to assign treatment. Investigator-assigned wound numbers were randomised using a pre-generated randomisation schedule. Randomisation schemes were generated via a customised program prior to the study, and randomisation assignments for the treatment sites of each study patient were provided in sealed envelopes. Once the wound pairs were identified and labelled, the randomisation envelope was opened, and the assigned dose was then given.
Method of blinding	None. Open label. Wound images were assessed by the unblinded principal investigator and by two independent blinded physician-dermatologists with bullous disease expertise.^{19, 25, 26}
Intervention(s) and comparator(s)	GEM-1 enrolled N=12 patients (9 distinct patients enrolled in the study; 3 enrolled in both phase 2a and 2b). Wounds were randomly assigned in a 1:1 (phase 1 and 2c) or 2:1 (phase 2a and 2b) ratio to be treated with B-VEC or placebo. B-VEC (N=12): • Thawed cryopreserved drug product mixed with excipient gel (Velesco Lot [phases 1, 2b, and 2c] or PluroGel® [phase 2a]) • Topical doses: – Phase 1 (n=2 adults): 1×10^8 PFU at Days 0, 2, 28, and 30; additional dose on Day 42 for patient 2 – Phase 2a (n=2 adults and n=2 paediatric patients): 6×10^8 PFU initially administered on Days 1, 2, 3, 4, and 5 ▪ Patient 1 had additional administrations at Day 30, Day 44 (unscheduled), and Day 60 ▪ Patient 3 had an additional administration on Day 30 ▪ Patient 4 had an additional administration on Day 30 and Day 46 (unscheduled) – Phase 2b (n=3 adults and n=2 paediatric patients): 1×10^8 to 1.2×10^9 PFU per administration day dosed approximately every 2–3 days for 2 consecutive weeks and then at Days 30, 60, and 90 if wounds were open during study visits – Phase 2c (n=1 paediatric patient): 8×10^8 to 1.57×10^9 PFU per wound per administration. Wounds underwent 2 cycles of treatment: ▪ Cycle 1 was 25 days and consisted of 20 administrations ▪ Cycle 2 was 24 days and consisted of 21 administrations Placebo (N=12): Isotonic saline mixed with excipient gel
Permitted and disallowed concomitant medication	• Patients were encouraged to restrict topical administration of any therapy to the wounds under study for a minimum of 48 hours following administration of the investigational product. • Throughout the study, any concomitant medications or treatments deemed necessary to provide adequate supportive care could be prescribed, including medication for the intradermal injections and biopsies to treat pain and/or anxiety (e.g., lidocaine, lorazepam). • Patients continued routine skin care throughout the study.
Duration of follow-up, lost to follow-up information	Study period: May 2018 to November 2019 Up to 2-month intervention (depending on phase) followed by long-term

	follow-up period consisting of annual telephone contacts (up to 5 years) with the patient and their primary care physician, which began after each patient completed the interventional portion of the study. Treatment discontinuation: n=4 • 3 patients were discontinued from phase 2a by the sponsor so they could roll over to phase 2b. These patients are considered to have completed the study. • 1 patient completed their last dose on Day 61 and was discontinued by the sponsor due to not being able to participate further. This patient is considered to have completed the study. Study withdrawal: n=1 (due to inability to travel to study assessments)
Primary outcomes (including scoring methods and timings of assessments)	• Proportion of wounds with complete wound closure (was defined as at least 90% reduction in wound surface from baseline) at Weeks 8, 10, or 12. • Time to wound closure, defined as the time from the first treatment to complete wound closure (at least 90% reduction in wound surface from baseline). • Duration of wound closure, defined as the time from the complete closure ($\geq 90\%$ reduction in wound surface from baseline) to the first reopening of the same wound.
Other outcomes used in the economic model/specified in the final NICE scope	• Investigator global assessment (IGA) score (wounds were compared against baseline at Days 3, 5, 15, 30, 60, and 90) • Patient-reported outcome for pain (wounds were compared against baseline at Days 3, 5, 15, 30, 60, and 90)
Pre-planned subgroups	No subgroup analysis was planned or performed.
B-VEC=beremagene geperpavec; COL7=type VII collagen; DDEB=dominant dystrophic epidermolysis bullosa; DEB=dystrophic epidermolysis bullosa; HSV=herpes simplex virus; ITT=intent-to-treat; NC=noncollagenous; PFU=plaque-forming unit; RDEB=recessive dystrophic epidermolysis bullosa; Source: Gurevich <i>et al.</i> (2022)²⁵; GEM-1 CSR; Clinicaltrials.gov^{19, 26}	

Table 7: Summary of eligibility criteria and treatment randomisation for GEM-1 (reproduced from CS, Section B.2.3.3.3, Table 2.7)

Phase	Age	Antibody status		Wound size	Treatment randomisation (number of wounds)	
		NC1	NC2		B-VEC	Placebo
1	≥ 18 years	Positive	Negative	2 wounds up to 10 cm ²	1	1
2a	≥ 5 years	Positive or negative	Negative	At least 3 wounds up to 20 cm ²	2	1
2b	≥ 2 years	Positive or negative	Negative	At least 3 wounds up to 20 cm ²	2	1
2c	≥ 2 years	Positive or negative	Negative	At least 2 wounds up to 50 cm ²	≥ 1	≥ 1
B-VEC=beremagene geperpavec; NC=noncollagenous Source: Gurevich <i>et al.</i> (2022)²⁵; GEM-1 CSR; Clinicaltrials.gov^{19, 26}						

3.2.3 Study design: EASE

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).²⁰ 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, OLP.²⁰ In the DBP, patients were randomised (stratified by subtype) to receive either the BBE gel or a control gel; in the OLP, all patients received the BBE gel. The primary completion date was June 2020, with 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 (90-day DBP).²⁷ 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 phase (OLP).³⁵ Details of study location, treatments, trial inclusion and exclusion criteria, permitted and prohibited concomitant medications and relevant outcomes are reported in Table 8. Patients with DEB, JEB or Kindler epidermolysis bullosa (KEB) and a target partial-thickness wound lasting ≥ 21 days and < 9 months that was 10–50 cm², were enrolled.^{20, 27} Clinical advice to the EAG confirmed that there was no meaningful clinical difference between the ‘partial thickness’ wounds included in the EASE trial for the subgroup of patients with DEB and those target wounds in the GEM-3 and GEM-1 trials, which were not described in terms of ‘partial thickness.’ This is because all DEB wounds occur at or close to the dermal-epidermal junction (see Section 2.3.3). However, the EAG notes that the EASE criteria on wound duration indicates the inclusion only of chronic wounds (lasting ≥ 21 days) (CS, Section B.1.3.5, Table 1.3 and Eng *et al.*³³). The GEM-3 and GEM-1 trials did not apply eligibility criteria around wound duration.

Table 8: Summary of the trial design of EASE (adapted from CS, Section B.2.3.1, Table 2.5)

Study name	EASE (previously BEB-13; NCT03068780, EudraCT2016-002066-32)
Objectives	The objective of the EASE DBP was to compare the efficacy, safety and tolerability of BBE with a control gel in patients with DEB, JEB and KEB.
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.
Eligibility criteria	• Male and female patients with DEB, JEB, or KEB • ≥ 4 years of age (reduced to > 21 days following an IDMC safety review in 2019) • EB target wound 10–50 cm² in size aged ≥ 21 days and < 9 months outside of the anogenital region
Method of randomisation	Participants were randomised 1:1 to receive either BBE gel or control gel. Randomisation was conducted according to blinded patient number, and the randomisation key was held solely by an independent statistician.

Study name	EASE (previously BEB-13; NCT03068780, EudraCT2016-002066-32)
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.^{20, 27, 35}
Intervention(s) and comparator(s)	BBE gel (n=109 randomised and received treatment) • 100g of BBE gel consists of 10g active pharmaceutical ingredient BBE 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 end of the DBP. 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 end of the DBP.
Permitted and disallowed concomitant medication	Medications/ therapies were permitted during both the DBP and OLP of the trial, including liquid antiseptics at each dressing change, bathing, 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	The duration of the DB phase was 90 days. Of the 223 randomised participants, 199 (89.2%) completed the DBP (91.7%,

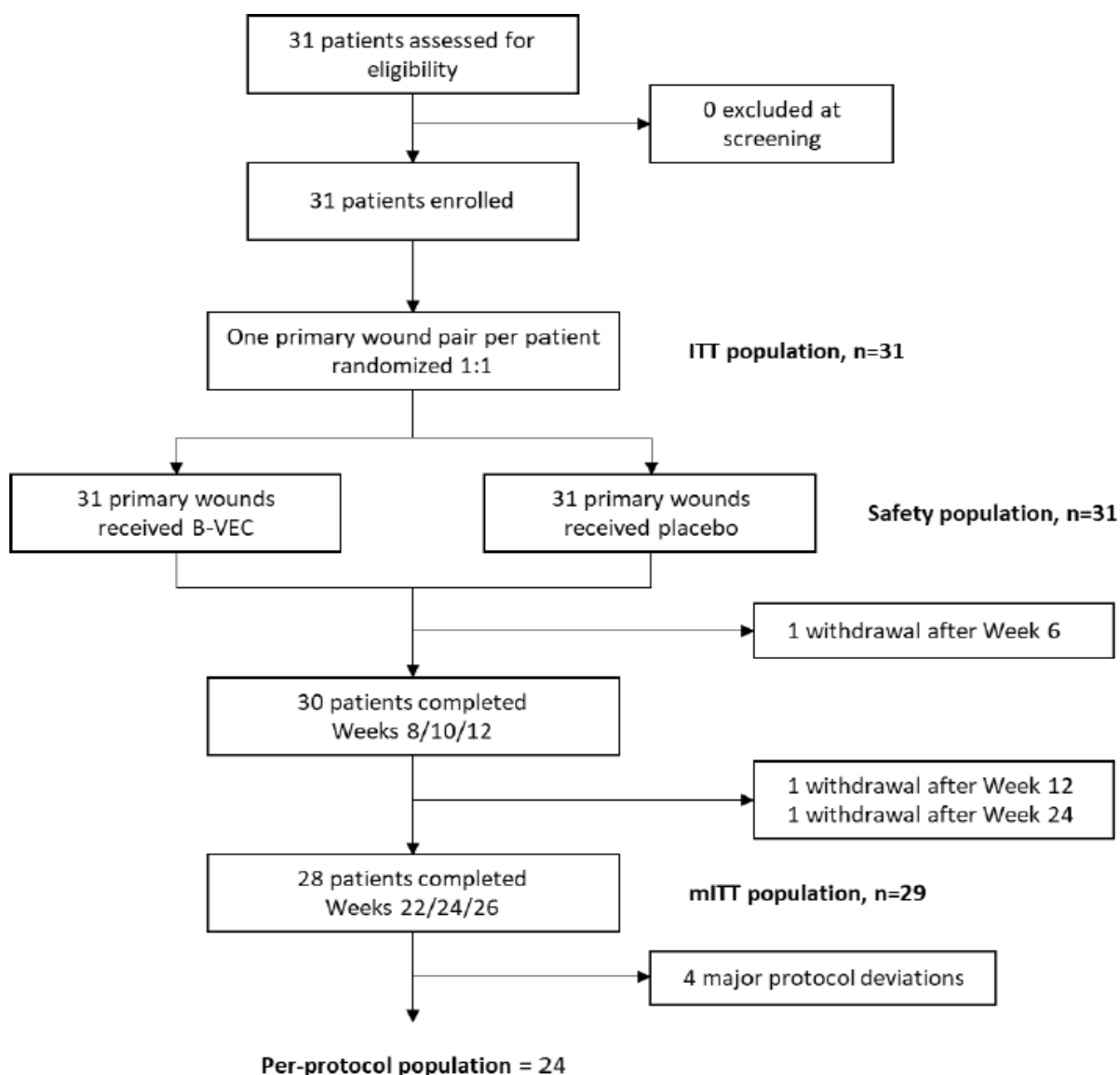
Study name	EASE (previously BEB-13; NCT03068780, EudraCT2016-002066-32)
	BBE gel vs. 86.8%, control gel), and 24 (10.8%) discontinued (8.3%, BBE gel vs. 13.2%, control gel).
Primary outcomes (including scoring methods and timings of assessments)	Primary outcome: Proportion of patients with first complete target wound closure within 45 days based on INV assessment
Other outcomes used in the economic model/specified in the final NICE scope	Key secondary (confirmatory) efficacy endpoints: • 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)
Pre-planned subgroups	Participants 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 10 to < 20; • JEB/ KEB 20 to < 30; • JEB/ KEB 30 to 50.
AE=adverse event; BBE=birch bark extract; CFB=change from baseline; DB=double-blind; DDEB=dominant dystrophic epidermolysis bullosa; DEB=dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; EBDASI=Epidermolysis Bullosa Disease Activity and Scarring Index; INV =investigator; JEB=junctional epidermolysis bullosa; KEB=kindler epidermolysis bullosa; OLP=open label phase Source: Kern <i>et al.</i> (2019, 2022, 2023) ^{20, 27, 36} ; NICE (2023) ¹⁰	

Participant flow and analysis populations

3.2.4 GEM-3

In GEM-3, overall, 31 paediatric and adult patients with DEB were enrolled, and all 31 patients satisfied the eligibility criteria and had appropriate target wounds randomised (Figure 2). Three patients withdrew from the trial. One patient was lost to follow-up at Week 6; one patient relocated at Week 12; and one patient withdrew at Week 24 because of travel constraints due to COVID-19. Four patients had major protocol deviations. Full details of these deviations are not provided in the CS, but the CSR (section 10.2) reports that these deviations were “*most often visits that occurred outside of the specified visit window*”.¹⁸

Figure 2: Overview of trial design and participant of GEM-3 (reproduced from CS, Section B.2.3.2.2, Figure 2.1)

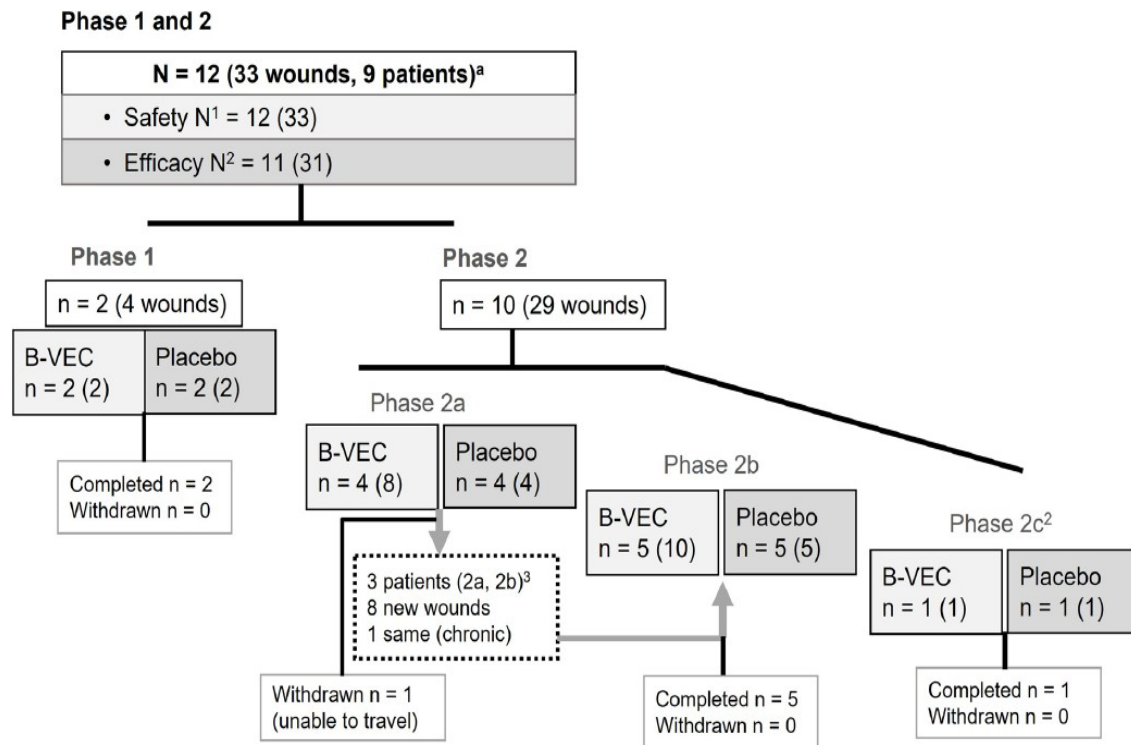


B-VEC=B-VEC=beremagene geperpavec; ITT=intent-to-treat; mITT=modified intent-to-treat. Source: CS, Figure 2.1

3.2.5 GEM-1

In GEM-1, overall, nine paediatric and adult patients with RDEB were enrolled, and all nine patients satisfied the eligibility criteria and had appropriate target wounds randomised (Figure 3). Three patients were discontinued from phase 2a by the sponsor so they could roll over to phase 2b. These patients are considered to have completed the study. One patient in phase 2a completed their last dose on Day 61 and was discontinued by the sponsor due to not being able to participate further. This patient is considered to have completed the study. One patient withdrew from phase 2a due to inability to travel to study assessments. The CSR (section 10.2) notes a single patient with a protocol deviation “*due to the lack of wound pairing based on the baseline wound measurement*”.¹⁹

Figure 3: Overview of trial design and participant flow of GEM-1 (reproduced from CS, Section B.2.3.3.2, Figure 2.2)



^aThree patients were enrolled into both Phase 2a and Phase 2b. These patients' Phase 2b wounds were treatment-naïve except for a chronic (5-year) dorsal foot wound on patient 3. A wash-out period of 3 months passed between treatments in phase 2a and 2b. Patients were enrolled in phase 2a as Pts 3, 5, and 6, and in phase 2b as Pts 11, 8, and 7, respectively.

¹Phase 1, 2a, 2b, 2c; all interventions all wounds.

²Phase 1, 2a, 2b; randomised wounds (Patient 12, 2c considered separately for efficacy).

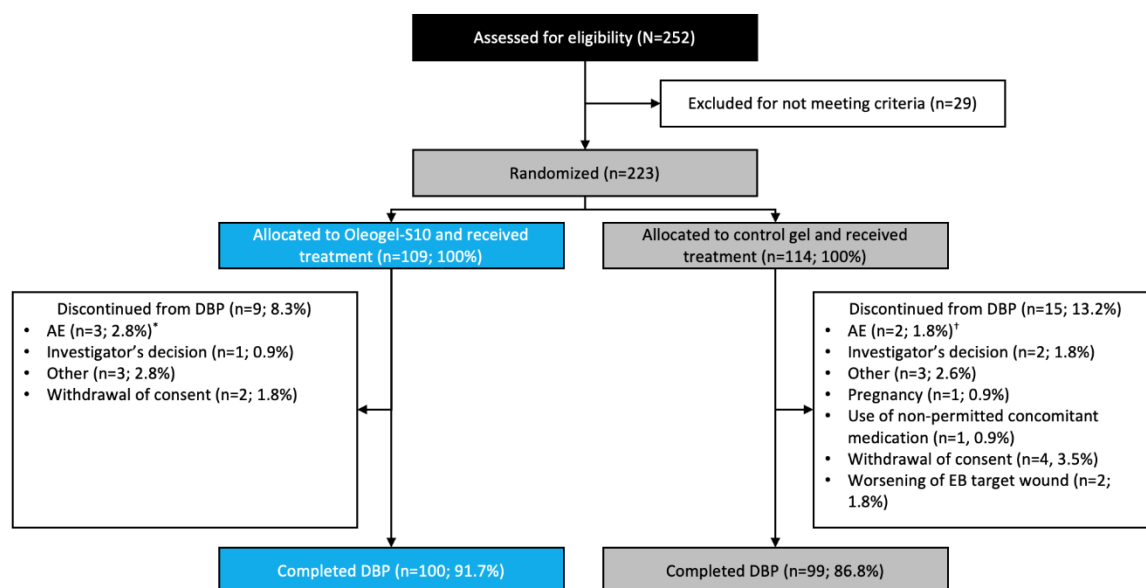
³Patients were enrolled in phase 2a as patients 3, 5, and 6 and in phase 2b as Pts 11, 8, and 7, respectively. B-VEC=beremagene geperpavec.

Source: Gurevich *et al.* (2022)²⁵

3.2.6 EASE

In EASE, 223 paediatric and adult patients with EB were randomised either to BBE gel (referred to as Oleogel-S10 in some of the figures below) (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: 8.3%; control gel: 13.2%) (Figure 4). 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.

Figure 4: Overview of trial design of EASE (reproduced Kern 2022, Figure S3²⁷)



*1 patient with procedural pain, 1 patient with squamous cell carcinoma, 1 patient with wound haemorrhage

†1 patient with allergic rash, 1 patient with increase in wound size compared to baseline

AE, adverse event; DBP, double-blind phase; EB, epidermolysis bullosa

BE=birch bark extract; DEB=dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; JEB=junctional epidermolysis bullosa; KS=Kindler syndrome; SoC=standard of care

Note: BBE is referred to as Oleogel-S10 in this figure Source: Kern *et al.* (2022)²⁷

3.3 Baseline characteristics

3.3.1 GEM-3

Demographic and baseline characteristics of patients enrolled in GEM-3 are presented in Table 9. For each patient, the site investigator selected two wounds of similar size, anatomical region, and appearance (see Table 5). One wound was randomised to receive B-VEC, while the other received placebo. Therefore, each patient served as their own control. The EAG notes that all but one of the participants had RDEB, the median age was 16.1 years (range 1-44 years) which was consistent with the inclusion criteria of patients being aged ≥ 6 months old; and the median wound size is relatively small (74% of wounds were $<20\text{cm}^2$ in the B-VEC arm) and was similar between the B-VEC-exposed (10.6cm^2) and placebo-exposed wounds (10.4cm^2). Given the intra-patient randomisation design, the target wounds were balanced across potentially relevant prognostic factors such as age.

Clinical advice to the EAG confirmed that the characteristics of the trial participants in GEM-3 were largely similar to the population in clinical practice in England and Wales. The EAG notes that details of wound duration were not reported, although this is a potential prognostic factor: the older the wound, the less likely the wound will achieve the primary outcome and completely heal.³⁴

The company confirmed, in response to an EAG question, that data on age of target wound were not collected for GEM-3 (Clarification response, A11).³¹

Table 9: GEM-3: Demographic and baseline characteristics (ITT population) (reproduced from CS, Section B.2.3.2.3, Table 2.6)

Characteristic	Total patients (N=31)*
Age	
Median (range), years	16.1 (1–44)
≤12 years, n (%)	10 (32)
>12 to ≤18 years, n (%)	9 (29)
>18 years, n (%)	12 (39)
Sex, n (%)	
Female	11 (35)
Male	20 (65)
Race or ethnic group other than Hispanic or Latino, n (%) [†]	
White	20 (65)
Black	0
Asian	6 (19)
American Indian or Alaska Native	5 (16)
Native Hawaiian or another Pacific Islander	0
Hispanic or Latino ethnic group, n (%) [†]	16 (52)
Genotype	
Dominant dystrophic epidermolysis bullosa	1 (3)
Recessive dystrophic epidermolysis bullosa	30 (97)
Area of primary wound exposed to B-VEC	
Median (range), cm ²	10.6 (2.3–57.3)
<20 cm ² , n (%)	23 (74)
20 to <40 cm ² , n (%)	6 (19)
40 to 60 cm ² , n (%)	2 (6)
Area of primary wound exposed to placebo	
Median (range), cm ²	10.4 (2.3–51.5)
<20 cm ² , n (%)	22 (71)
20 to <40 cm ² , n (%)	8 (26)
40 to 60 cm ² , n (%)	1 (3)
*Percentages may not total 100% due to rounding. [†] Race and ethnic groups were reported by the patient, parent, or guardian. B-VEC=beremagene geperpavec; ITT=intention-to-treat Source: Guide <i>et al.</i> (2022) ²²	

3.3.2 GEM-1

Demographic and baseline characteristics for patients enrolled in GEM-1 are presented in Table 10. The EAG notes that all participants had RDEB, the median age was 19.5 and 21.0 years (range 10–35 years) for the safety and ITT populations respectively (slightly older than the GEM-3 and EASE trials), and that the median wound size and wound duration was not reported – both of which are potential prognostic factors.^{33, 34}

Table 10: GEM-1: Demographic and baseline characteristics (ITT population) (reproduced from CS, Section B.2.3.3.3, Table 2.8)

Characteristic	Safety (N=12)	ITT (n=11)
Age		
Mean (SD), years	20.3 (8.05)	21.3 (7.72)
Median (range), years	19.5 (10–35)	21.0 (13–35)
Sex, n (%)		
Female	3 (25.0)	3 (27.3)
Male	9 (75.0)	8 (72.7)
Race or ethnic group, n (%)		
Not Hispanic or Latino	9 (75.0)	8 (72.7)
Hispanic or Latino	3 (25.0)	3 (27.3)
Female of childbearing potential, n (%)	3 (25.0)	3 (27.3)
B-VEC=beremagene geperpavec; ITT=intent-to-treat; SD=standard deviation Source: GEM-1 CSR ²⁶		

3.3.3 EASE

Demographic and baseline characteristics for patients enrolled in the DBP of the EASE RCT were not presented in the CS but are reported in Table 11.²⁷ The characteristics of the EASE participants were similar to the GEM-3 participants in terms of sex and race. However, the EAG notes the following differences. The EASE trial recruited <7% of participants from the USA compared with 100% in GEM-3. The EASE trial randomisation process was stratified by subtype and wound size. 195/223 (87.4%) of EASE participants had DEB (78.5% RDEB, although this was 83.5% in the BBE group) compared with 100% (RDEB 97.5%) in GEM-3; the median age in EASE was 12.0 years (range 6 months to 81 years) (median: 16.1 years in GEM-3) - this age range is consistent with the final NICE scope of ≥ 6 months of age - and median wound size (15.6 cm²) was larger than the GEM-3 trial (10.4 cm²-10.6 cm²).

Unlike the GEM-3 and GEM-1 trials, wound duration was reported for EASE: the median duration of target wounds was 35.5 days (39.0 days in the BBE group), suggesting that these were chronic rather than recurrent wounds (CS, Section B.1.3.5, Table 1.3 and Eng *et al.*³³). Clinical advice to the EAG confirmed that the characteristics of the trial participants in EASE were also largely similar to the population in clinical practice in England and Wales.¹⁰

Table 11: Characteristics of participants in EASE across treatment groups at DBP baseline^{10, 27}

		EASE DBP		
		Filsuvez gel (n= 109)	Control gel (n=114)	All subjects (N=223)
Demographics				
Age, years	Mean (SD)	16.8 (13.89)	16.5 (14.57)	16.7 (14.21)
	Median (range)	13.0 (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)
	4 to <12 years	42 (38.5)	43 (37.7)	85 (38.1)
	12 to <18 years	25 (22.9)	29 (25.4)	54 (24.2)
	≥18 years	35 (32.1)	32 (28.1)	67 (30.0)
Gender, n (%)	Male	68 (62.4)	66 (57.9)	134 (60.1)
	Female	41 (37.6)	48 (42.1)	89 (39.9)
Geographic region, n (%)	Europe	48 (44.0)	55 (48.2)	103 (46.2)
	South America	33 (30.3)	35 (30.7)	68 (30.5)
	Rest of world	21 (19.3)	17 (14.9)	38 (17.0)
	United States	7 (6.4)	7 (6.1)	14 (6.3)
Race, n (%)	White	95 (87.2)	91 (79.8)	186 (83.4)
	Black or Af/Am	1 (0.9)	2 (1.8)	3 (1.3)
	Asian	4 (3.7)	7 (6.1)	11 (4.9)
	Am/Ind or Ala/nat	0	1 (0.9)	1 (0.4)
	Unknown	1 (0.9)	1 (0.9)	2 (0.9)
	N/A^b	4 (3.7)	8 (7.0)	12 (5.4)
	Other^c	4 (3.7)	4 (3.5)	8 (3.6)
BMI (kg/m²)	Mean (SD)	16.05 (4.979)	16.31 (5.037)	16.18 (4.999)
EB subtype, n (%)	RDEB	91 (83.5)	84 (73.7)	175 (78.5)
	DDEB	6 (5.5)	14 (12.3)	20 (9.0)
	JEB	11 (10.1)	15 (13.2)	26 (11.7)
	EBS	1 (0.9)	1 (0.9)	2 (0.9)
	Kindler	0	0	0
Wound characteristics				
Age of target wound/ days	Mean (SD)	124.3 (327.44)	126.4 (459.99)	125.4 (399.54)

		EASE DBP		
		Filsuvez gel (n= 109)	Control gel (n=114)	All subjects (N=223)
	Median (range)	39.0 (21- 2920)	32.0 (21- 4745)	35.5 (21- 4745)
Size of target wound/ cm ²	Mean (SD)	18.99 (8.640)	19.41 (10.104)	19.20 (9.398)
	Median (range)	16.00 (10.0- 45.6)	15.45 (10.0- 49.5)	15.60 (10.0-49.5)
Abbreviations: Af/AM=African American; Am/Ind, American or American Indian; Ala/nat=Alaska Native; BMI=body mass index; BSAP, body surface area percentage; cm ² , 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/m ² , 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				

Study endpoints and statistical analysis sets

3.3.4 GEM-3

Primary and secondary endpoints for GEM-3 are summarised in Table 5 and briefly below. Complete closure was defined as 100% healing of the exact wound area selected at baseline, specified as skin re-epithelialization without drainage. (CSR section 8.3.1).¹⁸ The GEM-3 trial also stated that only wounds that were healed for at least two consecutive weeks were counted as having had a response (CSR, section 8.3.1).¹⁸ Wound assessments were performed by an investigator blinded to treatment. A trained, qualified designated individual only performed the wound assessments if the investigator was unavailable. A Canfield tracing and imaging system was used (CSR section 9.6.1.1).¹⁸ Primary wounds were assessed by the investigator for closure at Weeks 8, 10, 12, 22, 24, and 26, corresponding to timing of the primary and key secondary efficacy endpoints (CSR section 9.6.1.2).¹⁸ The EAG accepts that no validated measure for the outcome of ‘complete wound closure’ currently exists, and that the majority of the outcome measures are accepted measures.

- Primary endpoint: Proportion of primary wounds with complete wound closure at 6 months (Week 22+24 or Week 24+26). The plus sign means that the wound was found closed in two consecutive visits at the designated weeks.
- Key secondary endpoint: Primary wounds with complete closure at 3 months (Week 8+10 or Week 10+12). In response to a question from the EAG, the company clarified that all primary wounds were assessed by the blinded investigator at all time points, i.e., Weeks 8, 10, 12, 22,

24, and 26, corresponding to timing of the primary and key secondary efficacy endpoint definitions (Clarification response, A22).³¹

- Other secondary end points: Change from baseline to Week 22, 24, and 26 in pain severity during changes in wound dressing was assessed using a visual analogue scale (VAS; scores ranging from 0–10, with higher scores indicating most severe pain).¹⁸ The FLACC-R scale³⁷ for patients aged <6 years was used for young children who cannot accurately report their pain because they are too young or unable to understand what is being asked of them.¹⁸ Children aged <6 years were evaluated for each primary wound dressing change and received a score of 0, 1, or 2 in each category based on their behaviour during the dressing removal. A total score was to determine the overall pain and discomfort the subject was experiencing. The child's carer completed the scale at scheduled visits. It was important that the same carer completed the assessment at all visits, whenever feasible, to reduce inter-evaluator variability. FLACC-R was used throughout the study even if the age of the child changed. Both VAS and FLACC-R are generic instruments that can be used across different health conditions.
- HRQoL: This exploratory endpoint was measured using EuroQol 5-Dimension 5-Level questionnaire (EQ-5D-5L; generic HRQoL) and the 29-Item Skindex instrument (Skindex-29; HRQoL in dermatology) in patients aged ≥12 years at consent. Skindex-29 is a HRQoL measure composed of three domains (i.e., symptoms, functioning, and emotions) designed to be used across different skin conditions. Both EQ-5D-5L and Skindex-29 were administered at baseline and at Week 26.
- Immunology: Immunologic evaluation included testing for antibodies against HSV-1 and COL7.
- Safety: Assessments included monitoring of AEs that emerged or worsened after the first application of B-VEC or placebo, physical examination, vital signs, and clinical laboratory tests. The severity of AEs was reported and graded by the investigator.

The EAG notes that the following outcomes in the final NICE Scope were not recorded for the GEM-3 trial: time to wound closure; duration of wound closure; severity of wound infections; itching; total wound burden.

Statistical analyses used to evaluate outcomes in GEM-3 are summarised in Table 12. The CS notes that no interim analyses were planned or performed.

Table 12: Analysis of primary and secondary endpoints in GEM-3 (reproduced from CS, B.2.4.1.3, Table 2.9)

Endpoint	Statistical method	Analysis population
Primary endpoint		
Proportion of primary wounds with complete wound closure at 6 months (Weeks 22+24 or Weeks 24+26)	Exact McNemar test (two-sided type I error rate of 0.05) A multiple imputation approach assuming MAR was used to impute missing endpoint data	ITT* Sensitivity analyses: PP, mITT, ITT with observed data (no imputation) ^{†,‡}
Secondary endpoints		
Proportion of primary wounds with complete closure at 3 months (Weeks 8+10 or Weeks 10+12).	Exact McNemar test (two-sided type I error rate of 0.05, if the primary endpoint was statistically significant) A multiple imputation approach assuming MAR was used to impute missing endpoint data	ITT* Sensitivity analyses: PP, mITT, ITT with observed data (no imputation) ^{†,‡}
Change from BL to Weeks 22, 24, and 26 in pain severity during changes in wound dressing:	ANCOVA with treatment as the fixed effect and baseline value as the covariate	ITT* Sensitivity analyses: PP, mITT ^{†,‡}
VAS (patients aged ≥6 years)		
FLACC-R (patients <6 years)		
Change from BL to Week 26 in generic HRQoL (EQ-5D-5L)	No statistical analysis or data imputation	ITT (observed data)*
Change from BL to Week 26 in skin-specific HRQoL (Skindex-29)	No statistical analysis or data imputation	ITT (observed data)*
*ITT population comprised patients whose primary wounds were randomised regardless of whether they received randomised treatment or not. [†]mITT population comprised patients whose primary wounds were randomised and received B-VEC or placebo treatment with at least one postbaseline primary endpoint assessment. [‡]PP population comprised all safety population patients (i.e., patients who were administered either B-VEC or placebo) who completed the study without any major protocol deviations. ANCOVA=analysis of covariance; BL=baseline; B-VEC=beremagene geperpavec; EQ-5D-5L=EuroQol 5-Dimension 5-Level questionnaire; FLACC-R=Face, Legs, Activity, Cry, and Consolability-Revised; HRQoL=health-related quality of life; ITT=intent-to-treat; mITT=modified intent-to-treat; MAR=missing at random; PP=per protocol; VAS=visual analogue scale Source: Guide <i>et al.</i> (2022)²²; GEM-3 CSR¹⁸		

3.3.5 GEM-1

Primary and secondary endpoints for GEM-1 are summarised in Table 6. The primary endpoint was ‘complete wound closure’ defined as ≥95% reduction in wound surface from baseline (Table 6). The EAG notes that this threshold is higher than the ≥90% reported in Table 3 and in the CSR and trial protocol.^{19, 26} The company clarified these different thresholds in response to a question by the EAG: the authors of the full paper²⁵ applied a ‘more stringent definition’ to explore whether the threshold affected the outcome; the company concluded that it did not (Clarification response, A27).³¹ Closure was assessed by imaging of the wounds during clinical visits by the investigator or assigned designee and at home by the patient or caregiver during bandage changes using a wound monitoring application. The investigator-assessed wound surface area in all of the images for 100%, 90%, 75% and 50% closure

at the end of the study (CSR, Section 9.7.2.1.1).¹⁹ Statistical analyses used to evaluate outcomes in GEM-1 are summarised in Table 13. The CS notes that no interim analyses were planned or performed.

Table 13: Analysis of primary and secondary endpoints in GEM-1 (modified from CS, Section B.2.4.2.3, Table 2.10)

Primary endpoints	Statistical method	Analysis population
Proportion of wounds with complete wound closure, defined as $\geq 95\%$ reduction in wound surface from baseline Stratified by timepoints (Weeks 8, 10, or 12)	CMH (stratified by timepoint) Breslow-Day (independence of weekly evaluations) Missing data were replaced by the last recorded observed value	ITT* Sensitivity analyses: PP [†]
*ITT population comprised patients whose primary wounds were randomised regardless of whether they received randomised treatment or not. †PP population comprised all safety population patients (i.e., patients who were administered either B-VEC or placebo) who completed the study without any major protocol deviations.		

The CS states that safety assessments were conducted “*with a single systemic patient response as the independent outcome.*” The EAG interprets this to mean that safety outcomes were not reported separately for B-VEC and placebo treated wounds, but were instead reported for each patient included in the safety analysis. AEs and concomitant medications were assessed at each visit. Blood and urine were assessed for B-VEC DNA using a validated quantitative polymerase chain reaction assay, and blood was assayed for COL7 and HSV-1 antibodies (CS, Section B.2.3.3.6).

3.3.6 EASE

Primary and secondary endpoints for EASE are summarised in Table 8. The primary outcome in the DBP was the proportion of patients with first complete closure of the target wound closure within 45 days (± 7 days) based on blinded investigator assessment. Complete closure was defined as skin re-epithelialization without drainage of the target wound area selected at baseline.²⁷ For the assessment of wound closure and re-epithelialisation, the investigators photographed the EB target wound and all other wounds that match target wound criteria with the ARANZ Silhouette[®] system. A 3D model of the wound based on photographic data, derives measurements of the model, and records standardised notes. Patients were assessed during specific visit days, which included Days 0, 7 (± 2), 14 (± 5), 30 (± 7), 45 (± 7), 60 (± 7), 90 (± 7 ; end of double-blind period [DBP]).³⁸ The EAG notes that this definition of complete closure is less rigorous than used in the GEM-3 trial (which required closure to persist for a minimum of two weeks).

The EAG also notes that an additional assessment was undertaken as an endpoint in EASE: the confirmation of complete closure (CCC). The CCC was based on the clinical assessment of first wound closure by the investigator being confirmed by a second observation after 7 days (+ 2 days) at the CCC visit.²⁷ These data might be considered more similar to the GEM-3 definition of complete closure. However, the trial publication reported that these data were not presented because the number of patients who completed this additional assessment was low and was not balanced across both groups (30 of 45 patients treated with BBE, 13 of 33 patients treated with control gel).²⁷

Secondary endpoints included time to first wound closure up to 90±7 days of treatment; incidence of wound infection; maximum severity of wound infection; change from baseline in a) total body wound burden (EBDASI, Section I: Skin, Activity (not Damage), only); and b) itching (Itch Man Scale/ Leuven Itch Scale), as well safety outcomes.²⁷

3.4 Quality Assessment

3.4.1 GEM-3

The CS reported risk of bias assessments in Section B.2.5 (Tables 2.12, 2.13 and 2.14). The appraisal of the quality of relevant clinical trials was conducted using a checklist adapted from the CRD Guidance for Undertaking Reviews in Health Care in accordance with NICE guidance (Clarification response, A15).³¹ This is an acceptable tool for risk of bias assessment. The assessments are based on information in the CSRs, protocols and full publications.

The CS and EAG judgements for the GEM-3, GEM-1 and EASE trials are presented in Table 14, Table 15 and Table 16.

For GEM-3, the EAG agreed with the company's judgements on the appropriateness of the randomisation process, the adequacy of blinding of participants and outcome assessors (although assessment of the primary outcome was by a single blinded assessor, Clarification response A12),³¹ the adequacy of allocation concealment and absence of unexpected imbalances in drop-outs between arms (given the intra-patient trial design), the absence of selective reporting and the application of an appropriate ITT analysis. On account of the intra-patient design, the groups were similar at the outset in terms of prognostic factors such as age and EB subtype and wounds were matched based on size, anatomical region and appearance.¹⁸

However, the EAG questioned the company's judgement that the intra-patient design of the trial rendered an assessment of prognostic factors across groups to be 'Not applicable'. For example, wound duration represents a potential prognostic factor as the older the wound, the less likely the

wound will achieve the primary outcome and completely heal.^{33, 34} This was not controlled for, but could differ between randomised wounds within this study design. The EAG requested clarification of some of the judgements reported in the CS. The company confirmed that intra-patient design did not render concealment of allocation redundant, due to the blinding of assessors, and amended its original judgement (Clarification response, A13).³¹ However, the potential issue of wound duration as a prognostic factor was not addressed (two wounds might be the same size, appearance and anatomical region, but of different age), except to confirm that these data were not collected for GEM-3 (Clarification response, A11 & A16).³¹ The EAG therefore disagreed with the company's assessment that any judgement on groups' similarity at baseline in terms of prognostic factors was 'Not Applicable' (on account of the intra-patient design) and assessed this item as Unclear. The overall risk of bias was therefore assessed by the EAG to be low to moderate.

Table 14: Quality assessment results for GEM-3 (modified from CS, Section B.2.5, Table 2.12)

Trial	CS	EAG
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	*Yes Wound level: the patients, investigators, site staff, and the sponsor were blinded to allocation of treatment to each wound	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	NA – Intra-patient design. Primary wounds were similar in size between those exposed to B-VEC and those exposed to placebo.	Unclear – Intra-patient design, but while primary wounds were similar in size between those exposed to B-VEC and those exposed to placebo, the possible prognostic factor of wound duration ^{33, 34} was not recorded
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes All the patients, investigators, site staff, and the sponsor remained blinded to trial-group assignments, except for designated personnel, including the pharmacist who handled unblinded B-VEC or placebo	Yes
Were there any unexpected imbalances in dropouts between groups?	NA – Intra-patient design	NA – Intra-patient design
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No

Trial	CS	EAG
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
B-VEC=beremagene geperpavec; NA=not applicable *Revision based on Clarification response, A13. ³¹		

3.4.2 GEM-1

For GEM-1, the EAG agreed with the company's judgements on: the appropriateness of the randomisation and process; the absence of unexpected imbalances in dropouts between treatment groups (given the intra-patient trial design); the absence of selective reporting; and the application of an appropriate ITT analysis. On account of the intra-patient design, the groups were similar at the outset in terms of prognostic factors such as age and EB subtype. However, the EAG questioned the company's judgement that the intra-patient design of the trial rendered an assessment of prognostic factors across groups to be 'Not applicable'. For example, wound duration represents a potential prognostic factor that was not controlled for, but which could differ between randomised wounds within this study design.^{33, 34} The company also acknowledged that the prognostic factor of wound size potentially varied between treatment groups (CS, Section B.2.5, Table 2.13). The EAG therefore recorded 'No' for whether treatment groups were similar for prognostic factors at baseline. The EAG also questioned the judgement in the CS that participants and outcome assessors were blinded to treatment allocation. GEM-1 was an open-label trial, and some endpoints included wound assessment by an unblinded investigator and patient-reported outcomes, such as pain (see Table 3). The EAG therefore recorded 'Unclear' for blinding. Allocation concealment was also confirmed as 'Unclear' following an EAG question to the company (Clarification response, A13).³¹ The EAG therefore assessed the overall risk of bias of GEM-1 to be high.

Table 15: Quality assessment results for GEM-1 (modified from CS, Section B.2.5, Table 2.13)

Trial	CS	EAG
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	*Unclear Wound level: while participants and carers were not blinded to treatment allocation (open label), clinicians assessing wound images were blinded.	Unclear
Were the groups similar at the outset of the study in terms of prognostic factors?	NA – Intra-patient design, but there was variability in wound size observed across the small participant sample.	No – Intra-patient design, but there was variability in wound size observed across the small participant sample, and wound durations was not recorded.
Were the care providers, participants and outcome assessors blind to treatment allocation?	*Yes/unclear Participants and direct care providers were not blinded, B-VEC and placebo were applied open-label. However, wound images were assessed by two independent blinded physician-dermatologists with bullous disease expertise to evaluate wound closure therefore impact on wound closure outcomes is likely to be small.	Unclear Unblinded investigator also made assessments, plus some where outcomes were patient-reported (patients were not blinded)
Were there any unexpected imbalances in dropouts between groups?	NA – Intra-patient design	NA – Intra-patient design
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
NA=not applicable *Revision based on Clarification response, A13. ³¹		

3.4.3 EASE

The company and EAG quality assessments for the EASE trial (DBP) are presented in Table 16. For EASE, the EAG agreed with the company's judgements on: the appropriateness of the randomisation and allocation concealment processes; the blinding of caregivers, patients and outcome assessors; the absence of unexpected imbalances in drop-outs between treatment groups; the absence of selective reporting; and the application of an appropriate ITT analysis. On the whole, the groups were similar at the outset in terms of prognostic factors such as age, EB subtype and

wound size, although the EAG noted that the median wound duration was slightly longer in the BBE group than the placebo group (39.0 days compared with 32.0 days respectively), which might favour placebo. Overall, the company and the EAG assessed the EASE trial to be at low risk of bias according to this tool.

Table 16: Quality assessment results for EASE (modified from CS, Section B.2.5, Table 2.14)

Trial	CS	EAG
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in dropouts between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

3.5 Clinical effectiveness

3.5.1 GEM-3

Complete wound closure at 6 months and 3 months

The primary efficacy endpoint was percentage of wounds with complete closure at 6 months. The definition of complete wound closure used in GEM-3 required that wounds be completely healed (100% wound closure from the exact wound area selected at baseline, specified as skin reepithelialisation without drainage, as determined by the investigator) for at least two consecutive weeks. Of the 31 wound pairs in the ITT population, 67% of wounds treated with B-VEC and 22% of wounds treated with placebo were completely healed at 6 months, a statistically significant difference of 46% (95% CI 24, 68; $p=0.002$; Table 17). The key secondary endpoint was percentage of wounds with complete closure at 3 months. The EAG notes that 20% of wounds in the GEM-3 trial placebo group achieved complete closure, which might indicate the presence of so-called ‘recurrent’ wounds, a large proportion of which might be expected to close within 21 days (CS,

Section B.1.3.5 and Table 1.3 and Eng *et al.*³³). The potential proportion of such wounds in each group is unclear and might not be balanced across groups.

Table 17: GEM-3: Primary and key secondary endpoint analyses (imputed data) (modified from CS, Section B.2.6.1, Table 2.15)

Endpoint	B-VEC (n=31)	Placebo (n=31)	Absolute difference, % (95% CI)	p value
Primary endpoint: complete wound closure at 6 months,* n (%)	20.9 (67)	6.7 (22)	46 (24–68)	0.002
Key secondary endpoint: complete wound closure at 3 months,† n (%)	21.9 (71)	6.1 (20)	51 (29–73)	<0.001

Complete wound closure was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin reepithelialisation without drainage, as determined by the investigator. The primary and key secondary endpoints were analysed in the ITT population. Multiple imputation methods were used to account for missing data. Fractional counts are due to the multiple imputation procedure (MAR) used for analysis. In the first stage of multiple imputation, imputations for missing data are generated based on statistical characteristics of the data and this procedure is repeated many times, resulting in data sets with replaced missing information. In the second stage, any analysis of the imputed data sets can be conducted within each of the imputed data sets as if there were no missing data. After the statistical analysis is run separately on each imputed data set, the estimates of interest from all the imputed datasets are combined into a single estimate using standard combining rules. Hypothesis testing was performed with the use of an exact McNemar test.

*Primary wounds were assessed at Weeks 22+24 or Weeks 24+26.

†Primary wounds were assessed at Weeks 8+10 or Weeks 10+12. B-VEC=beremagene geperpavec; CI=confidence interval; ITT=intent-to-treat; MAR=missing at random

Source: Guide *et al.* (2022)²²

The 6-month data reported in Table 17 (modified from CS, Section B.2.6.1, Table 2.15) differed from the data reported in other documents (Table 18). The EAG therefore requested clarification from the company on this point. The company clarified that the different data were due to the application of different methods of imputation (or the non-imputation of missing data) (Clarification response, A19).³¹ The EAG notes that, where reported, the difference remained statistically significant, but the absolute difference between B-VEC and placebo, depending on imputation method, was as much as 7.3%.

Table 18: GEM-3: Primary endpoint analyses (imputed data) (modified from Clarification response, A19)³¹

Results including imputation for missing data – N=31				
Document	B-VEC (n=31)	Placebo (n=31)	Absolute difference, % (95% CI)	p value
^a CS, Table 2.15	20.9 (67)	6.7 (22)	46 (24–68)	0.002
^b Guide 2022, Table S3**	19 (61.3)	6 (19.4)	41.9 (NR)	NR
^c FDA Summary Basis for Regulatory Action	20 (64.5)	8 (25.8)	38.7 (13.9-63.5)	0.012
Results excluding 3 patients with missing data - N=28				
Document	B-VEC (n=28)	Placebo (n=28)	Absolute difference, % (95% CI)	p value
Guide 2022, Table S1***	19 (67.9)	6 (21.4)	NR	NR
^a Multiple imputation ^b Open imputation ^c Worst case imputation *Primary wounds were assessed at Weeks 22+24 or Weeks 24+26. **Summary statistics generated by the EAG by summing across rows for primary wound area in Table S3 of Guide <i>et al</i> 2022 ²² . *** Summary statistics generated by the EAG from the patient level data reported in Table S1 of Guide <i>et al</i> 2022 ²² .				

Other secondary endpoints

In patients ≥ 6 years of age, pain severity was assessed as a secondary outcome. Secondary endpoint analyses found that once-weekly treatment with B-VEC led to numerically greater reduction in VAS pain scores vs placebo when assessed at 6 months, but this difference was not statistically significant (Table 19).

Table 19: GEM-3: Secondary endpoint analysis for pain severity during wound dressing changes (reproduced from CS, Section B.2.6.1.5, Table 2.17).

Change from baseline pain severity during wound dressing changes	B-VEC (n=31)	Placebo (n=31)	Absolute difference, % (95% CI)*
Wounds evaluated at Week 22, n	24	24	-0.61 (-1.10 to -0.13)
Mean change on VAS	-0.88	-0.71	
Wounds evaluated at Week 24, n	25	25	-0.88 (-1.79 to 0.03)
Mean change on VAS	-0.64	-0.08	
Wounds evaluated at Week 26, n	24	24	-0.56 (-1.17 to 0.05)
Mean change on VAS	-0.63	-0.38	
Data shown are for pain severity (secondary end point) as assessed with the use of a VAS (scores range from 0 to 10, with higher scores indicating greater pain) among patients aged ≥ 6 years. *Least-squares mean differences were generated from an analysis of covariance linear model, with trial product and patient (paired) as the fixed effect and the baseline value as the covariate. The widths of the 95% CIs were not adjusted for multiple comparisons, and no definite conclusions can be drawn from these data. B-VEC=beremagene geperpavec; CI=confidence interval; VAS=visual analogue scale Source: Guide <i>et al.</i> (2022)²²			

The CS reported no data on pain assessed by the FLACC-R scale (assessed on patients ≤ 6 years). The CSR (section 11.4.8) reported the following results for the ITT population: mean change from baseline at Weeks 22, 24, and 26, respectively: -0.25, -1.25, and -1.50 for B-VEC-treated wounds and -1.00, -1.25, and -1.50 for placebo-treated wounds. The CS and full publication²² reported that conclusions should not be drawn from these findings because of the small sample size (n=4) assessed for this outcome.

Exploratory endpoints

Change in general and skin-specific HRQoL was measured at baseline and at Week 26 using the EQ-5D and Skindex-29 questionnaires, respectively, in patients aged ≥ 12 years. The CS reported that most patients improved by at least one health level or had no change in the EQ-5D-5L dimensions at 6 months as compared to baseline. The CS did not report any data and some limited data are available in the full publication (Figure S3).²² The EAG notes that, given the intra-patient design of the trial, these data cannot distinguish between the effect of B-VEC or placebo. The Skindex-29 scores were generally similar.²²

Post hoc analysis: Durable wound closure

This endpoint was not listed in the published protocols and described as ‘supplementary analysis’ in the CS (Section 2.6.1.3) and CSR (section 11.4.7).¹⁸ The company confirmed that this was a post-hoc analysis (Clarification response, A20).³¹ Durability of response was defined as a wound closure

meeting the responder definition for complete wound closure at both 3 months (Weeks 8 and 10 *or* Weeks 10 and 12) and 6 months (Weeks 22 and 24 *or* Weeks 24 and 26), meeting both the primary and key secondary endpoints simultaneously (these data are reproduced from Guide *et al* (2022, Table S4²² in Table 20) (rather than the definition of complete closure, which was closure at Weeks 8, 10 *and* 12) and 6 months (Weeks 22, 24 *and* 26).^{18, 22} The CS reported (Section 2.6.1.3) that once-weekly treatment with B-VEC led to durable complete wound closure in 49.7% treated wounds compared with 7.1% placebo-treated wounds (p=0.002).^{18, 22}

Table 20: GEM-3: Supplementary analyses for durability of wound closure (imputed data) (modified from CS, Section B.2.6.1, Table 2.16 and Guide et al 2022, Table S4²²)

Endpoint	B-VEC (n=31)	Placebo (n=31)	Absolute difference, % (95% CI)
Durability of response,* n (%)	15.4 (49.7)	2.2 (7.1)	42.6 (22.6–62.6)
Complete wound closure, n (%)			
Weeks 8, 10 and 12, Weeks 22, 24 and 26	14.8 (47.7)	5.1 (16.5) 2.0 (6.5)	31.3 (10.6–51.9) 36.8 (19.8–53.7)
Weeks 8 and 10 Weeks 10 and 12	13.4 (43.2)	6.1 (19.7)	
Weeks 22 and 24 Weeks 24 and 26	14.9 (48.1)	5.1 (16.5)	28.4 (6.2, 50.6) 53.9 (34.2, 73.6)
	21.8 (70.3)	5.3 (17.1)	39.4 (19.8, 58.9)
	17.5 (56.5)	3.4 (11.0)	43.2 (23.2, 63.2)
	16.8 (54.2)		
Complete wound closure was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin reepithelialisation without drainage, as determined by the investigator. Percentages are based on the number of participants in the ITT population; CIs are based on McNemar test. Fractional counts are due to the multiple imputation procedure (MAR) used for analysis. In the first stage of multiple imputation, imputations for missing data are generated based on statistical characteristics of the data and this procedure is repeated many times, resulting in data sets with replaced missing information. In the second stage, any analysis of the imputed data sets can be conducted within each of the imputed data sets as if there were no missing data. After the statistical analysis is run separately on each imputed data set, the estimates of interest from all the imputed datasets are combined into a single estimate using standard combining rules. *Defined as meeting the responder definition for complete wound closure both at 3 months (Weeks 8+10 <i>or</i> Weeks 10+12) <u>and</u> at 6 months (Weeks 22+24 <i>or</i> Weeks 24+26). B-VEC=beremagene geperpavec; CI=confidence interval; ITT=intent-to treat; MAR=missing at random Source: Guide <i>et al.</i> (2022)²² and GEM-3 CSR¹⁸			

3.5.2 GEM-1

This phase I/II trial reported two similar endpoints to the phase III trial, but with different definitions or scales, and some data on molecular correction of COL7.

Primary endpoint: Complete wound closure at 3 months

This was one of two primary efficacy endpoints in GEM-1. The definition of complete wound closure used in GEM-1 required that wounds be healed, i.e., $\geq 90\%$ wound closure of the exact wound area selected at baseline (or $\geq 95\%$ as an exploratory ‘more stringent’ definition, Clarification response, A27).³¹ The findings for B-VEC were significantly better than for placebo in the complete closure responder analysis ($p < 0.0026$) (Table 21). It should be noted that using this less rigorous definition for complete closure ($\geq 90\%$ in GEM-1 compared with 100% in GEM-3), a higher proportion of wounds achieved ‘complete closure’ at 3 months in GEM-1 (79%) compared with GEM-3 (71%). The EAG notes that 20% of wounds in the GEM-3 trial placebo group achieved complete closure at 3 months compared with 0% in the GEM-1 trial.

Table 21: GEM-1: Primary endpoint analysis for wound closure at 3 months (observed data) (modified from CS, Section B.2.6.2.1, Table 2.18).

Endpoint	B-VEC	Placebo*	Difference, %
Complete wound closure, n (%)†			
Weeks 8+10 (n=21)	11/14 (79)	0/7 (0)	79
Weeks 10+12 (n=19)	9/12 (75)	0/7 (0)	75
Responder analysis: complete wound closure† at Weeks 8+10 or Weeks 10+12 (3 months); (n=21)	11/14 (79)	0/7 (0)	79 p=0.0026‡
Results and analysis reported are based upon observed data without imputed values for missing data. *One patient was not imaged and was excluded from the responder analysis. †Complete closure defined as $\geq 95\%$ reduction in wound surface area from baseline. ‡Significant at $p < 0.025$. The phase 1 protocol collected wound closure data at weeks 6 and 12 (no Week 8 or Week 10 datapoints), therefore the phase 1 patients (patients 1 and 2) were excluded from the responder analysis. Patient 4 withdrew after initial dosing due to inability to travel. Included in the analysis are data from Week 8 for patients 3–10, Week 10 for patients 3–10 (missing datapoint for patient 10, placebo), and Week 12 for patients 3–10 (missing datapoints for patient 7, B-VEC). B-VEC=beremagene geperpavec Source: Gurevich <i>et al.</i> (2022)²⁵			

Primary endpoint: Durability of response

This is a second of two primary endpoints in the GEM-1 trial. The definition of complete wound closure used in GEM-1 for this endpoint required that wounds be healed, i.e., $\geq 95\%$ wound closure of the exact wound area selected at baseline and observed for two consecutive weeks.

The median time to complete closure (time from first treatment to closure as defined above) was reported to be shorter with B-VEC (13.5 days) than with placebo (22.5 days), and the median duration of wound closure was reported to be longer with B-VEC than placebo (103.0 vs. 16.5 days) (Table 22). The EAG notes that these data are based on nine patients from the second phase of the GEM-1 trial (CSR, section 11.4.1.1.3).¹⁹

It should be noted that the primary outcome in the GEM-1 trial related to whether the target wound was completely closed at 3 months (see Table 21) and therefore a wound that closed and then reopened before 3 months would contribute to the secondary outcome of median time to complete closure, shown in Table 22, but would not count towards the primary outcome of proportion with complete closure at 3 months, shown in Table 21.

Table 22: GEM-1: Primary endpoint analysis for time to and durability of wound closure (observed data) (modified from CS, Section B.2.6.2.2, Table 2.19).

Endpoint	B-VEC	Placebo	p value*
Time to complete closure, 95% CI, days ^{†,‡}	13.5 (8–21)	22.5 (8–64)	0.0216
Duration of closure, median (95% CI), days [†]	103.0 (94–118)	16.5 (0–66)	0.0009
*p value based on log-rank test. [†]Complete closure defined as $\geq 95\%$ reduction in wound surface area from baseline. [‡]Time to wound closure was defined as the time from the first treatment to complete wound closure ($\geq 95\%$ reduction in wound surface area from baseline) for two consecutive weeks (this qualification is reported in Gurevich <i>et al</i> 2022²⁵, but absent from the CSR¹⁹). Results and analysis reported are based upon observed data without imputed values for missing data. B-VEC=beremagene geperpavec; CI, confidence interval Source: Gurevich <i>et al.</i> (2022)²⁵; GEM-1 CSR¹⁹			

Secondary endpoints: Investigator Global Assessment and pain

The CS reported that Investigator Global Assessment (IGA) scores and patient-reported pain scale were evaluated at Days 3, 5, 15, 30, 60, and 90, for wounds exposed to B-VEC or placebo and compared with baseline. The wounds treated with B-VEC had a numerically higher proportion of closures than placebo-treated wounds according to IGA scores and numerically lower mean pain scores than placebo-treated wounds over a 3-month period. Data were reported in the CSR (sections 11.4.2.1 and 11.4.2.2).¹⁹ No formal statistical comparisons were performed on IGA or patient-reported pain scores (CS, Section B.2.6.2.4).

Exploratory endpoints

The CS reported that an analysis of microscopy data from GEM-1 indicated that B-VEC treatment restored COL7 NC1 and NC2 expression at the dermal–epidermal basement membrane consistent with the location of anchoring fibrils in normal skin (CS, Section B.2.6.2.3, Figure 2.5).

3.5.3 EASE

This phase III trial reported two similar endpoints to the GEM-3 trial, but with different definitions or scales.

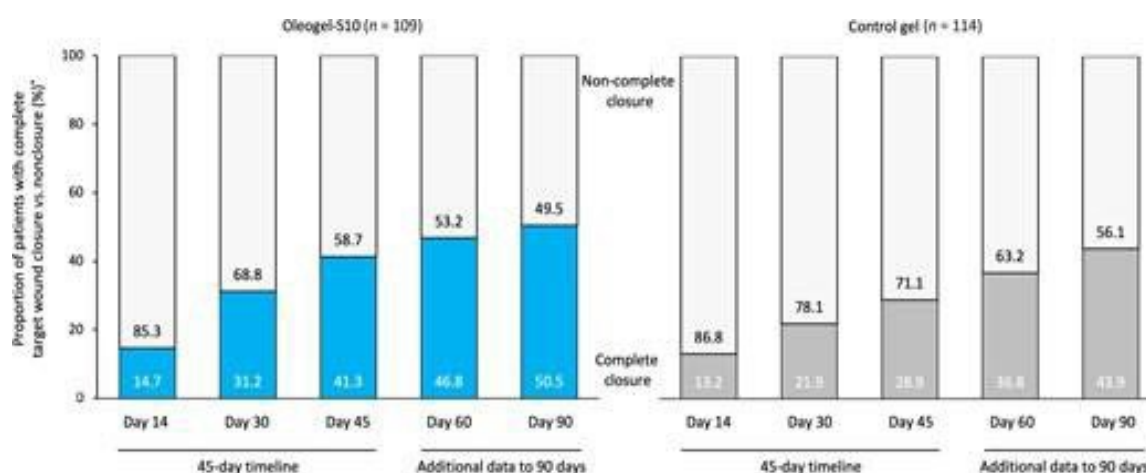
Complete wound closure within 45 days and 90 days

The primary efficacy endpoint was percentage of wounds with complete closure within 45 (+/- 7) days. The definition of complete wound closure used in EASE required that wounds be completely healed (100% wound closure from the exact wound area selected at baseline, specified as skin reepithelialisation without drainage, as determined by a blinded investigator). In terms of the primary endpoint, 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% CI: 1.01, 2.05, p=0.013) (Table 23 and Figure 5). This represents a 44% higher likelihood of wound closure with BBE versus control gel. In terms of the secondary endpoint, BBE gel treatment increased the probability of target wound closure by Day 90 (+/- 7) compared with the control gel, but this difference was not statistically significant: 50.5% vs 43.9%; risk ratio (RR) 1.16 (95% CI: 0.88, 1.52, p=0.296) (Table 23). Across a similar time period (3 months), the GEM-3 trial reported 71% of wounds treated with B-VEC were completely healed and 20% of wounds treated with placebo (using a more demanding threshold of confirmed closure at consecutive visits 2 weeks apart), a statistically significant difference of 51% (95% CI 29, 73; p<0.001; Table 17).

Table 23: EASE: Primary and key secondary endpoint analyses

Endpoint	BBE (n=109)	Placebo (n=114)	RR (95% CI)	p value
Primary endpoint: complete wound closure within 45 days (%)	45 (41.3)	33 (28.9)	1.44 (1.01, 2.05)	0.013
Key secondary endpoint: complete wound closure within 90 days n (%)	55 (50.5)	50 (43.9)	1.16 (0.88, 1.52)	0.296
Complete wound closure was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin reepithelialisation without drainage, as determined by the blinded investigator. BBE=Birk Bark Extract; CI=confidence interval; RR=risk ratio Source: Kern <i>et al</i> 2022 ²⁷				

Figure 5: Proportion of patients with first complete closure of EB wound by visit (reproduced from CS, Section B.2.6.3.1, Figure 2.6)



Note: In the BBE (Oleogel S10) group, 91 (83.5%) had RDEB, 6 (5.5%) had DDEB, and 11 (10.1%) had JEB. In the control group, 84 (73.7%) had RDEB, 14 (12.3%) had DDEB, and 15 (13.2%) had JEB. Two patients with EB simplex (EBS) were enrolled and were included in the analysis; a subsequent protocol amendment excluded EBS. DDEB=dominant dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; RDEB=recessive dystrophic epidermolysis bullosa Source: Kern *et al.* (2022)²⁷

Other secondary outcomes

Data on procedural pain (pain during dressing changes) showed a significantly greater mean reduction in pain with BBE compared to the control gel on Day 14 (BBE -1.4, 95% CI -1.9 to 0.9; control gel -0.8, 95% CI -1.3 to -0.2; $p=0.02$). However, this difference was not statistically significant on Day 30, 45, 60, or 90. On Day 90, the reduction was -1.3 (95% CI -2.0 to -0.6) for BBE compared to -0.2 (95% CI -0.8 to 0.5) for the control gel ($p=0.051$). The CS also reported that, while 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 any differences between the two treatments were non-significant (CS, Section B.2.6.3.3). GEM-3 reported pain assessments using the VAS, and also reported no statistically significant difference between treatment arms (see 4.5.1 GEM-3).

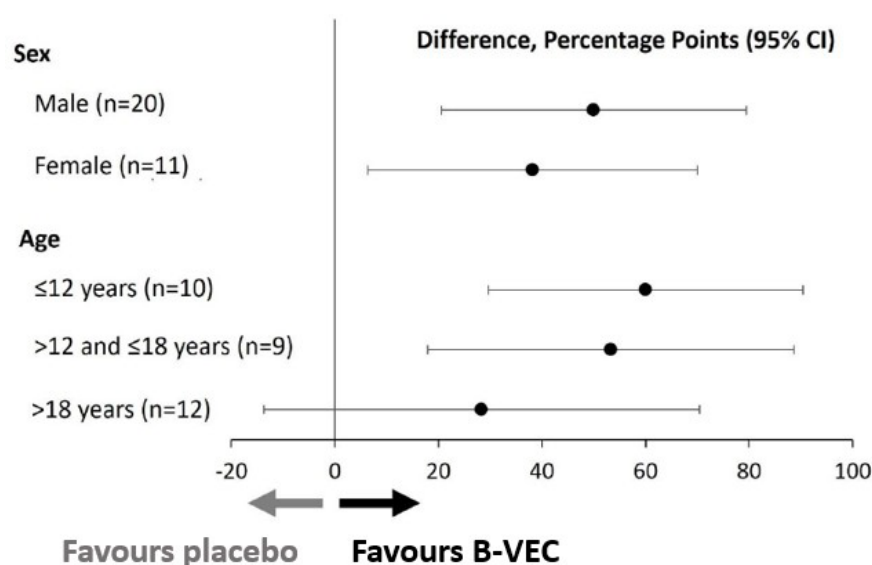
The NICE scope outcome of time to wound closure was reported for the EASE trial and the GEM-1 trial, but not for the GEM-3 trial. The CS reported time to first complete target wound closure up to day 90 during the DBP of EASE (CS, Section B.2.6.3.2 and Kern *et al* 2022 Table S4²⁷). This was a mean of 37.7 days in the BBE group and 44.5 days in the control group.²⁷ No statistical difference was observed in any of the EB subtypes, including RDEB or DEB. The reported time to complete closure in GEM-1 was shorter for both the B-VEC treated wounds (13.5 days) and the placebo treated wounds (22.5 days).¹⁹

HRQoL was not reported in the EASE RCT, however HRQoL outcomes including EQ-5D-5L and EQ-5D-Y were collected in the EASE open label extension (OLE) study. The EASE OLE is only described in the CS when discussing the safety data for BBE (CS, Section 2.10.5), therefore the HRQoL from the EASE OLE are not summarised in the clinical effectiveness section of the CS. However, the CS references the utility values obtained from the EASE OLE in its description of its cost-effectiveness analysis, as these data are employed in a scenario analysis (CS, Section 3.4.1.2)

3.5.4 Subgroup analyses

In GEM-3, subgroup analyses by sex and age were carried out for the primary efficacy endpoint (Figure 5). Although subgroups were not powered to demonstrate statistical significance, consistent treatment response favouring B-VEC was reported to be observed for both sexes (male; female) and all age groups (≤ 12 years; >12 and ≤ 18 years; >18 years), but with a relatively better response in younger age groups (Figure 6). No subgroup analyses were performed in GEM-1.

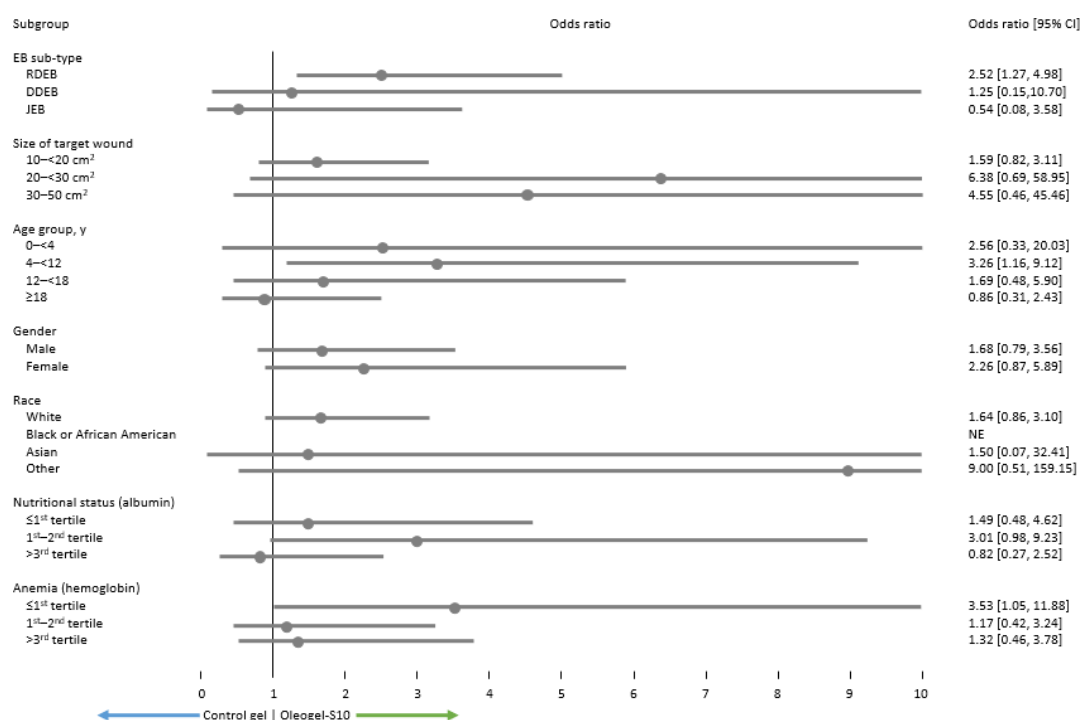
Figure 6: Subgroup analyses for complete wound closure at 6 months in GEM-3 (reproduced from CS, Section B.2.7, Figure 2.8)



B-VEC=beremagene geperpavec; CI=confidence interval; ITT=intent-to-treat Source: Guide *et al.* (2022)³²

Subgroup analysis by EB subtype in the EASE trial showed that, in patients with RDEB (the population of the GEM-3 and GEM-1 trials, with the exception of a single patient in GEM-3), the likelihood of complete wound closure by Day 45 was significantly higher in the BBE group than in the control group (odds ratio [OR] 2.52, 95% CI 1.27, 4.98) (Figure 7). However, there were no differences between BBE and control gel in patients with DDEB (OR 1.25, 95% CI 0.15, 10.7).

Figure 7: Subgroup analyses of the primary efficacy endpoint in EASE (reproduced from CS, Section B.2.7, Figure 2.9)



CI=confidence interval; CMH=Cochran-Mantel-Haenszel; DDEB=dominant dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; EBS=epidermolysis bullosa simplex; eCRF=electronic case report form; EB=junctional epidermolysis bullosa; NE, not estimable (due to small number of patients available); RDEB, recessive dystrophic epidermolysis bullosa.

The CS also noted that, although the EASE trial conducted subgroup analyses to compare the outcomes of people with DDEB and RDEB, the study was underpowered to determine a significant difference between subtypes (CS, Section B.2.7).

3.6 Safety

The CS reported safety data for the three principal trials, as well as longer-term data from the OLE of GEM-3 and the OLP of EASE.

3.6.1 GEM-3 (including OLE)

The safety findings from the double-blind phase III GEM-3 study are presented in Table 24. A total of 18 patients (58%) experienced at least one AE. Moderate, severe or serious AEs were uncommon. No AE led to treatment discontinuation or death, and only one AE (3%; mild erythema) was deemed possibly related to the study drug. The most common AEs were (three events each) pruritus, chills, and SCC. Cases of SCC did not occur at sites of B-VEC or placebo administration. Three patients (10%) experienced a total of five serious AEs, of which none were related to the

study drug. No clinically significant immunologic reactions were reported. Furthermore, treatment response to B-VEC was not associated with baseline HSV-1 serostatus or COL7 seroconversion. The EAG notes that these data were based on repeated weekly treatment with B-VEC for a period of 6 months (28/31 participants completed 22-26 weeks of treatment, Figure 2).

Table 24: GEM-3: Summary of AEs (modified from CS, Section B.2.10, Table 2.20)

Event	Safety population (N=31)
Total AEs, n*	45
Patients with ≥ 1 AE, n (%) [†]	18 (58)
Mild	15 (48)
Moderate	3 (10)
Severe	2 (6)
Serious [‡]	3 (10)
Related to B-VEC or placebo	1 (3)
Leading to discontinuation of B-VEC or placebo	0
AEs reported in $\geq 5\%$ of patients, n (%)^{†§}	
Skin and subcutaneous disorders	
Pruritus	3 (10)
Erythema	2 (6)
Rash	2 (6)
General disorders and site conditions: chills	3 (10)
Neoplasms: squamous-cell carcinoma of skin	3 (10)
Respiratory, thoracic, and mediastinal disorders	
Cough	2 (6)
Rhinorrhoea	2 (6)
*Data are for AEs that emerged or worsened after the first application of B-VEC or placebo. [†]At each level of summarisation, a patient was counted once if one or more events occurred. [‡]Five serious AEs occurred in three patients: one patient was hospitalised three times, once for diarrhoea (severe AE) and twice for severe anaemia (both severe AEs); one patient was hospitalised for treatment of cellulitis (severe AE); and one patient was hospitalised for a positive blood culture related to a haemodialysis catheter (moderate AE). [§]AEs were classified according to system organ class and preferred term in the Medical Dictionary for Regulatory Activities, version 24.1. AE=adverse event; B-VEC=beremagene geperpavec Source: Guide <i>et al.</i> (2022)²²	

The safety findings of the 112-week open-label, long term extension study (B-VEC OLE) are presented in Table 25. This study included participants who completed GEM-3 (rollover) (n=24), plus B-VEC treatment for newly enrolling (naïve) participants with DEB (n=23). The length of the interval between end of treatment in the phase III study and entry into this OLE study was not specified.²³ Thirty-five patients (74.5%) experienced at least one treatment-emergent AE (TEAE) during the study. Of the 173 TEAEs with severity reported, 137 were mild, 22 were moderate, and 14 were severe. Severe or serious AEs affected fewer than 30% of patients over the study period. The 14 severe events occurred in 10 patients and included cellulitis (2 patients), dehydration, pain (2 events for 1 patient), stridor, skin infection (2 patients), bacteraemia, pancreatitis, anaemia,

oesophageal stenosis, staphylococcal infection and SCC. Of the 173 TEAEs reported as having some relationship to study treatment, no event was considered by the investigator to be probably related to study treatment, two were considered to be possibly related (both events of wound haemorrhage), 10 unlikely related, and 161 as not related. Wound infection – an outcome listed in the final NICE scope – occurred in three patients (four events). No treatment-emergent serious AE was deemed related to the study drug. No AE led to treatment discontinuation or death.

Table 25: GEM-3 OLE: Summary of AEs (modified from CS, Section B.2.10, Tables 2.22 and 2.23)

Adverse Events	Rollover patients (N=24)		B-VEC naïve patients (N=23)		All patients (N=47)	
	n (%)	Events	n (%)	Events	n (%)	Events
Patients with ≥1 event						
TEAE	17 (70.8)	102	18 (78.3)	72	35 (74.5)	174
Drug-related TEAE	0	0	1 (4.3)	2	1 (2.1)	2
Severe TEAE	8 (33.3)	12	2 (8.7)	2	10 (21.3)	14
Serious TEAE	9 (37.5)	11	5 (21.7)	6	14 (29.8)	17
Drug-related serious TEAE	0	0	0	0	0	0
Serious TEAE leading to death	0	0	0	0	0	0
AE leading to premature discontinuation of study	0	0	0	0	0	0
Patients who died	0	0	0	0	0	0
TEAEs by organ class preferred term (≥5%)						
COVID-19	9 (37.5)	9	6 (26.1)	8	15 (31.9)	17
Skin infection	4 (16.7)	4	2 (8.7)	4	6 (12.8)	8
Cellulitis	3 (12.5)	4	1 (4.3)	1	4 (8.5)	5
Rhinitis	3 (12.5)	3	1 (4.3)	1	4 (8.5)	4
Wound infection	2 (8.3)	2	1 (4.3)	2	3 (6.4)	4
Respiratory, thoracic, and mediastinal disorders						
Cough	6 (25.0)	8	3 (13.0)	3	9 (19.1)	11
Rhinorrhoea	2 (8.3)	2	2 (8.7)	2	4 (8.5)	4
General disorders and administration site conditions						
Pyrexia	5 (20.8)	7	2 (8.7)	2	7 (14.9)	9
Gastrointestinal disorders						
Vomiting	2 (8.3)	2	3 (13.0)	3	5 (10.6)	5
Diarrhoea	2 (8.3)	2	1 (4.3)	1	3 (6.4)	3
Metabolism and nutrition disorders						
Dehydration	2 (8.3)	2	1 (4.3)	1	3 (6.4)	3
AEs were coded using MedDRA, Version 25.0 AE=adverse event; B-VEC=beremagene geperpavec; TEAE=treatment-emergent adverse event. Source: B-VEC OLE CSR ²³						

The TEAEs reported for at least 5% of patients are also presented in Table 25. The most frequently reported TEAEs, reported for at least 10% of patients, were COVID-19 (17 events in 15 patients, 31.9%), cough (11 events in 9 patients, 19.1%), pyrexia (9 events in 7 patients, 14.9%), skin

infection (8 events in 6 patients, 12.8%), and vomiting (5 events in 5 patients, 10.6%). Otherwise, the types of TEAEs were similar to the double-blind phase of the GEM-3 study: skin infections, cough and rhinorrhoea.

The EAG notes that, with the exception of a small number of AEs, such as vomiting (8.3% for the DBP vs 13.0% for the OLE), the incidence of AEs was much higher in the rollover patients than the naïve patients (e.g., severe TEAEs 33.3% vs 8.7%, serious TEAEs 37.5% vs 21.7%, cough 25.0% vs 13.0%, and pyrexia 20.8% vs 8.7%). This might be due to longer exposure to the study treatment, a longer period of data collection, or differences in patient characteristics in the two groups: the median age was similar: 16.53 (rollover) vs 16.74 years (naïve) but the age distribution was different: 4.2% vs 17.4% respectively for participants aged <3 years).²³ There were also some differences in the OLE rollover and naïve patient groups, respectively, in terms of race and ethnicity: black patients: 0% vs 9%; American Indian or Alaskan native patients: 21% vs 13%, and Hispanic or Latino patients: 54% vs 35% (B-VEC OLE CSR, 11.2.1, Table 5).²³

In response to a question by the EAG that the CSR states that [REDACTED] of patients enrolled discontinued GEM-3 OLE study and the most common reason ([REDACTED]) was study termination by sponsor, the company clarified that this was due to B-VEC being approved by the FDA and being made commercially available, with subjects able to access the therapy without the burden of study visits (Clarification response, A31).³¹

3.6.2 GEM-1

The CS (Section B.2.10) reported safety data as listed in the full publication²⁵: 21 AEs were observed following 129 topical B-VEC doses that were administered during the phase 1/2 GEM-1 trial (Table 26). All events except one were considered mild; Four mild events (fever, peculiar taste, rash, itch) were possibly related to the study drug. Two mild events (both application-site discharge) were probably related to the study drug. All AEs resolved without the need to reduce the B-VEC dosing or frequency. The CS and publication reported that there was a single moderate AE unlikely to be related to the study drug (Section B.2.10). The details of this AE were not reported. However, the CSR reports 35 AEs in nine patients, 33 of which were mild.²³ Two moderate events occurred in a single patient – again, no details were given in the documents provided.²³

Table 26: GEM-1: Summary of AEs (modified from CS, Section B.2.10, Table 2.21)

Adverse Events	Safety population (N=12)
Total AEs, n	21
Mild	20*
Moderate	1
Severe	0
Serious	0
Related to B-VEC or placebo	6†
Leading to discontinuation of B-VEC or placebo	0
*20 AEs were experienced by 9 patients †4 events were possibly and 2 probably related to study drug AE=adverse event; B-VEC=beremagene geperpavec Source: Gurevich <i>et al.</i> (2022) ²⁵	

No vector shedding was reported. HSV-1 antibodies, when present, were detected at variable levels before and after B-VEC treatment and did not affect efficacy or safety. Two patients had baseline COL7 antibodies (patients 2 and 5) and some COL7 titres increased after treatment; however, no tissue-bound skin immunoreactants were noted on immunofluorescence microscopy.²⁵ The serum of patient 2 was subsequently found to be COL7 antibody–negative at approximately 28 months following B-VEC treatment. “Patient 12” had no COL7 immunogenicity, despite having the greatest B- VEC exposure (8×10^8 PFU per dose every 1–2 days for two 25-day treatment cycles).²⁵

3.6.3 EASE (including OLP)

A summary of AEs for the DBP and OLP of the EASE trial is presented in Table 27. At least one AE was experienced by 81.7% and 80.7% of patients receiving of the BBE and control gel, respectively during the 90-day DBP of EASE, $n=223$ ²⁷ (higher than the 58% from the DBP of the phase II GEM-3 trial, $n=31$), but this incidence was lower during the 2-year OLP of EASE³⁵ (77.1% compared with 74.5% for the OLE phase of GEM-3) (Table 25). The EAG notes that, while the frequency of some types of AE is relatively high (>15%) during one or both phases of the EASE trial, the incidence was generally similar across the experimental and the placebo arms (e.g., AEs related to treatment in the DBP, 24.8% for BBE and 22.8% for placebo).²⁷

The incidence of severe (19.0% vs 21.3%) and serious AEs (26.0% vs 29.8%) was very similar for the treatment-exposed patients in the open label extension phases of both EASE ($n=100$) and GEM-3 ($n=47$), respectively. In these longer-term extension studies, TRAEs (8.0% vs 2.1%), serious treatment-related AEs (1% vs 0%) and TRAEs leading to discontinuation or study withdrawal (0% vs 0%), were also largely similar for the treatment-exposed patients in the EASE ($n=100$) and GEM-3 trials ($n=47$).

The EAG notes that the NICE scope outcome of incidence of wound infection was reported in the BBE arm of the EASE trial to be 0.9% in the DBP²⁷ and 4.0% in the 2-year OLE.¹⁰ By contrast, the incidence of wound infection in the B-VEC group in the 2-year OLE of the GEM-3 trial was 6.4% (CS, Section B.2.10.3, Table 2.23). This outcome was not reported for the blinded phase of the GEM-3 trial.

Table 27: Summary of safety and tolerability outcomes from EASE (DBP and OLP)

	EASE DBP (90-day)		EASE OLP (24-month) and Murrell 2025 ³⁵		
	BBE gel	Control gel	BBE gel	Control gel	All subjects
	n=109	n=114	n=100	n=105	N=205
AEs, n (%)	89 (81.7)	92 (80.7)	77 (77.0)	81 (77.1)	158 (77.1)
Severe AEs	13 (11.9)	6 (5.3)	19 (19.0)	18 (17.1)	37 (18.0)
Serious AEs, n (%)	7 (6.4)	6 (5.3)	26 (26.0)	24 (22.9)	50 (24.4)
AEs related to treatment leading to study withdrawal, n (%)	3 (2.8)	2 (1.8)	0 (0)	3 (2.9)	3 (1.5)
Serious AEs leading to study withdrawal, n (%)	2 (1.8)	0 (0)	9 (9.0)	3 (2.9)	12 (5.9)
Serious AEs related to treatment leading to study withdrawal, n (%)	1 (0.9)	0 (0)	0 (0)	1 (1.0)	1 (0.5)
AEs related to treatment, n (%)	27 (24.8)	26 (22.8)	8 (8.0)	17 (16.2)	25 (12.2)
Serious AEs related to treatment, n (%)	1 (0.9)	0 (0)	1 (1.0)	1 (1.0)	2 (1.0)
Serious AEs leading to death, n (%)	0 (0)	0 (0)	7 (7.0)	1 (1.0)	8 (3.9)
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.					

Summary

The data suggests that B-VEC has good safety and tolerability, with few or no treatment-related serious or severe AEs, in either the short- or the longer term. This profile is generally similar to the principal comparators, including BBE.

3.7 Ongoing studies

The CS reported (Section 2.11) that there were no ongoing studies of B-VEC in a population with DEB. The EAG confirms that it did not identify any relevant, ongoing trials or studies, only a single study of B-VEC in a DEB population with diagnosed SCC ([NCT06731933](#)).

3.8 Meta-analysis

The EAG agrees with the CS (section B.2.8) that no meta-analysis was required.

3.9 Indirect treatment comparison (ITC)

The CS reported (Section B.2.9) that a feasibility assessment of an ITC between BBE and B-VEC was conducted by the company and concluded that an ITC was not feasible given the following identified sources of uncertainty:

- Four studies were identified as the relevant evidence to inform an ITC: GEM-1 (phase 1/2) and GEM-3 (phase 3) for B-VEC, EASE (phase 3) and BEB-10 (phase 2) for BBE.
- **Significant differences in study designs:** different frequency of the application of placebo treatment; different permitted concomitant treatments; EASE was a parallel-group trial and other three studies were intra-patient trials; BEB-10 and GEM-1 were open-label studies; different study durations.
- **Heterogeneous patient population:** difference in median age, wounds size, and in the composition of the study populations across EB subtypes (i.e., RDEB, DDEB, JEB) between the trials.
- **Differences in definitions of endpoints:**
 - **Complete wound closure:** “EASE measured all wounds that had complete closure (definition not reported) at least once (without any confirmation of closure) by 90 days (even if the wound re-opened).” “The GEM studies measured only wounds that were closed at 3 months (i.e., wounds that had closed and re-opened would not be counted as a success), with complete closure defined as at least 95% in GEM-1 and 100% in GEM-3.” (CS, Section B.2.9 and response to clarification question A34)
 - **Time to wound closure:** “in GEM-1, the wound closure had to be observed in two consecutive weeks, this was not required in EASE or BEB-10, meaning that wounds that re-opened shortly after closing in EASE or BEB-10 would still be counted as a success.” (CS, Section B.2.9 and response to clarification question A34)
 - **Change in target wound size:** “While the endpoint definition was generally consistent, minor differences exist in the statistical summaries used (i.e., mean vs. median).” (CS, Section B.2.9 and response to clarification question A34)³¹

The EAG acknowledges the challenges involved in conducting an ITC to estimate the relative treatment effect between B-VEC and BBE. In the economic model, B-VEC and BBE were compared naively. The EAG considers the absence of any ITC results unhelpful for informing decision-making.

The EAG requested the company to perform an ITC for the endpoints listed above based on the reported results from the included studies (clarification question A34) and an ITC based on the transition matrices used in the economic model (clarification question B15).³¹ In response to clarification question A34, the company reiterated that a meaningful ITC was not feasible due to differences in endpoint definitions across the trials and did not perform the requested analysis. To provide some indication of the relative treatment effect between B-VEC and BBE, the EAG conducted a Bucher ITC for complete wound closure (see Section 3.10).

In response to clarification question B15, the company conducted a model-based ITC using the Bucher method.³⁹ This model-based analysis compared changes in health state occupancy over time for health states defined by BSAP affected by wounds. Health state occupancy based on BSAP was available from the model used in HST28 for BBE and BSC, based on the BBE and placebo arms of the EASE study. Due to the intra-patient design of the GEM-1 and GEM-3 studies, whereby individual wounds on the same patient were randomised to either B-VEC or placebo, these studies were unable to provide estimates of BSAP for patients receiving either B-VEC or BSC across all eligible wounds, as they would in clinical practice. Therefore, the modelling of BSAP for B-VEC and BSC relied on a patient level simulation (PLS) of wound outcomes for patients receiving treatment across all eligible wounds (details of this simulation can be found in Section 4.2.5.1.1). As understanding this ITC requires an understanding of various aspects of the economic modelling conducted by the company, the EAG has critiqued this ITC within Section 4.3.3.7. However, the EAG wishes to flag here that it has serious concerns regarding the company's model-based ITC because it used changes in health-state occupancy for individual health states as its measure of effectiveness without accounting for either the correlation in health state occupancy between different states or whether an increase in health state occupancy was related to patients moving into that health state from a more or less severe state. In addition, the ITC relied on the PLS of wound outcomes for B-VEC and BSC, and the EAG has additional concerns regarding the data sources used for this simulation, as well as the validity of the simulation outputs and associated assumptions (see the EAG's critique in Sections 4.3.3.4 and 4.3.3.5). For these reasons, the EAG did not consider the company's model-based ITC to be valid and it preferred to conduct its own trial-based ITC as detailed in Section 3.10.

3.10 Additional work on clinical effectiveness undertaken by the EAG

The EAG conducted an ITC using the Bucher method based on GEM-3 and EASE.³⁹ The data used, underlying assumptions, and results are presented in Table 28. The EAG notes that the results should be interpreted with caution, given the assumptions made. However, the analysis aims to provide the Committee with an indication of the relative treatment effect between B-VEC and BBE.

Table 28: EAG's additional analysis results

	Arm	Data	Assumptions	ITC results B-VEC vs BBE (95% CII)
Complete wound closure	B-VEC	GEM-3: the percentage of wounds with complete closure at 3 months confirmed at two consecutive visits two weeks apart B-VEC: 21.9% (n=31) Placebo: 6.1% (n=31)	The placebo arms from GEM-3 and EASE serve as a common comparator. This analysis ignores the differences in the definition of complete wound closure between the two trials.	Relative risk (RR): 3.12 (0.66, 14.82)
	BBE	EASE: the proportion of participants with first complete closure of EB wound within 90±7 days BBE: 50.5% (n=109) Placebo: 43.9% (n=114)		
Time to wound closure	B-VEC	GEM-3: not assessed.	NA	No analysis was conducted due to no data from GEM-3.
	BBE	EASE: Time to first complete closure of target wound by day 90 based on clinical assessment BBE: 92.0 days (50.0, NE) Placebo: 94.0 days (89.0, NE)		
Change in target wound size	B-VEC	GEM-3: not assessed.	NA	No analysis was conducted due to no data from GEM-3.
	BBE	EASE: mean change in target wound size based on investigator assessment at 90 days BBE: -64.57% Placebo: -62.09%		

Abbreviations: B-VEC, beremagene geperpavec; BBE, Birch Bark Extract; CI, Confidence Interval; n, number; NE, not estimable; RR, risk ratio

3.11 Conclusions of the clinical effectiveness section

3.11.1. Summary of principle findings

Clinical evidence: The clinical evidence in the CS was based on GEM-3 (intra-patient, multicentre, double-blind, randomised, placebo-controlled, phase 3) and GEM-1 (intra-patient, single centre,

open-label, randomised, placebo-controlled, phase 1/2) for B-VEC. The dosing used for B-VEC in GEM-3 aligns with the dosing regimen described in the EMA's SmPC, but various dosing regimens were applied in the different phases of GEM-1 and none of these aligned with the dosing regimen in GEM-3.

The GEM-3 trial shows 67% of wounds treated with B-VEC and 22% of wounds treated with placebo were completely healed at 6 months (the primary efficacy endpoint), a statistically significant difference of 46% (95% CI 24%, 68%; $p=0.002$). Secondary endpoint analyses found that complete wound closure at 3 months was also statistically significant better for B-VEC; once-weekly treatment with B-VEC led to numerical reductions in VAS pain scores and on the FLACC-R scale vs placebo when assessed at 6 months, but these differences were not significant. In GEM-3, subgroup analyses by sex and age suggested a consistent treatment response favouring B-VEC was reported to be observed for both sexes (male; female) and all age groups (≤ 12 years; >12 and ≤ 18 years; >18 years), but with a relatively better response in younger age groups.

The GEM-1 trial shows improved wound closure with B-VEC based on complete wound closure responder analysis. No subgroup analyses performed in GEM-1.

The data suggests that B-VEC has good safety and tolerability, with few or no treatment-related serious or severe AEs, in either the short- or the longer term.

Indirect treatment comparison: The company concluded that it's not feasible to conduct ITCs comparing B-VEC and BBE due to differences in study design, population, and endpoint definition among the included studies. The EAG's exploratory analysis suggests that patients receiving B-VEC were 3.12 times more likely to have complete wound closure at 3 months compared to those receiving BBE, but the result was not statistically significant (RR: 3.12 with 95% CI 0.66 to 14.82).

3.11.2 Uncertainties surrounding the reliability of the clinical effectiveness

Given the open-label design of the GEM-1 trial, the small sample size, and the presence of uncontrolled potential confounding factors (including wound size, wound duration, and the use of a non-licensed dose) the EAG assessed the overall risk of bias in GEM-1 to be high and deemed it unsuitable for informing clinical effectiveness in the economic model. Although the EAG assessed the overall risk of bias in GEM-3 to be low to moderate, the EAG notes that many of the secondary endpoint data from GEM-3, such as measures of HRQoL, cannot distinguish between the effect of B-VEC or placebo given the intra-patient design of the trial.

No clinically significant immunologic reactions were reported in GEM-3.

The EAG acknowledges the challenges involved in conducting an ITC to estimate the relative treatment effect between B-VEC and BBE. However, the absence of any ITC results limits the ability to inform decision-making. The company presented a model-based ITC based on health state occupancy during the clarification stage. However, the EAG considered this analysis not meaningful for assessing treatment effect, as it was unclear how patients transitioned between health states in each treatment arm, leading to the observed differences in occupancy. The B-VEC data used in the ITC analysis were derived from a PLS as data on wound outcomes for patients receiving treatment across all eligible wounds were not available from the GEM-1 and GEM-3 studies due to their intra-patient randomisation design. The EAG raised additional concerns about the data sources used in the simulation, as well as the validity of the simulation outputs and the assumptions underpinning them.

4. COST EFFECTIVENESS

4.1 EAG's comment on company's review of cost-effectiveness evidence

4.1.1 Company's search objective and methods

Search strategies for the economic evaluation SLRs are presented in CS Appendices E (cost-effectiveness), F (health-state utility values) and G (cost and healthcare resource use). Databases and supplementary sources were searched simultaneously using the search terms presented in CS Appendix E, and then screened for inclusion in any of the three SLRs. Searches were conducted in November 2024. The search strategy was designed for a wide population (all patients with EB and not limited to any intervention), which increases the sensitivity of the search.

A range of bibliographic databases were searched: MEDLINE (ALL); Embase; the Allied and Complementary Medicine Database; the Cumulated Index in Nursing and Allied Health Literature (CINAHL); PsycINFO; Retraction Watch via INAHTA; EconLit; NHS EED. The inclusion of databases such as CINAHL and PsycINFO is unusual for economic SLRs, although the company points out in clarification response A8 that they are worth searching for mental health related data and a nursing resource perspective, since EB services are often delivered via specialist nurses. Overall, the company searched a comprehensive range of databases, part of an overall strategy to increase sensitivity. The company appropriately points out this is particularly helpful in relation to rare diseases where there can be a lack of data (clarification response A8).

Supplementary searching included relevant conference proceedings from 2023, 2024 (and 2025 where available) and a comprehensive range of HTA websites, including the HTA database via INAHTA. As with the clinical SLR, hand-searching of the bibliographies of relevant systematic reviews and meta-analyses was undertaken to identify relevant primary studies. In Appendix E of the CS, '*Identification and selection of relevant studies*' section, the company mentions searching trial registers, but no more details were provided, and clarification was sought. Clarification response A7 explains that the clinical trial registers WHO ICTRP and ClinicalTrials.gov were searched as part of the clinical SLR, and results from these were screened for both the clinical and non-clinical SLR reviews simultaneously, and any eligible results were included in the non-clinical SLR.

Similarly to the clinical SLR, reporting of the search strings is comprehensive, with search results presented line by line for each database search. The supplementary searches have also been reported transparently and thoroughly in line with Stansfield *et al.* (2016).²⁹

Filters for economic evaluations and costs, and HRQoL have been used in the database searches where possible, although it is only in the MEDLINE search (Appendix E, Table 3) that a source for the filters

have been given. Once again, the reporting in this table provides the useful extra detail of specifying how the validated filters have been adapted to increase the sensitivity of the search.

Overall, the search strategy for the non-clinical SLRs takes a sensitive approach that is adequate to retrieve economic studies relating to treatments for patients with DEB, which were then screened for relevance to this particular submission.

4.1.2 Findings of the cost effectiveness review

The company's review identified 35 unique studies that were relevant to patients with EB and an additional two studies were identified through handsearching. Among these, four were economic evaluations, 14 studies reported on direct costs and HCRU, four studies addressed indirect costs and productivity losses, and 22 studies reported HRQoL or utility values (some records contributed to more than one category).

The company summarised the methodology and outcomes of the identified economic evaluation studies and its results (CS Appendix E, Tables 18). Of the four economic evaluations identified, two were *de novo* cost-effectiveness analyses of BBE, submitted to NICE and the Scottish Medicines Consortium (SMC), and others were a budget impact model and a cost-minimisation study. Two appraisals employed a seven-state model based on EASE trial data and reported incremental cost-effectiveness ratios (ICERs) ranging from £95,980 to £141,805 per QALY gained over a lifetime horizon. Two included cost-effectiveness analyses were assessed using a checklist adapted from Drummond *et al.*⁴⁰ Both NICE and SMC submissions were deemed of high methodological quality (CS, Appendix E, Table 19).

The CS states that “*Although two cost-effectiveness models were identified, they were both based on BBE. there are important heterogeneities between the clinical trials of BBE and B-VEC, which makes it impossible to adapt those models for the current analysis*”

4.1.3 Conclusions of the cost effectiveness review

Given the heterogeneities between the clinical trials of BBE and B-VEC, the company concludes that a *de novo* cost-effectiveness analysis is necessary. The EAG agrees with this conclusion. However, the company could have more clearly articulated how the findings from the systematic review of published cost-effectiveness analyses were used to inform the development of its economic model. Further justification is needed as to why the model was developed using four disease severity states, rather than the six levels of disease severity that was used in the previous appraisals of BBE (HST28).

4.2 Summary of the company's submitted economic analysis

This section focuses mainly on the *de novo* five-state Markov model (four disease severity states plus death) and the patient level simulation (PLS) model used to estimate the transition probability (TP) matrices for B-VEC and BSC, and B-VEC vial consumption. In addition to discussing the structure for both models, the underlying assumptions are highlighted with the rationale for these provided. In general, the company relied on GEM-1 to derive the efficacy of B-VEC relative to BSC (as discussed in detail in Section 4.2.5.1.1), and consulted three experts to validate some of the modelling assumptions as detailed in Appendix J.

The TP matrices for BBE were sourced directly from the committee papers for HST28,¹¹ and consequently the model provides a naïve ITC between B-VEC and BBE.

Unless specified, the information presented here concerns the post-clarification models submitted by the company.

4.2.1 Population

The population considered in the CS is people with DEB. This was further divided into three age groups; children between 0-6 years old; children/adolescents between 6-18 years old; and adults above 18 years old. The company justified this categorisation based on differences in body surface area (BSA) affected by wounds and in need of treatment. The proportion of patients and the average age per age group were estimated from GEM-3.

In addition to age groups, the model also differentiates between patients with RDEB and DDEB in terms of baseline characteristics (including weight, height, and BSAP affected) and mortality (as discussed in Section 4.2.5.4). Table 3.2 of the CS presents the baseline characteristics and distribution of patients according to age groups and DEB subtype. The proportion of patients and the average age per each age group do not differ by DEB subtype, however average weight and height varied where RDEB patients were smaller and lighter than their DDEB counterparts. These values were sourced from Reimer *et al.*⁴¹ The distribution of patients among the RDEB/DDEB subtypes (57.6% versus 42.4%) was based on Bruckner *et al.*⁴² Regardless of age group or DEB subtype, 64.5% of patients were considered males based on GEM-3 data.⁴³

In its clarification response to question B6, the company amended the DEB subtype split to reflect the whole patient population whether they represented themselves (N=33) or were represented by their carers (N=51). The EAG notes the company's updated model double counts the 33 patients representing themselves and amended that in its exploratory analysis.

Baseline distribution of patients over the different health states were sourced from Bruckner *et al.* for each DEB subtype as per Table 3.8 of the CS, and this was average weighed in the starting cohort.⁴² Finally, the model calculates an aggregated set of results for each treatment arm by distributing the cohort over the three age groups as per GEM-3 data where 12.9%, 48.4%, and 38.7% were 0-6, 6-18, and above 18 years old respectively.

4.2.2 Interventions and comparators

The intervention is B-VEC as detailed in Section 2.3.2; there are two comparators; BBE and BSC as detailed in Section 2.3.3.

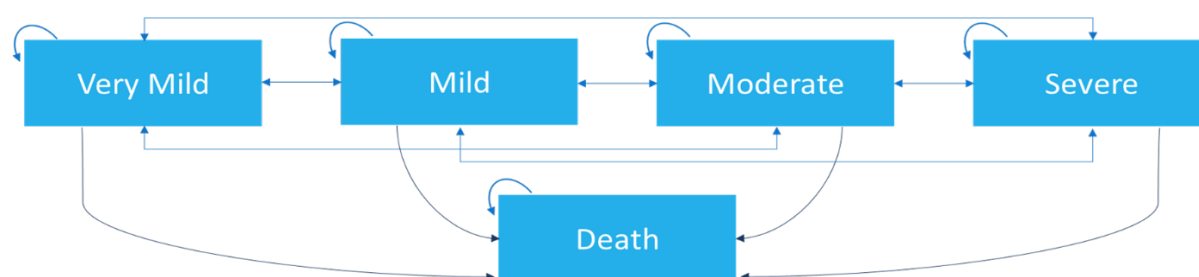
4.2.3 Perspective, time horizon and discounting

The perspective for costs in the company's base case is that of the NHS and Personal Social Services. For HRQoL, the perspective is of patients and carers, as detailed in Section 4.2.5.6. The company's base case analysis uses a time horizon of 100 years, although the model has the functionality to examine the impact of using shorter time periods. Cycle lengths were 13 weeks and half-cycle correction was employed. Both costs and benefits are discounted at 3.5% per annum.

4.2.4 Model structure and logic

The company's economic model uses a cohort-level, state transition approach, which consists of five mutually exclusive and exhaustive health states, four related to the severity of DEB and one representing death. These severity health states are based on BSAP and are shown in Figure 8 which is reproduced from Figure 3.1 in the CS.

Figure 8: The company's model structure (reproduced from Figure 3.1 of the CS)



The ranges of BSAP for the health states in the company's base case were 0.0-2.1%, 2.1-5.0%, 5.0%-25.0%, and 25.0% or more for the very mild, mild, moderate, and severe health states respectively.

The company also built a replication of the HST28 model as described in CS, Section 3.3.1. This was needed basically because several modelling inputs for the company's model were based on the six-

health state structure used in HST28 including the transition matrices for BBE, number and disutility associated with carers, and professional time spent on bandage change. To accommodate these data from HST28, the company developed a mapping algorithm to convert those inputs to inform the company's base case four-health state structure. This mapping was estimated by using a replicated version of the HST28 CS model and calibrating the mapping manually until the ICERs of BBE versus BSC from the six-state model aligned with those from the four-state model introduced in the replicated HST28 model. The company tried to estimate the PAS discount for BBE so that the total costs of the BBE arm of the replicated model matches those published for the HST28 CS model. Table 29 shows the results of the replication exercise, while Table 30 presents the mapping algorithm used to achieve the four-state model results. More details on the HST28 replicated model are discussed in the Appendix.

Table 29: Results of the replicated HST28 model for the 6-state versus 4-state structures

Technology	Total costs	Total LYs	Total QALYs	Incr Costs	Incr QALYs	ICER
Results - 6 health states from the replicated HST28 model						
BBE	1,155,726*	23.80	47.11	220,518	2.17	101,790
BSC	935,208	23.80	44.94			
Results - 4 health states from the replicated HST28 model						
BBE	1,300,037*	23.78	45.03	229,782	2.39	95,980
BSC	1,070,254	23.78	42.63			
Abbreviations: BBE - birch bark extract; BSC - best supportive care						
*Using an estimation of the PAS discount for BBE.						

Table 30: The mapping algorithm used to convert from 6-state to 4-state structure

The 6 states \ The 4 states	Very Mild (BSAP ≤2.1%)	Mild (BSAP 2.1-5%)	Moderate (BSAP 5-25%)	Severe (BSAP >25%)
HS1 (BSAP ≤4%)	5%	95%		
HS2 (BSAP 4-7%)	0%	100%	0%	
HS3 (BSAP 7-10%)	0%	3%	97%	
HS4 (BSAP 10-18%)		0%	100%	
HS5 (BSAP 18-25%)		0%	100%	
HS6 (BSAP >25%)				100%
Abbreviations: BSAP - body surface area proportion; HS - health state				

In response to clarification question B4, the company justified the use of the current Markov structure instead of the six disease severity states from the HST28. The reasons were that the chosen health states aligned with severity levels reported in the literature, allowing the model to capture the correlation between disease severity and the prevalence of clinical manifestations, as reported in Eng *et al.*³³

However, the EAG considers this justification is invalid, as the health states definitions from the CS and in Eng *et al.* states do not match. The CS defined health states based on BSAP, whereas Eng *et al.* categorised the severity by “*impact on performing activities of daily living and need for treatment*”.

In response to clarification question B4, the company reiterated its preference for the four-state severity categorisation “*primarily to align with published literature (i.e., Bruckner et al., Eng et al.) and to allow the model to incorporate both reversible and irreversible complications.*” However, as discussed later in Sections 4.3.3.9 and 4.3.3.13, the EAG disagrees with this rationale because the definition of the model health states does not match with the mentioned literature.

Additionally, the EAG observed a misalignment between the four health states and the HST28 six states, and considers the company's mapping algorithm to be methodologically flawed.. For example, all of health state 2 patients (BSAP 4-7%) were assumed to belong to the mild health state (2.1-5%). In response to clarification question B39, the company agreed with the EAG however it stated that “*the only possible solution to making the mapping algorithm converge was with the currently used approach*”.

The key structural assumptions employed within the company’s model are presented in CS Section 3.9, with key points presented here:

- The model applies different transition probabilities, mortality risks and B-VEC vial consumption for patients according to their age category at baseline (0 to 6 years, 6 to 18 years and over 18 years) which is achieved by programming separate Markov traces for each age category and then aggregating costs and QALY across the whole cohort.
- Assumptions related to the PLS (used to estimate transitions for B-VEC and BSC, and B-VEC vial consumption):
 - The PLS tracked BSAP on weekly basis and as a result reassigned the health state for each simulated patient.
 - Wounds are divided into recurrent and chronic wounds, with the latter assumed to heal only through treatment with B-VEC.
 - Number of each type of wounds, and related BSAP, are correlated with health state severity (i.e., number of wounds and BSAP increase for more severe states and decrease for less severe states).
 - GEM-1 data measuring the weekly change in wound area open was used to estimate a fixed weekly rate of wound closure on B-VEC and BSC and weekly rate of wound reopening on BSC.

- The weekly rate of wound reopening on B-VEC was derived from GEM-3 and OLE data assuming wound closure during the time period these studies.
- GEM-1 data on average wound size in the week they reopened (pooled across both B-VEC and placebo treated wounds) was applied as the size of reopened wounds in the B-VEC arm.
- In the B-VEC arm, treatment was assumed to be applied immediately to reopened wounds, so reopened wounds were assumed not to increase from their initial size upon reopening.
- Reopened wound size for BSC was based on GEM-1 data on maximum wound size for placebo-treated reopened wounds and this was applied as a one-off increase in BSAP at the time of wound reopening even though the observed time to reach maximum size was 1 to 9 weeks.
- A weekly conversion rate of wounds from recurrent to chronic was assumed and calculated based on the wound closure rates per treatment arm.
- No simulated patient can progress to a health state more severe than their baseline state.
- 90% compliance was assumed on B-VEC.
- Vial sharing was applied 80% of the time when simulating treatment needed per patient per week.
- Each syringe of B-VEC covers a fixed area of 50 cm², with a maximum treatable area of 200 cm² eligible for treatment within a week.
- Assumptions related to the company's Markov model:
 - Patients who discontinue B-VEC or BBE are assumed to reside in the same health state for the rest of the time horizon.
 - Annual discontinuation rate for B-VEC was assumed to be 1% based on the annual discontinuation rate for BBE after 90 days in HST28.
 - Mortality was assumed to differ by age group, DEB type, and disease severity according to current health state occupied.
 - The CS base case included costs associated with reversible and irreversible clinical manifestations. These included infections, anaemia, osteoporosis, foot and hand deformities and SCC, and were assumed to correlate with the modelled health state.
 - Similar to HST28, the number of carers and associated utility loss varied across the health states.
 - Professional assistance for B-VEC administration is only needed for the first administration.
 - The CS base case included costs associated with concomitant medications (psychiatric medications, analgesics, anti-itch medications, laxatives, topical antibiotics, and Medi honey), which varied across the health states.

- Costs related to outpatient visits and dressing changes were estimated using the same methods as in HST28.
- Extra assumptions characterised the very mild state as discussed in Section 4.3.3.13.

4.2.5 Evidence used to inform the company's model parameters

Table 31 summarises the evidence sources used to inform the parameters of the company's model. The derivation of the model parameter values using these sources is described in further detail in the following sections.

Table 31: Summary of evidence sources used to inform the model parameters for the company's base-case

Parameter type	Parameter	B-VEC	BSC	BBE
Patient characteristics	Age group split	GEM-3 ⁴³		
	Baseline age			
	Percent male			
	DEB type split	Bruckner <i>et al.</i> ⁴⁴		
	Baseline distribution on health states			
	Weight and height	General population growth curves for DDEB patients Reimer <i>et al.</i> ⁴¹ for RDEB patients		
Transition probabilities	Between the severity states	PLS model for first 2 years, thereafter patients remain in the same health state	PLS model for first 3 months, thereafter patients remain in the same health state	HST28 ¹¹ using the company's mapping algorithm to convert from six to four
	Mortality (DDEB)	ONS National Life Tables for the years 2020 – 2022 ⁴⁵		
	Mortality (RDEB)	Petrof <i>et al.</i> ⁷		
Treatment discontinuation		Assumption		HST28 ¹¹
Clinical manifestations	Incidence and prevalence	Eng <i>et al.</i> ³³		
Health-related quality of life	Patients	The company's vignette study		
	Carers	HST28 ¹¹		
Resource use	Outpatient visits and dressing changes	HST28 ¹¹		
	Concomitant medication	Eng <i>et al.</i> ³³		

Unit costs	Drug acquisition and administration	List price ¹ and YHEC report ⁴⁶		HST28 ¹¹
	Concomitant medication	British National Formulary ¹⁷		
	Clinical manifestations	National Schedule of NHS Costs 2023/24 ⁴⁷		
	Outpatient visits and dressing changes	HST28 ¹¹ inflated to 2024 values using the NHS Cost Inflation Index ⁴⁸		

Abbreviations: CS - company's submission; DDEB - dominant dystrophic epidermolysis bullosa; HST - Highly Specialised Technology; NHS - National Health Service; PLS - patient-level simulation; RDEB - recessive dystrophic epidermolysis bullosa

4.2.5.1 Treatment effectiveness and extrapolation in the base case

4.2.5.1.1 Patient level simulation to estimate the TP matrices for B-VEC and BSC and B-VEC vial consumption

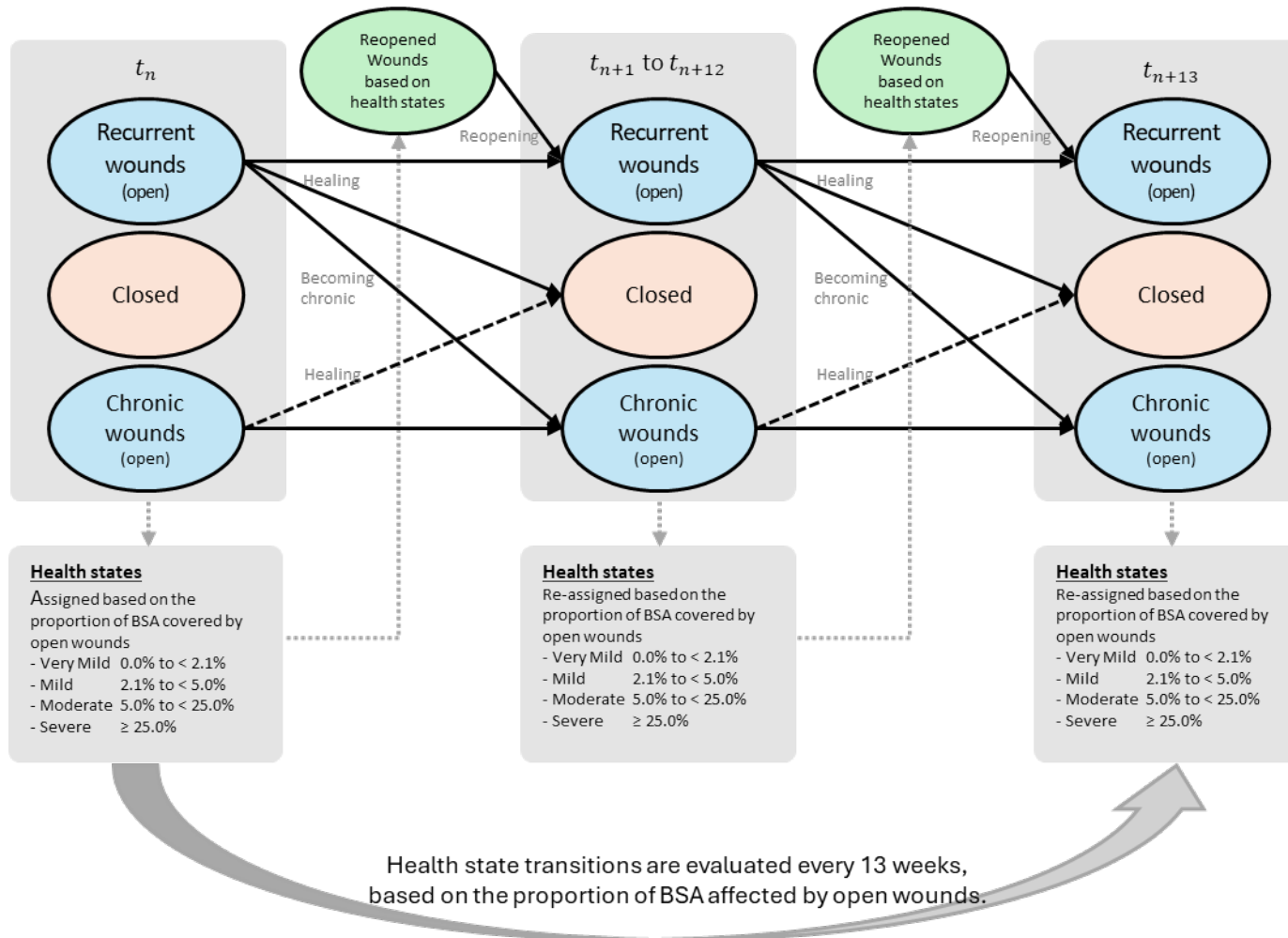
The company submitted a PLS model to inform the economic evaluation of B-VEC versus BSC in the treatment of DEB. BBE was not included because its inputs were informed by HST28. The model translates wound-level clinical evidence from GEM-1 into a disease severity-based framework based on BSAP affected, enabling the simulation of disease progression, treatment effects, and the consumption of B-VEC vials over time.

The GEM-1 and GEM-3 trials did not track changes in BSAP of participants due to its intra-patient design, so the company designed the PLS model to use the wound closure and reopening rates from the GEM trials to simulate the progression of wound burden for patients either on B-VEC or BSC across time. Some key model inputs (e.g., rate of wound closure, size and increase in size of reopened wounds) were source from GEM-1 data rather than GEM-3 because “*GEM-1 tracked the size of B-VEC and placebo-treated wounds on a weekly basis for 24 weeks, while GEM-3 only provided data on complete closure at 3 and 6 months.*” In response to clarification question B3, the company stated “*it was necessary to simulate wound-level healing trajectories on a weekly basis, capturing how individual wounds respond to treatment and when they close or recur. This level of temporal granularity is not available from GEM-3 and could not be derived from its 3-monthly outcome measurements.*”

The simulation is implemented in R and estimates health state transitions and B-VEC vial consumption, within a hypothetical cohort. Each simulation iteration represents a single patient. Baseline characteristics, including age group, BSA, initial BSA open (i.e., covered with wounds), and wound burden, are assigned stochastically via random sampling. The model operates on a weekly cycle over a 156-week (3-year) horizon, tracking individual-level outcomes such as health status, wound progression, treatment application, and vial use. Figure 1 illustrates the wound progression model

structure used in the simulation. At each weekly cycle, wounds may heal, become chronic, or reopen depending on their current state. Every week, health states are re-assigned based on the BSAP affected by open wounds (recurrent or chronic). Transition probabilities between health states are derived from health state classifications observed at 13-week intervals.

Figure 9: Cycle-based simulation of wound dynamics and health state reclassification (EAG interpretation of the PLS R code)



Chronic wounds are assumed to heal only through treatment with B-VEC, as represented by the black dashed line.
BSA=body surface area

Baseline characteristics

In the PLS model, BSA is incorporated in two steps: through age group assignment and age group-specific sampling of BSA. First, each simulated patient is randomly assigned to one of three age groups (0 to < 6 years, 6 to < 18 years, or 18 years and older) using a uniform distribution (i.e., there is a 33% probability to get into one of the three age groups) to ensure balanced representation across groups. Following this, the patient's total BSA is sampled from a normal distribution, with the mean and standard deviation specific to each age group. These parameters are derived from published sources, such as Reimer *et al.*⁴¹ for RDEB patients and general population references for DDEB. Importantly, the model does not explicitly assign a numerical age (e.g., 7.2 years or 15 years) to each patient. Instead, individual age-related characteristics such as BSA are indirectly captured through this group-based sampling approach. Neither ageing nor change in BSA is captured as the PLS' time horizon is limited to three years.

For patients with RDEB, the company used the 3rd, 50th, and 97th percentile values from RDEB-specific anthropometric data reported in Reimer *et al.*,⁴¹ that were closely matched with the mean age within each age group (2.25 years for children, 12.62 years for adolescents, and 27.99 years for adults). Sex-adjusted averages of the 3rd, 50th, and 97th percentile estimates were used to derive the mean and standard deviation (SD) for sampling patients' weight and height, respectively. The EAG notes that the company derived the average weight and height for the adult group of female and male from the oldest age group reported in Reimer *et al.*,⁴¹ with the exception of adult male height. For height of adult male, the company used the value at age 22.8 years rather than the peak value reported at age 23.5 years. In contrast, for DDEB patients, height and weight estimates were drawn from the 50th percentile of UK general population growth curves, again matched to the average age of each subgroup. The height and weight were sampled from normal distributions reflecting variability observed between the 3rd and 97th percentiles for patients with the average age.

Based on the mean, lower and upper bound of height and weight in each group (specified by age, sex and DEB type), individual BSA values were calculated using the Du Bois equation.⁴⁹

$$BSA[m^2] = Weight [kg]^{0.425} \times Height [cm]^{0.725} \times 0.007184$$

The BSA values used in the model were calculated by applying a weighted average to the subtype-specific BSA estimates (RDEB and DDEB), using the distribution of patients across subtypes observed in Bruckner *et al.* (61.5% for RDEB; 38.5% for DDEB) to give an average weighted BSA for each simulated patient. In response to clarification question B6, the company stated that the percentages had been corrected; however, the specific proportions used are still inaccurate in the revised analysis and

fixed by the EAG in their exploratory analysis as mentioned in Section 4.4. The mean and SD, used in a simulation are presented in Table 32.

Table 32: Age stratified BSA estimates for RDEB and DDEB

Age subgroups	Average age from GEM-3	BSA ^a (cm ²), mean (SD)		
		RDEB ^b	DDEB ^c	Weighted average for model simulation ^{de}
0 to <6 years	2.25	5,128 (675)	5,608 (482)	5,312 (601)
6 to <18 years	12.62	10,101 (1695)	13,406 (1622)	11,373 (1,667)
≥18 years	27.99	13,774 (2626)	17,552 (1549)	15,228 (2,211)

BSA=body surface area; DDEB=dominant dystrophic epidermolysis bullosa; RDEB=recessive epidermolysis bullosa

^a The EAG notes that the values were extracted from executing the provided R code and differ from those reported in Table 3.2 of the company submission.

^b based on Reimer *et al*⁴¹ in the respective age and weighted by gender in GEM-3 data for each age group

^c based on WHO growth tables for the general population⁵⁰

^d weighted by the proportion of patients with RDEB and DDEB (61.5% and 38.5%, respectively)

^e SDs used in a simulation for each age group are weighted means of SD values for RDEB and DDEB.

In the PLS model, each patient's initial health state is assigned using a uniform distribution across three categories: mild, moderate, and severe with no patients allowed to start in the very mild state. The company mentioned that this approach ensures that 33% of patients are allocated to each state, allowing for balanced representation of disease severity at baseline. The intention behind this is to ensure that the TP matrices are informed by a similar number of simulated patients for each severity state so that convergence of results for each starting state could be achieved faster. It does not need to reflect the distribution in the cohort being treated as this is being modelled in the Markov model.

The assigned health state then determines the sampling range for chronic and recurrent wound coverage, expressed as BSAP. BSAP affected by chronic and recurrent wounds at baseline is sampled independently from uniform distributions defined specifically for each health state. The model applies a 40% cap on the open BSA for patients in the Severe state, based on clinical plausibility. Table 33 provides a summary of the key parameters for patient sampling.

Table 33: Summary of parameters for sampling patients

Parameter (variable name in R)	Distribution and input value	Source
Age group (live_agegroup)	Uniform distribution - 0-6 years: 33% - 6-8 years: 33% - 18 years and older: 33%	Assumed
Total BSA in each age group (live_totalBSA)	Normal distribution (see Table 32)	Calculated based on weight and height reported in Reimer <i>et al.</i> ⁴¹ for RDEB, and general population ⁵¹ for DDEB
Heath states (live_BL_healthstate)	Uniform distribution - Mild: 33% - Moderate: 33% - Severe: 33%	Assumed
Open recurrent wounds	Uniform in each health state - Very mild: 0% to < 2% - Mild: 2% to < 4% - Moderate: 4% to < 15% - Severe: 15% to 20%	Assumed
Open chronic wounds	Uniform in each health state - Very mild : 0% to < 0.1% - Mild: 0.1% to < 1% - Moderate: 1% to < 10% - Severe: 10% to 20%	Assumed

Modelling wound dynamics

The model tracks individual-level wound progression on a weekly cycle over a 156-week (3-year) horizon. Table 34 provides a summary of the key parameters and inputs used in the simulation.

Table 34 Summary of parameters for modelling wound dynamics

Parameter	B-VEC	Placebo	Source
Recurrent wound closure per week	42.54% (if treated)	14.17%	GEM-1
Chronic wound closure per week	42.54% (if treated)	0%	
Reopening probability per week	██████	25.48%	Calculated based on values from GEM-3 and OLE (B-VEC) and GEM-1 (BSC)
Reopened wound size	Normal distribution (Mean: ██████, SD: 0.96)	Same distribution as B-VEC but increased by ratio of 4.5	GEM-1
Recurrent → Chronic transition per week	1.19%	29.45%	Assumed and calculated based on recurrent wound closure rates
Max area treated per week	200 cm ²	N/A	
Compliance	90%	N/A	GEM-3 ¹⁸

1) Wound closure

Wound closure refers to the reduction in open wound area, either recurrent or chronic, over time. In the model, closure is quantified weekly and occurs via two mechanisms: 1) treated closure (when a wound is treated with B-VEC) and 2) untreated (spontaneous) closure (i.e., natural healing under placebo or untreated conditions). For B-VEC, it was assumed that 42.54% of the treated open wound area closes each week. This closure rate was applied to both chronic and recurrent wounds, as B-VEC was used for both in trials (although GEM-3 did not collect information on whether wounds were chronic or recurrent, clarification response A2, and GEM-1 had only one chronic wound). For BSC, recurrent wounds were assumed spontaneously to close at a rate of 14.17% per week, derived from GEM-1 (placebo arm) and chronic wounds was assumed not to close on BSC.

According to the company's clarification response (B16), the company aggregated the area open across all placebo-treated wounds as if from a single patient, calculating weekly changes in area open to estimate the weekly closure rate for wounds treated with placebo in the GEM-1 trial. The weekly averages were derived from uncensored data, with wounds censored at first closure to isolate closure dynamics. Due to this censoring, the number of wounds contributing to the analysis declined over time, with fewer than 50% remaining open beyond week 6. To avoid biased weighting, only weeks with sufficient contributing wounds were included.

In response to EAG concerns about equal weighting of weeks, the company conducted an alternative analysis in which weekly closure rates were weighted by the number of contributing wounds. This approach yielded revised weekly closure rates of 5.75% for placebo (vs. 14.17%) and 33.53% for

B-VEC (vs. 42.54%). Scenario analyses using these adjusted rates suggested that the cost-effectiveness estimates are very sensitive to these parameters (response to clarification question B1).

In the patient level simulation, if a patient has a total area open of 2 cm² or less, the open area is assumed to close completely in a given week once treated.. Closed wounds can reopen, and reopened areas are re-added to the open area in the next cycle.

2) Wound reopening

In the PLS model, the number of wounds reopening per week is derived using a probabilistic approach based on the health state-specific risk of reopening and the cumulative area of previously closed wounds. First, the expected number of reopening wounds is computed by multiplying the average number of wounds (chronic and recurrent) per the patient's current health state by the weekly probability of reopening. The number of wounds was assumed based on data from Eng *et al.*³³ because data on the number of wounds were not collected in GEM trials. Eng *et al.*³³ did not stratify results by patient age group or overall BSA. But it reported that patients had on average, 11 recurrent wounds (SD 10; range 0–45) and 3 chronic wounds (SD 2; range 0–9). The company used the mean values to define the lower boundary of the moderate health state, while the 25th and 75th percentiles informed the boundaries of the mild and severe health states, respectively (Table 35). The midpoints for each health state were used to calculate total number of wounds. The expected number of wounds were 2, 9, 17.5, and 38.5 for the very mild, mild, moderate, and severe states, respectively. In the response to clarification question B23, the company mentioned that the wound count estimates were reviewed and validated by clinical experts.

Table 35: Assumed wound counts and expected reopened wounds by health state and treatment arm

Health State	Chronic wounds		Recurrent wounds		Total number of wounds	Expected wounds reopened, ^a (range)	
	Range	Used value	Range	Used value		B-VEC	BSC
Very mild	0	0	0-4	2	2	0.03 (0-1)	0.51 (0-1)
Mild	1-2	1.5	5-10	7.5	9	0.14 (0-1)	2.29 (2-3)
Moderate	3-4	3.5	11-17	14	17.5	0.28 (0-1)	4.46 (4-5)
Severe	5-9	7	18-45	31.5	38.5	0.62 (0-1)	9.81 (9-10)

^a Expected wounds reopened = Total number of wounds × reopening probability. The values presented are outputs from the R model

Wound reopening was modelled using an exponential distribution, with the probability of reopening derived from the median duration of closure. For BSC, a median closure duration of 16.5 days was used, based on the GEM-1 trial, resulting in a weekly reopening probability of 25.48%. For the B-VEC arm, pooled data from pooled GEM-3 and OLE indicated a median duration of closure of [REDACTED], corresponding to a weekly reopening probability of [REDACTED].

$$\text{Weekly reopening probability for BSC} = 1 - e^{-\left(\frac{\ln(2)}{16.5 \text{ days}}\right) * 7 \text{ days}} \approx 25.48\%$$

$$\text{Weekly reopening probability for B - VEC} = \blacksquare$$

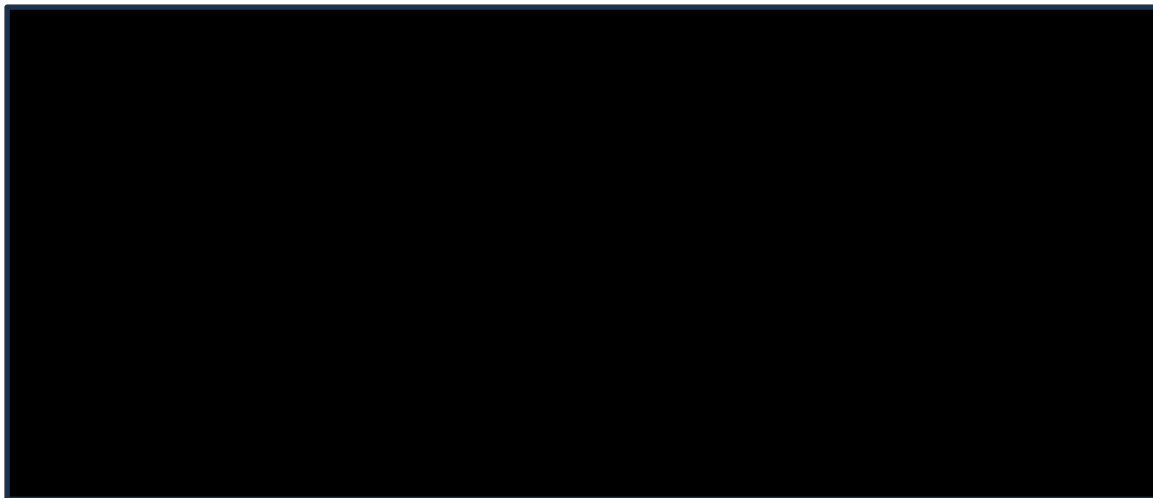
The company stated that, due to differences in study design between GEM-1 and GEM-3, it was not appropriate to directly compare the duration of wound closure across these studies. In GEM-1, patients received variable dosing regimens over approximately 12 weeks, with closure duration monitored for up to 12 weeks post-administration, resulting in a median closure duration of 103 days. In contrast, GEM-3 involved a standardised weekly dosing schedule over 26 weeks followed by a 30-day safety observation, with additional follow-up through the open-label extension. The company's analysis, which combined data from GEM-3 and the OLE (including interim periods), reported a longer median closure duration of $\blacksquare$ days, based on a total observation period of up to 26 months. Scenario analyses were provided by the company in response to clarification question B19, which incorporated the median closure duration of 103 days, based on GEM-1 data, and a median duration of $\blacksquare$ days, using OLE data only. These scenario analyses highlight the sensitivity of the cost-effectiveness results to assumptions regarding the duration of treatment effect.

As shown in Table 35, the expected number of wounds reopened was derived as the product of the total number of wounds in each health state and the estimated probability of reopening. Since this calculation yields a non-integer expected value, it is converted to an integer by taking the floor of the value (i.e. rounding to the nearest smaller integer), and an additional wound is reopened with a probability equal to the remaining fractional part. For example, an expected value of 3.7 would always result in 3 wounds reopening, with a 70% chance of a fourth wound reopening.

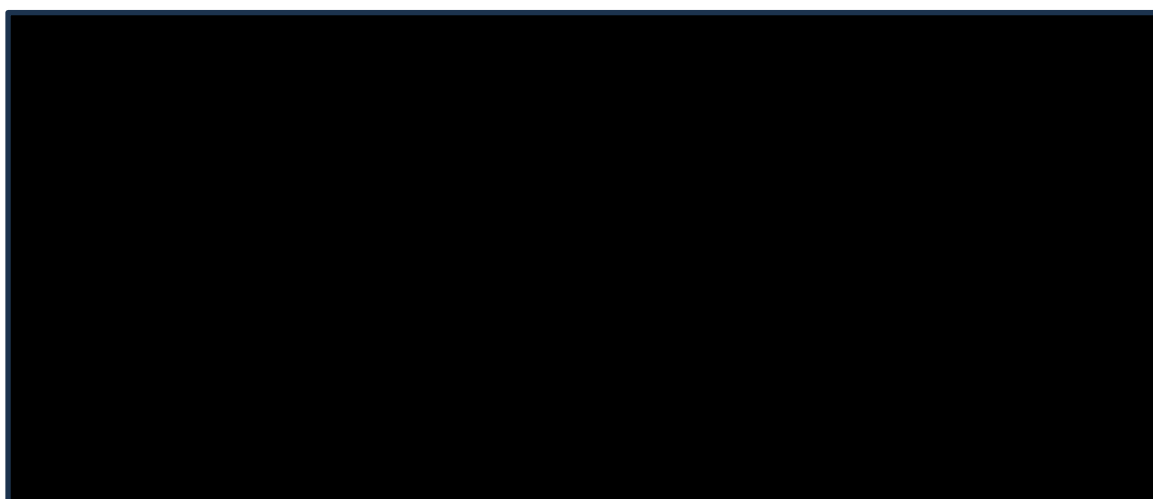
Finally, the reopened wound count is translated into area by sampling wound sizes from a normal distribution based on empirical data from the GEM-1 clinical trial. The baseline size of a reopened wound is assumed to follow a normal distribution with a mean of $\blacksquare$ cm² and a standard deviation (SD) of $\blacksquare$ cm². The EAG notes that the qnorm function was implemented using the standard error (SE = $\blacksquare$) instead of the standard deviation (SD = $\blacksquare$). As illustrated in Figure 11, use of the SE in place of the SD results in a substantially narrower normal distribution, despite the same mean value being used in both cases. This applies to both B-VEC and placebo arms.

Figure 10 Normal distributions with identical mean () and different SD

A) SD=



B) SD=



A key difference between treatment arms lies in the modelling of wound size enlargement after reopening. In the placebo arm, reopened wounds are assumed to grow substantially after they reappear. Based on GEM-1 data, reopened wounds treated with placebo were observed to reach a maximum average size of cm², which is approximately 4.45 times larger than the initial size. To reflect this, the model applies a multiplicative factor of 1 + 3.45 (i.e., 4.45) to the initially sampled wound size (mean , SD) in the placebo group. This increase is implemented as a one-time adjustment upon reopening, rather than a progressive enlargement over time. In contrast, wounds that reopen in the B-VEC arm are assumed to remain unchanged. The multiplier for enlargement in this case is set to 1 (i.e., no increase), meaning that the initially sampled size remains unchanged.

The total reopened area is capped to the cumulative previously closed area to prevent reopening more wounds than actually closed. This is equivalent to assuming that no patient can progress to a health state more severe than their baseline state.

3) Recurrent wounds becoming chronic

In the PLS model, a specific proportion of recurrent wounds are assumed to become chronic. The probability of becoming chronic was calculated as the probability of a recurrent wound remaining open for eight consecutive weeks. This is based on clinical evidence from Eng *et al.* (2021), which reported that wounds persisting beyond eight weeks do not typically heal and are classified as chronic. To operationalize this in the model, a weekly conversion probability is calculated as the likelihood that a wound fails to close for eight consecutive weeks, using the formula:

$$\text{Weekly conversion probability for BSC} = \frac{(1 - 14.17\%)^8}{1} \approx 29.45\%$$

$$\text{Weekly conversion probability for B-VEC} = \frac{(1 - 42.84\%)^8}{1} \approx 1.19\%$$

In the placebo arm, where it is estimated that 14.17% of the open area closes per week, the proportion of the original area open at week 8 is estimated to be 29.45%. This figure is then applied in the model as the percentage of recurrent wound area that becomes chronic each week. Conversely, in the B-VEC treatment arm, where the percentage of wound area closing each week is 42.54%, the chance of chronic conversion of wound area from recurrent to chronic drops significantly to about 1.19%. Once a recurrent wound becomes chronic in BSC arm, it no longer heals spontaneously in the simulation and contributes persistently to the total BSA affected by open wounds. However, in the B-VEC treatment arm, chronic wounds have the same rate of healing as recurrent wounds. The EAG critique on this aspect of the PLS can be found in Section 4.3.3.5.

4) Treated area

In the PLS model, the treated area refers to the surface area of open wounds that receive B-VEC treatment during a given week. This value is computed weekly and plays a critical role in determining both clinical outcomes (i.e., wound healing) and treatment-related costs (i.e., vial consumption). The process begins by summing the chronic and recurrent open wound areas to obtain the total open area. A patient is eligible for treatment if this area is greater than zero and if they are compliant that week, with compliance modelled stochastically (assuming 90% compliance). In response to clarification question B11, the company stated that mean compliance in the intention to treat population of GEM-3 was [REDACTED] and provided a scenario analysis using [REDACTED].

If the patient is compliant during the week, the model applies a treatment cap of 200 cm² per week, as specified in the B-VEC EMA SmPC. If the total open area exceeds this cap, only 200 cm² is treated. Within the treated area, chronic wounds are prioritised: the model first allocates treatment to chronic wounds up to their total open area, and any remaining capacity is then applied to recurrent wounds. The final treated area values including total, chronic, and recurrent, are stored weekly for each simulated patient and feed into subsequent calculations of wound closure, reopening, and vial use.

Reassigning health states

In the PLS model, health states are assigned weekly based on the patient's BSAP covered by open wounds (both chronic and recurrent). This classification reflects the severity of disease in patients with DEB. Four mutually exclusive health states are defined: very mild (0.0%–2.1% BSA open), mild (2.1%–5.0%), moderate (5.0%–25.0%), and severe ($\geq 25.0\%$). Each patient is dynamically reassigned to a health state, including their current one, every week according to the sum of their chronic and recurrent wound areas, expressed as total BSAP.

Estimating transition probabilities between health states

In the PLS model, transition probabilities are estimated empirically based on simulated changes in health states over time. Each patient is tracked weekly for a three-year period, and their health state, defined by the proportion of BSA affected by open wounds, is recorded every week. However, health state transitions were estimated for a period of up to 104 weeks (2 years) because transition patterns tend to stabilise within the first two years of simulation. Health state transitions are measured over fixed 13-week cycles, resulting in a total of 8 transitions per patient. For each 13-week cycle, the model captures whether a patient moved from one state to another (e.g., from moderate to severe) and aggregates these movements into 4×4 transition count matrices, stratified by age group (children, adolescents, adults) and treatment arm (B-VEC or placebo). These counts are then row-normalised to derive transition probabilities (i.e., to convert counts into probabilities). The probabilities were used as inputs for the Markov model.

To ensure statistical stability, the model checks for convergence by monitoring the maximum difference between successive transition matrices and their moving average, terminating early if the variation remains below a predefined threshold (0.01) across ten consecutive iterations. This was defined as the maximum value of the of all TP differences between the most recent TP matrix and the average of all predecessor TP matrices. The EAG notes that 188, 168, 148 patients were simulated for children, adolescents, and adults, respectively. Despite the convergence criteria being met, it is plausible that increasing the number of simulated patients could have reduced variability and improved the precision of the estimated parameters.

Vial calculation

Patient-level dynamics such as wound progression and B-VEC vial consumption continue to be simulated until 156 weeks (3 years). B-VEC vial use is calculated weekly by converting the treated wound area into the number of syringes needed, and subsequently into vials, using scenario-specific assumptions about syringe-to-vial ratios (4 or 4.5) and vial optimisation strategies (0.7, 0.8, and 0.9). In the company's base case, *“80% of patients were assumed to be participating in vial optimisation and sharing, whereby patients were able to maximise vial usage so that four (4) syringes were obtained from one (1) vial. The remaining 20% of patients were assumed to use one (1) entire vial regardless of the number of syringes required.”* The following formula was used to calculate the number of B-VEC vials used per week in the PLS model where the chance of the vial being shared was assumed to be 80%. For the remaining proportion, it was assumed a whole vial was consumed per patient regardless of the total BSA in need of treatment.

$$\begin{aligned} \text{Vials} = & \text{Optimization proportion} \times \left\lceil \frac{\text{Treated BSA}}{\text{Area per syringe} \times \text{Number of syringes per vial}} \right\rceil + (1 \\ & - \text{Optimization proportion}) \times \text{Indicator (1 if Treated BSA} > 0; \text{ otherwise 0)} \end{aligned}$$

The total wound area eligible for treatment is subject to a maximum treatable area of 200 cm², as specified in the B-VEC EMA SmPC. Each syringe is assumed to cover a fixed area of 50 cm². Vial consumption is then aggregated across simulation cycles and patient subgroups to inform annual vial usage.

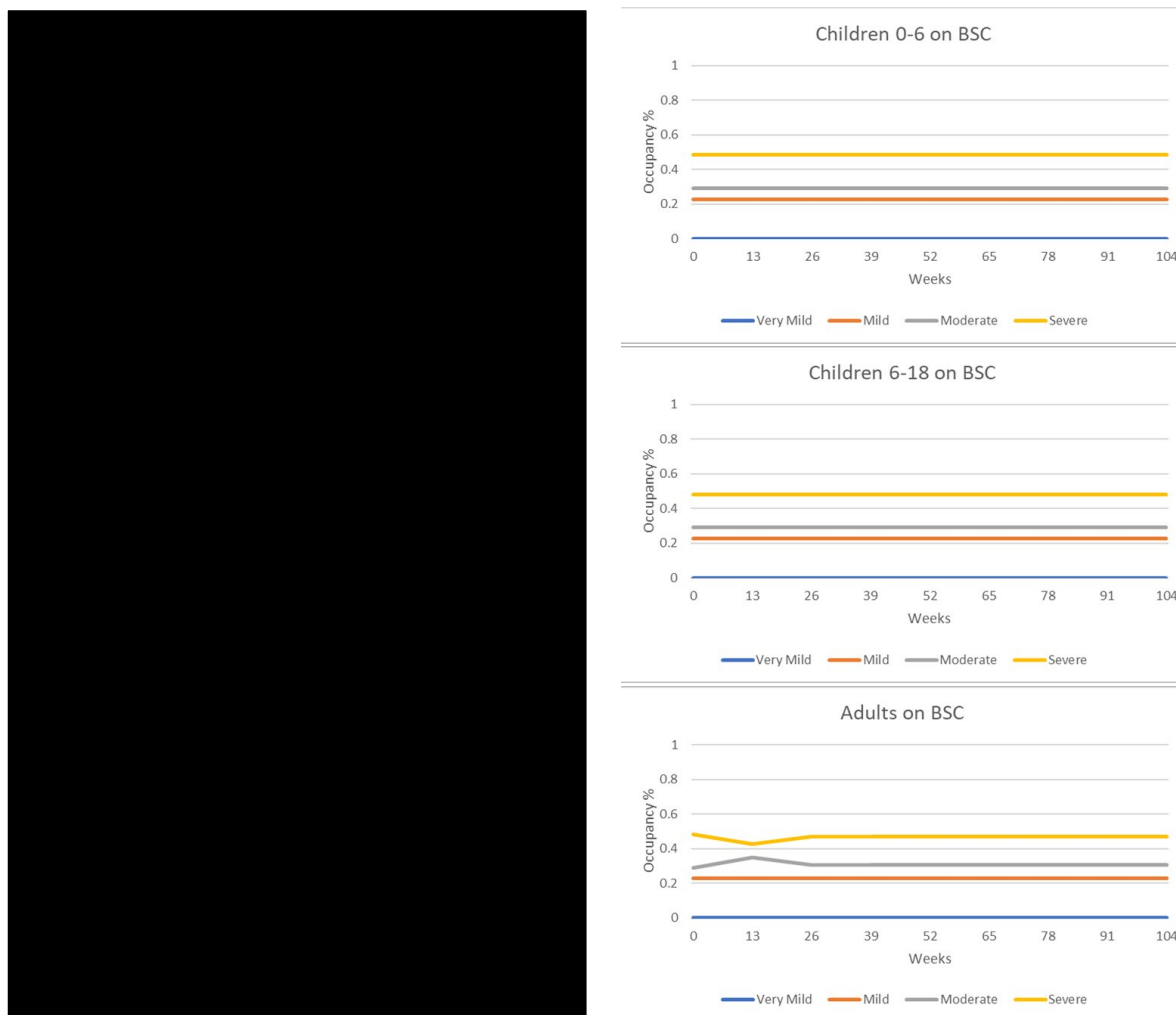
4.2.5.1.2 Transition matrices for B-VEC and BSC resulting from the PLS model

The PLS output resulted in eight transition matrices per treatment arm for each age group. For B-VEC, these were covering the first eight 13-week cycles (i.e., 2 years) where the last matrix from week 91 to 104 carries forward for the rest of the model as long as patients are on treatment. For BSC and patients who discontinued B-VEC, the output TP matrices were used only for the first two cycles in the model after which all patients remain in their respective health state for the model's time horizon.

Figure 12 shows the distribution of patients among the four health states during the first two years. The EAG notes that based on the TP matrices applied, all patients on B-VEC were assumed to occupy the very mild state after 39-91 weeks and stay there afterwards compared to 0% occupying this state in the BSC arm. This means that B-VEC is proposed to be nearly curative even after patients discontinue treatment (as discussed in Section 4.2.5.2, and critiqued

in Section 4.3.3.12). Patients in the BSC arm were assumed to stabilise in the starting health state with very minimal transitions allowed in the first two cycles for the adult group.

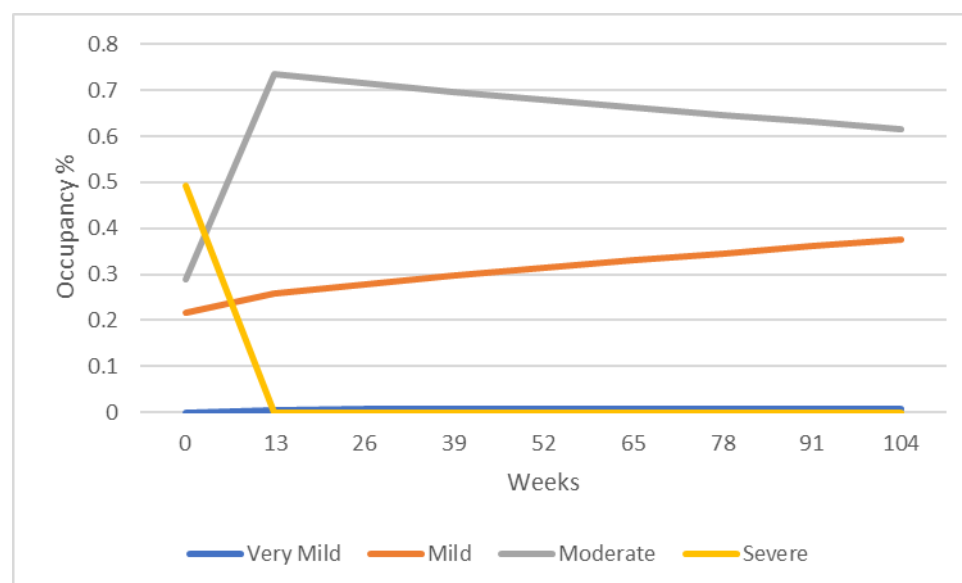
Figure 11: Health state occupancy in the first two years of the company's base case model for B-VEC and BSC



4.2.5.1.3 BBE effectiveness modelling

The TP matrices for BBE in the company's base case were derived from HST28 and converted to four-state matrices using the mapping algorithm presented in Table 29. The company also conducted scenario analyses where the TP matrices were estimated based on a model-based ITC as mentioned in Section 3.9, but as the model-based ITC estimates were not employed in the company's base-case analysis, they are not described in detail here (see 4.3.3.7 for a more detailed description and critique of the model-based ITC). Figure 13 shows the modelled health state occupancy in the first two years for BBE in the company's base case. The matrices did not differ by age group; hence the transitions were the same regardless of the age group.

Figure 12: Health state occupancy in the first two years of the company’s base case model for BBE



4.2.5.2 Treatment discontinuation

No discontinuations were observed for B-VEC in the GEM trials, so the company assumed that 1% discontinue B-VEC annually in their base case equating to 0.25% per cycle. For BBE, it was assumed that 8.3% would discontinue at 90 days (i.e., the first model cycle) followed by 1% annual rate.

When patients discontinue treatment, they are assumed to use the transition probabilities associated with BSC, which would mean that the patient stayed within the same health state, as the patients in BSC were assumed to have reached steady state by 26 weeks. This meant that patients discontinuing B-VEC did not return to their baseline health state despite this being the general pattern in patients receiving BSC. The EAG’s critique on the handling of treatment discontinuation can be found in Section 4.3.3.12.

4.2.5.3 Adverse events

The company did not include any cost or disutility associated with AEs stating that “*Considering that most AEs in the GEM trials were of low severity, no SAEs were related to B-VEC, and that patients served as their own control, utility decrements or HCRU/costs associated with AEs have not been included in the model*”.

4.2.5.4 Mortality

Section B.3.3.5 of the CS details the assumptions relating to mortality made in the modelling which differed by DEB subtype, health state and age subgroup. The company used the general population mortality to model mortality for all DDEB patients.

For RDEB patients, the company fitted exponential models to two sets of Kaplan-Meier (KM) data reported by Petrof *et al.* to estimate their mortality; one reported for all types of RDEB except severe and the second for severe RDEB cases.⁷ In response to clarification question B8, the company explained that “*the Exponential curve was selected for the model base case as it had the best statistical fit to the RDEB-Non-Severe curve*” and that it was also the preferred extrapolation fit for the severe curve because “*the curves in the publication by Petrof et al represent survival from birth.22 As patients enter the model at a later age (depending on the age subgroup), it would not be appropriate to use a parametric curve that does not represent a constant hazard of death,*” and that other “*alternatives are technically not appropriate.*”

The mortality risks that the company intended to apply across the different modelled patient groups are shown in Table 36. It can be seen that in the moderate and severe health states the company intended to apply lower mortality risks for RDEB patients starting treatment aged under 6 years old (highlighted by italics in Table 36). However, the EAG identified during its model verification that the data specified for ages 6 and over were inadvertently applied to all age categories.

Table 36: Sources of mortality according to health state, DEB subtype, and model start age (replicated from CS, Table 3.21)

	DDEB	RDEB	
		Enter model at age <6	Enter model at age ≥6
Very Mild	General population ⁴⁵	Average between general population and RDEB (except severe) ⁷	Average between general population and RDEB (except severe) ⁷
Mild	General population ⁴⁵	RDEB (except severe) ⁷	RDEB (except severe) ⁷
Moderate	General population ⁴⁵	<i>RDEB (except severe)^{7 a}</i>	Average of RDEB (except severe) ⁷ and RDEB severe ⁷
Severe	General population ⁴⁵	<i>Average of RDEB (except severe)⁷ and RDEB severe^{7 a}</i>	RDEB severe ⁷
DDEB=dominant dystrophic epidermolysis bullosa; RDEB=recessive dystrophic epidermolysis bullosa ^a these are the data the company stated that they had applied but in fact they incorrectly apply the same data in this age group as applied in patients aged ≥6 years old.			

4.2.5.5 Clinical manifestations

Eng *et al.* reported several clinical manifestations by DEB disease severity which the company included in the model as costs. The company assumed six of these manifestations could be improved or prevented by B-VEC which are: anaemia, complete or partial mitten deformity of foot, complete mitten deformity of hand, infections, osteoporosis, and SCC. When questioned about why non-cutaneous clinical manifestations (in addition to mortality and concomitant medications) not related to the wounds would differ between the health states considering that B-VEC acts only on the skin level, the company responded to clarification question B10 that “*although B-VEC does not directly address extracutaneous manifestations of DEB, it keeps patients in less severe health states, which are associated with a lower rate of these complications.*”

The company divided these into reversible (patients can develop more than once) and irreversible (for those that can develop only once in a lifetime) manifestations. Reversible manifestations included infections, anaemia, and osteoporosis, whereas foot and hand deformities and SCC were considered irreversible.

The publication reported the number of patients for three disease severities which were assumed to cover the mild, moderate, and severe states. For the very mild state, based on the company’s clinician input, it was assumed that no irreversible manifestations or osteoporosis would occur, and that infections and anaemia would have the same probability as with the mild state. The number of events reported for each irreversible manifestation were considered to occur over 21 years, and per-cycle rates were calculated, whereas these numbers were considered to directly represent the probabilities a patient could experience a reversible manifestation each cycle. Table 3.19 and 3.20 of the CS show the probabilities used for developing each of the six manifestations by health state.

4.2.5.6 Health-related quality of life for patients

EQ-5D data were collected in the GEM-3 trial. However, the company states that these were not used in the model because the percentage of patient’s BSA affected by wounds was not recorded in GEM-3, meaning that patients could not be allocated to health states. In addition, the sample size was small with only a small proportion of the ITT population (N=18/31) able to provide both a baseline and a follow-up EQ-5D measurement. This was largely because around a third of participants (N=10/31) were not asked to complete the EQ-5D because they were under 12 years old. The EAG agrees that the EQ-5D data collected in GEM-3 are not suitable for populating the company’s model. It would, however, have been useful if the average EQ-5D score across the GEM-3 cohort had been presented as this could have been used to validate the EQ-5D scores predicted by the model.

The company conducted a systematic review to identify published utility estimates in patients with DEB (methods reported in CS, Appendix E and included studies reported in CS, Appendix F). The company's review included 3 studies, of which two reported a preference-based measure of utility (EQ-5D). The third study reported an EB specific quality of life measure (QOLEB); however, no mapping algorithm was identified to allow utility values to be estimated from this non-preference-based HRQoL measure. Neither of the studies identified by the company which reported EQ-5D provided utilities stratified by BSAP affected by wounds. Therefore, these estimates could not be used to populate the model.

The company identified that the committee papers for HST28 included estimates of utility from the EASE study and it presents the set of utility values applied in the company's base case analysis in HST28 (CS, Table 3.24). These estimates were based on an ordinary least squared (OLS) regression applied to the 12-month data from the EASE OLE. As the values in HST28 were estimated for the six health states required for the HST28 model, the company then used their mapping algorithm (as presented in Section 4.2.4) to obtain utility values for the four health states in the company's model (see Table 29). These data are applied by the company in a scenario analysis only. A critique of the company's application of these data is provided in Section 4.3.3.2.

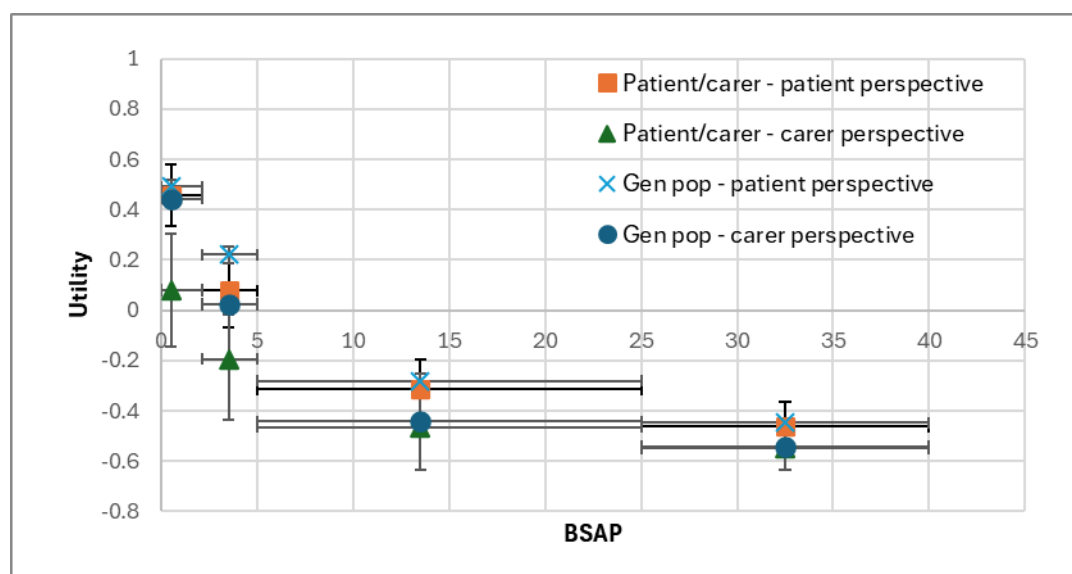
The CS describes an additional unpublished source of utility data from which the utility values applied in its base-case analysis were derived. This was a research project sponsored by the company, with the specific intention of generating utility values to inform its cost-effectiveness model. In response to the clarification request, the company provided a copy of a research report, by Lewis *et al.*,⁵² describing this project. This project is described in the CS as including two vignette studies and a discrete choice experiment (DCE). The two vignette studies involved the same vignettes being assigned scores using a generic HRQoL measure by a sample of the general population in the first instance, and by a sample of patients and carers in the second instance. In both vignette studies, the participants were asked to either provide responses from the 'patient perspective', where they imagined experiencing the health state themselves and completed the EQ-5D-3L accordingly, or from the 'caregiver perspective', where they imaged their child was experiencing the health state and they completed the EQ-5D-Y proxy version. Therefore, despite the latter being described as a 'caregiver perspective' in the vignette study, the participants were still being asked to value the health state of the person with DEB disease rather than the health state of the caregiver. For the patient perspective, utilities were generated from the EQ-5D-3L responses using UK preference weights. As no such set of preference weights exist for the EQ-5D-Y, the EQ-5D-3L value set was applied to the EQ-5D-Y responses.

The vignettes presented to the study participants were intended to represent each of the four modelled health states. The participants were presented with information on the BSAP affected by wounds, global pain, pruritus (itch), hours spent managing wounds and pain during wound management. The size of

wounds was illustrated using fruit-based imagery (e.g., an orange with a 6cm diameter). The Wong-Baker FACES pain rating scale was used to describe both itch and pain severity. The company notes that the scale was developed to measure pain and not itch, and it was adapted, with permission from the Wong-Baker Foundation, for the purposes of measuring itch. Other aspects of DEB, (e.g., mitten deformities, SCC, gastrointestinal complications), were not included in the vignettes as being either present or absent. The impact of these was instead explored in the separate DCE study. The EAG's clinical expert noted that wound healing, pain and itch are the three most important outcomes for patients suggesting that these were sensible areas for the vignettes to focus on. The adult and child vignettes are summarised later in Section 4.3.3 where the methods of the vignette study are further critiqued by the EAG.

The company's vignette studies provide four different estimates of utility for each health state (two different perspectives evaluated in two separate samples). These values are plotted in Figure 1 with the vertical error bars showing the 95% CI around the utility estimates and the horizontal error bars showing the BSAP range falling within the relevant health state. It can be seen that the estimates when taking the patient perspective are always higher than the estimates when taking the carer perspective; in the general population sample, Lewis *et al.* report that these differences are statistically significant. For the patient/carers estimates, the smaller sample size resulted in wider confidence intervals and the company did not report a comparison between the patient and carer perspective for the patient/carers sample. However, it is clear from the graph that for the very mild health state (BSAP 0 to 2.1%), the estimates for utility from the carer perspective have 95% confidence intervals that do not cross with the other three estimates and the value is numerically much lower. For the mild health state (BSAP 2.1% to 5%), the estimate from the caregiver perspective for the patient/carers sample is lower than the other estimates but the confidence intervals overlap. For the moderate and severe states, the estimates appear fairly consistent between the general population and the patient/carers sample for both perspectives. For the patient perspective, Lewis *et al.* provides a formal comparison between the general population and the patient/carers samples and state that there is no statistically significant difference, but a formal comparison is not provided for the carer perspective. The estimates from the general population sample using the patient perspective were applied to adult patients in the company's base case analysis and the estimates from the general population sample using the carer perspective were applied to people under the age of 18 (See Table 37). The methods of the vignette study and the company's choice of utilities is further critiqued in Section 4.3.3.3.

Figure 13 Vignette estimates of utility for the company's four health states and the BSAP range they apply across



The DCE is not used to inform the company's base-case analysis, although a scenario analysis incorporating some utility values from the DCE was presented in response to clarification request B12. This scenario analysis aimed to include utility decrements for clinical manifestations separately from any QALY gains associated with moving to a less severe health state. The company states in response to clarification question B12, that it did not include separate utility decrements for clinical manifestations in their base case to avoid the potential for double counting because the health states descriptions already integrated the typical clinical and functional burden associated with each severity level of DEB (e.g., wound area, pain, disability, infection risk).

Table 37: Patient utility values by health states as applied in the company's base-case and scenario analysis (adapted from CS, Table 3.22)

Health state	Vignette study - General population sample (base case) ^a	BBE NICE submission HST28 (scenario analysis)
Very mild		
0 to <6 years	0.44	0.56
6 to <18 years	0.44	0.56
≥18 years	0.49	0.56
Mild		
0 to <6 years	0.02	0.53
6 to <18 years	0.02	0.53
≥18 years	0.22	0.53
Moderate		
0 to <6 years	-0.44	0.34
6 to <18 years	-0.44	0.34
≥18 years	-0.28	0.34
Severe		
0 to <6 years	-0.54	0.08
6 to <18 years	-0.54	0.08
≥18 years	-0.45	0.08
BBE=birch bark extract; NICE= National Institute for Health and Care Excellence ^a Vignette study by Lewis <i>et al.</i> - patient perspective for adults valued using EQ-5D-3L, carer perspective for under 18-year olds valued using the EQ-5D-Y proxy version but with utilities estimated using the EQ-5D-3L UK preference weights.		

4.2.5.7 Health-related quality of life for carers

The company used caregiver utility estimates from HST28. The values applied were calculated from a vignette study conducted by the company for BBE. It used a time-trade-off (TTO) methodology to estimate utilities for three carer vignettes in a general population sample. Caregiver vignettes were restricted to health states 2, 4 and 6 but these were also assumed to apply to health states 1, 3, and 5 respectively. The company in HST28 assumed that the number of carers varied across the health states ranging from 0.5 in the least affected health states to 1.78 carers in the most affected health states. The company used its six to four state mapping algorithm (Table 32) to estimate the number of carers and the utility values for the four states in its model. During technical engagement for HST28, the company for BBE implemented an assumption that the full utility loss associated with caregiving would apply

only to the primary caregiver and that any additional caregivers would incur only 77% of the utility decrement applied to the primary carer. This assumption has been incorporated also into the company's four state model. The original data applied for the six health states in HST28 and the mapped values for the four health states in the company's model are shown in Table 38. Rather than applying a disutility per caregiver, the model estimates absolute QALYs gained across a maximum of 1.78 carers, which is shown in the final column of Table 38. In the post-clarification model, the company incorporated QALYs accrued for the carer after the death of the patient by applying the utility for the general population. In addition, all carer QALYs were adjusted for age-related declines in utility and carer mortality based on general population estimates. The values shown in Table 38 do not reflect these additional adjustments as they vary year by year as the caregivers age. The caregiver age at the start of the model was corrected from 16 to 43 in the post-clarification version of the model.

Table 38 Data used to incorporate carer QALYs

Health state	HST 28 company's base case	Number of carers	Proportion of utility loss for additional carers	Carer QALYs accrued per year in health state
HST28 data*				
HST 28 HS 1 (BSAP $\leq 4\%$)	0.85	0.5	NA	1.57
HST 28 HS 2 (BSAP 5-7%)	0.85	0.5	NA	1.57
HST 28 HS 3 (BSAP 8-10%)	0.76	1	NA	1.46
HST 28 HS 4 (BSAP 11-18%)	0.76	1	NA	1.46
HST 28 HS 5 (BSAP 19-24%)	0.64	1.78	77%	1.18
HST 28 HS 6 (BSAP $\geq 25\%$)	0.64	1.78	77%	1.18
Data applied in the company's four state cost-effectiveness model - estimated by applying the company's mapping algorithm (see Table 32) to the data above				
Very mild (BSAP 0 to 2.1%)	0.85	0.5	NA	1.57
Mild (BSAP 2.1% to 5%)	0.85	0.51	NA	1.57
Moderate (BSAP 5% to 25%)	0.72	1.26	77%	1.38
Severe (BSAP 25% to 40%)	0.64	1.78	77%	1.18
No carer decrement (general population utility)	0.89	1.78	Not applicable	1.59
* The 77% proportion for second caregivers was only applied in the post technical engagement model in HST28 and therefore the company did not apply this in their replication of the HST28 which was based on the model presented in the original CS.				

4.2.5.8 Costs and resource use

4.2.5.8.1 Treatment costs

B-VEC

The list price is £21,500 per one 2.5mL vial including the expedient required for the mix (no PAS or discounts were submitted). This represents the maximum weekly dose a patient can receive. One vial is used to constitute four syringes, each administered to a maximum open wound area of 50 cm². Each syringe contains 0.5mL of B-VEC (i.e., the four syringes use 2mL of the vial) with the remaining 0.5mL of B-VEC judged to be wastage due to potential remaining pockets of air during the preparation phase. The company explored a scenario where one syringe could be constituted from the waste of two vials amounting to nine syringes from two vials. Further details about constitution and administration are provided in Section 2.3.2.

One to four syringes can be administered weekly per patient depending on the total BSA needing to be treated. The company assumed in their PLS model that vial sharing (i.e., the four syringes shared among two or more patients) would happen 80% of the time. This was assumed based on B-VEC's chemical and physical in-use stability which the company states have been demonstrated for 7 days (when stored at 2-8°C). 70% and 90% vial sharing were explored as scenarios. Tables 3.26 and 3.27 of the CS presents the PLS 3-year outcomes for the number of vials used per cycle and the B-VEC acquisition cost per cycle respectively. The EAG's critique of the company's vial sharing assumptions can be found in Section 4.3.3.10.

Administration costs were determined based on a targeted literature review carried out by York Health Economics Consortium (YHEC). These included costs related to transport to pharmacy and storage, preparation, home delivery, application, and disposal. Application was assumed to require 30 minutes of a band 6 specialist nurse only at the first time as per the company's clarification response to B46 stating that *"the healthcare provider will use the first administration to train the patient or their caregiver(s) and that they can self-administer after that."*³¹ Hence, the overall cost for B-VEC administration applied in the model was £151.10 for the first administration and £122.91 for all subsequent administrations.

BBE

An acquisition cost of £275.33 per [23.4g] tube (list price) of BBE gel is applied in the model.¹¹ The company did not have access either to the number of tubes used per cycle nor the PAS discount for the product. A mean of 29.67 tubes per month was reported during the DBP of the EASE trial, so this consumption was applied in all health states in the base case for people on treatment to calculate costs

associated with BBE gel usage regardless of age or severity of the disease. Although the HST28 Committee papers mentions lower consumption in the EASE OLP, this was redacted.

As BBE gel is a topical treatment that can be administered easily by patients compared to B-VEC, there are no additional healthcare professional costs assumed to be associated with administration or monitoring.

BSC

No treatment costs were applied for BSC. Instead, people on BSC receive concomitant medication only.

4.2.5.8.2 Concomitant medication costs

Concomitant medications are the only drugs used in the BSC arm and are used as an add-on to B-VEC and BBE. These mainly include psychiatric medications, analgesics, anti-itch medications, laxatives, topical antibiotics, and Medi honey. Percentage of patients using each medication for the mild, moderate and severe states is presented in CS, Table 3.28 and sourced from Eng *et al.*,³³ with details of pack size and recommended dose referenced from BNF.¹⁷ Patients in the very mild state were assumed not to need these medications.

Resulting costs per cycle were £0.00, £39.57, £53.20, and £71.96 for the very mild, mild, moderate, and severe states respectively.

4.2.5.8.3 Clinical manifestation costs

Both reversible (multiple occurrences are allowed) and irreversible (only one occurrence is allowed) clinical manifestations are considered. Reversible manifestations include infections, anaemia, and osteoporosis; whereas irreversible manifestations comprises SCC, complete or partial mitten deformity of foot, and complete mitten deformity of hand. Costs per cycle were based on National Schedule of NHS costs 2023/24 as presented in CS, Table 3.29.^{1, 47}

4.2.5.8.4 Costs of outpatient visits

Frequency of outpatient visits were sourced from the structured expert elicitation conducted by the submitting company in HST28. 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. These were mapped to the four health states of the current model resulting in a

monthly frequency of 0.28, 0.30, 0.53, and 0.83 for the very mild, mild, moderate, and severe states respectively.

The cost of an outpatient visit was sourced from Personal Social Services Research Unit (PSSRU) (£137 per session), and was inflated to £146.63 using the consumer price index for 2022/2023.⁴⁸

4.2.5.8.5 Costs of dressing changes and associated formal care

The largest component of costs was associated with the cost of wound dressing which was reported by Pillay *et al.*⁵³ to be £45,884 annually per patient with RDEB. The company adopted the same assumptions as applied in HST28 that the number of dressings required would increase as the severity of EB increased. HST28 CS then used the results from the structured expert elicitation (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 was the inflated average from Pillay *et al.* used for HST28.¹¹ After mapping to the four health states of the current model and further inflating using the consumer price index for 2022/2023,⁴⁸ the resulting total per cycle (i.e., 3-monthly) costs are £2,699, £3,816, £13,980, and £27,378 for the very mild, mild, moderate, and severe states respectively. The company's model further halves the costs for the very mild state to £1,350.

Similarly, the company's base case derives the monthly formal carer hours spent changing dressings from the SEE conducted by the company for BBE HST28. After mapping to the four health states of the current model, the resulting monthly hours are 0.21, 0.36, 10.09, and 30.24 for the very mild, mild, moderate, and severe states respectively. Assuming that the cost associated with formal care to be £58.00 per hour from Jones *et al.*⁴⁸ (which is the cost of a band 6 hospital-based nurse) results in total costs of £36, £63, £1,750, and £5,244 for the very mild, mild, moderate, and severe states respectively per cycle (i.e., 3-monthly).

A summary of the costs by health state per cycle is presented in Table 39. 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 equally to B-VEC, BBE and BSC.

Table 39: Summary of health state costs per cycle

Health state	Dressing costs (£)	Dressing changing costs associated with nurses (£)	Outpatient costs (£)	Total costs (£)
Very mild	1,350	36	123	1,509
Mild	3,816	63	133	4,012
Moderate	13,980	1,750	232	15,962
Severe	27,378	5,244	364	32,985

4.2.6 Severity modifier

The company's severity modifier calculation for their original pre-clarification model is provided in CS, Section 3.6. The CS provides no information on how the lifetime QALYs for people without the condition has been calculated. Neither does it state what the average age was for the cohort modelled. The modelled cohort is separated into three age subgroups and the starting ages for these subgroups and distribution of the cohort across these subgroups is based on GEM-3 data. The EAG calculated the weighted average of age across these three subgroups to be 17 years. This seemed reasonable as the median age reported for the GEM-3 cohort was 16 years. The male proportion of the cohort in GEM-3 was 64.5%. The EAG used the Schneider *et al.* tool to calculate the expected QALYs in the general population for a starting age of 17 years assuming 64.5% of the cohort are male.⁵⁴ This gave a figure of 23.15 QALYs which matched the estimate provided by the company. The company's model estimates negative QALYs for patients receiving either BSC or BBE in its post clarification base case. This results in a proportional QALY shortfall that is greater than 100%, meaning that DEB meets the requirement for the maximum severity modifier of 1.7 to be applied under the company's base case regardless of whether BBE or BSC is considered the current standard of care.

However, the severity modifier is dependent on several factors including the utility values applied. In the company's scenario analysis using utility values from HST28, the lifetime expected QALY gain is positive in both the BSC and BBE arms. As the size of the absolute QALY shortfall is between 12 and 18 QALYs in this scenario when using either BSC or BBE to represent the current standard of care, this scenario analysis would imply a shortfall multiplier of 1.2. Based on this, the EAG considers that the appropriate QALY shortfall multiplier is uncertain and is dependent on the choice of utility values chosen. The QALY shortfall calculation for the EAG's preferred scenario is presented in Section 4.4.3.

Table 40 QALY shortfall calculation when using either BSC or BBE as comparator for the company's base case and their scenario analysis using HST28 utility values (estimated by the EAG from the company's post clarification model)

Measures	Company base case vs BSC	Scenario using HST28 utilities vs BSC	Company base case vs BBE	Scenario using HST28 utilities vs BBE
QALYs without the disease (discounted)	23.15	23.15	23.15	23.15
QALYs with the disease (discounted)	-4.87	5.57	-2.07	9.37
Absolute shortfall	28.02	17.58	25.22	13.78
Proportional shortfall	1.210	0.759	1.089	0.595
QALY weight	1.7	1.2	1.7	1.2
QALY=quality-adjusted life-years; WTP=willingness to pay				

4.2.7 Model validation and face validity check

4.2.8 Cost effectiveness results

The probabilistic and deterministic results presented in this section are based on the updated version of the company's model submitted in response to the clarification process.

Table 41 presents the central cost-effectiveness estimates from the probabilistic (1,000 iterations) and deterministic models comparing B-VEC with BSC. B-VEC was associated with an incremental gain of 22.09 QALYs and ██████████ making it dominant over BSC. The total costs were £████████ for B-VEC and £████████ for BSC. The deterministic model produced similar findings, with B-VEC providing an additional 22.47 QALYs and resulting in ██████████ relative to BSC. In this analysis, total costs were £████████ for B-VEC and £████████ for BSC. B-VEC was therefore also dominant under the deterministic base case.

Table 41: Company's base-case results (generated by the EAG based on the company's post clarification model)

Option	Absolute outcomes by treatment arm			Incremental outcomes for B-VEC versus BSC			ICER (£/QALY)
	LYGs*	QALYs	Costs	LYGs	QALYs	Costs	
Probabilistic model (1000 iterations)							
B-VEC	61.99	51.26	████████	15.40	22.09	████████	B-VEC dominates
BSC	46.59	29.17	2,016,841				
Deterministic model							
B-VEC	61.99	51.34	████████	16.29	22.47	████████	B-VEC dominates
BSC	45.70	28.87	2,011,845				

*Undiscounted

Abbreviations: ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year

The scatter plot (Figure 15), generated by the EAG running the probabilistic analysis for the company's base-case, showed that most of PSA iterations resulted in lower costs for B-VEC versus BSC (██████) and all resulted in greater QALYs. The cost-effectiveness acceptability curve suggests that the probability that B-VEC generates more net benefit than BSC at willingness-to-pay thresholds below £30,000 is ██████%.

Figure 14: Cost-effectiveness plane, B-VEC versus BSC

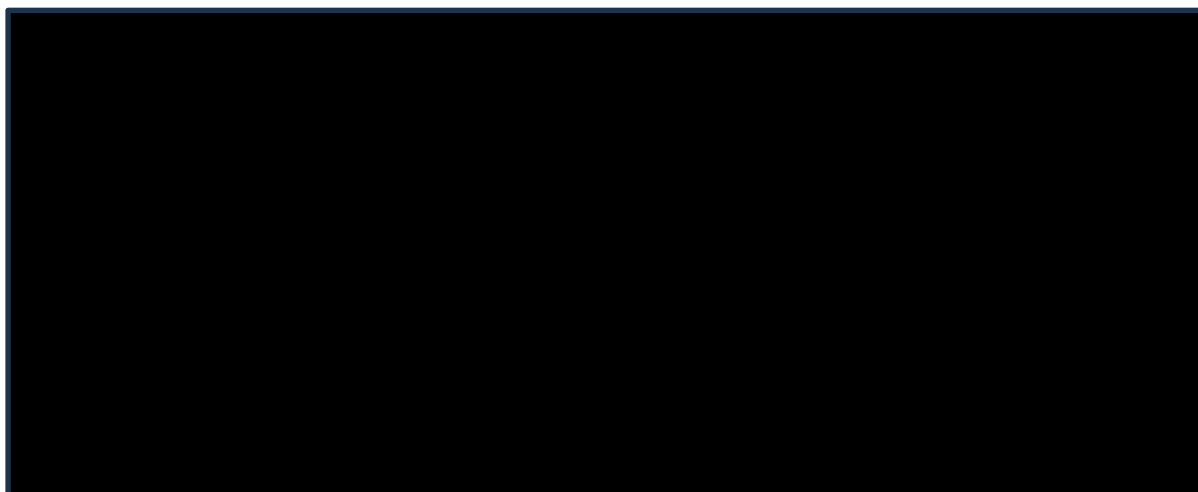


Table 42 presents the cost-effectiveness results from the probabilistic (1,000 iterations) and deterministic models comparing B-VEC with BBE. B-VEC generated 16.19 additional QALYs and ██████ relative to BBE, resulting in B-VEC being dominant. In the deterministic model, B-VEC was associated with an incremental gain of 16.43 QALYs and ██████ compared with BBE. B-VEC was therefore also dominant under deterministic assumptions.

Table 42: Company's base-case results (generated by the EAG based on the company's post clarification model)

Option	Absolute outcomes by treatment arm			Incremental outcomes for B-VEC versus BBE			ICER (£/QALY)
	LYGs*	QALYs	Costs	LYGs	QALYs	Costs	
Probabilistic model (1000 iterations)							
B-VEC	61.99	51.26	██████████	7.57	16.19	██████████	B-VEC dominates
BBE	54.41	35.07	3,047,728				
Deterministic model							
B-VEC	61.99	51.34	██████████	7.96	16.43	██████████	B-VEC dominates
BBE	54.02	34.91	3,042,222				

*Undiscounted

Abbreviations: ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year

The scatter plot (Figure 16), generated by the EAG running the probabilistic analysis for the company's base-case, showed that all PSA iterations resulted in lower costs and greater QALYs for B-VEC versus BBE. The cost-effectiveness acceptability curve suggests that the probability that B-VEC generates more net benefit than BSC at willingness-to-pay thresholds below £30,000 is ████%.

Figure 15: Cost-effectiveness plane, B-VEC versus BBE

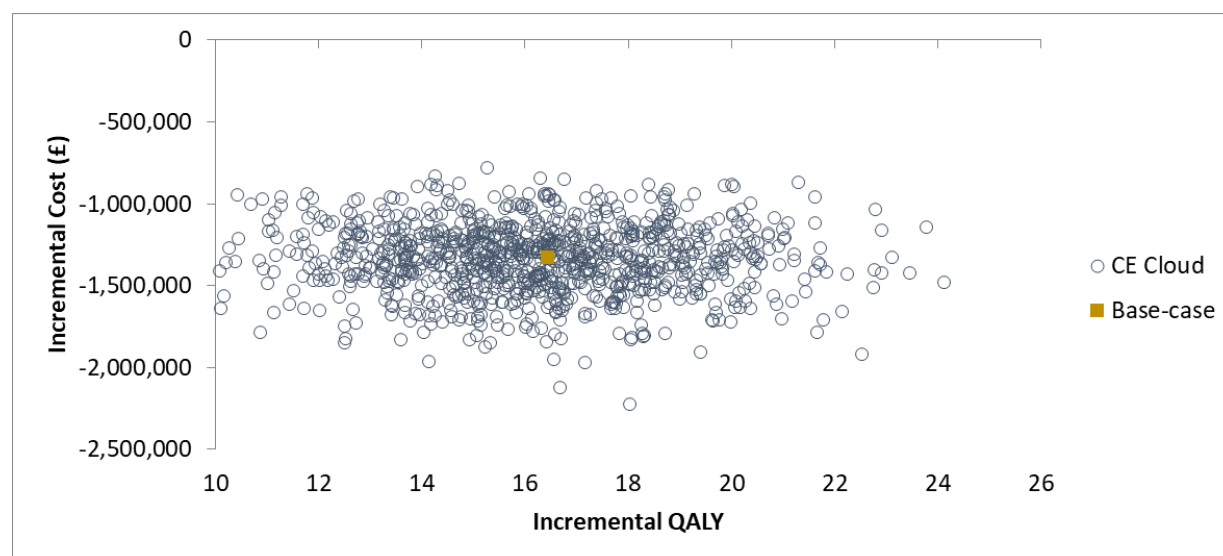


Table 43 presents the disaggregated outcomes for the deterministic model in terms of costs accrued by different types of resource use and LYs / QALYs accrued in different health states, as extracted by the EAG from the CS model. The differences in costs are primarily driven by the higher clinical manifestation and bandage costs associated with the more severe states. This offsets the drug costs associated with B-VEC and leads to B-VEC being ██████ even compared to BSC. This is evident with LYs and QALYs as the model suggests that patients on B-VEC accrue most of their health benefit in the very mild state, which benefits the carers too.

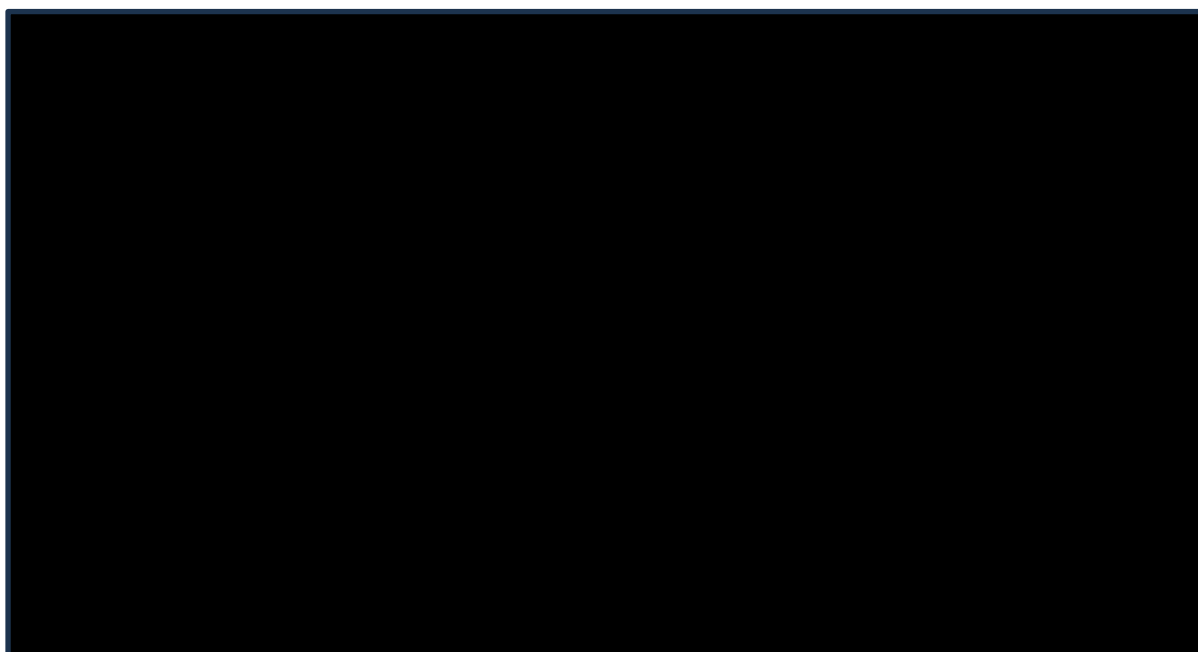
Table 43: Base case disaggregated outcomes for the post-clarification company's deterministic model

	B-VEC	BBE	BSC
Disaggregated costs (discounted)			
Drug costs (acquisition and administration)	██████████	£1,723,797	£0
Concomitant medication costs	£185	£4,310	£4,728
Clinical manifestation costs	£160,595	£327,236	£366,801
Monitoring costs	£12,850	£17,333	£21,467
Bandage costs	£204,145	£969,545	£1,618,848
Total	██████████	£3,042,222	£2,011,845
Disaggregated LYs (Undiscounted)			
Very mild health state	61.06	0.58	0.00
Mild health state	0.11	23.99	13.48
Moderate health state	0.39	29.39	14.45
Severe health state	0.43	0.06	17.76
Total	61.99	54.02	45.70
Disaggregated QALYs (Discounted)			
Very mild health state	11.25	0.11	0.00
Mild health state	0.01	1.74	0.98
Moderate health state	-0.11	-3.88	-1.91
Severe health state	-0.18	-0.03	-3.94
Carers	40.37	36.98	33.74
Total	51.34	34.91	28.87
<i>B-VEC - beremagene geperpavec; BBE - birch bark extract; BSC - best supportive care; LYs - life years; QALYs - quality-adjusted life years</i>			

4.2.9 Company's deterministic sensitivity analyses

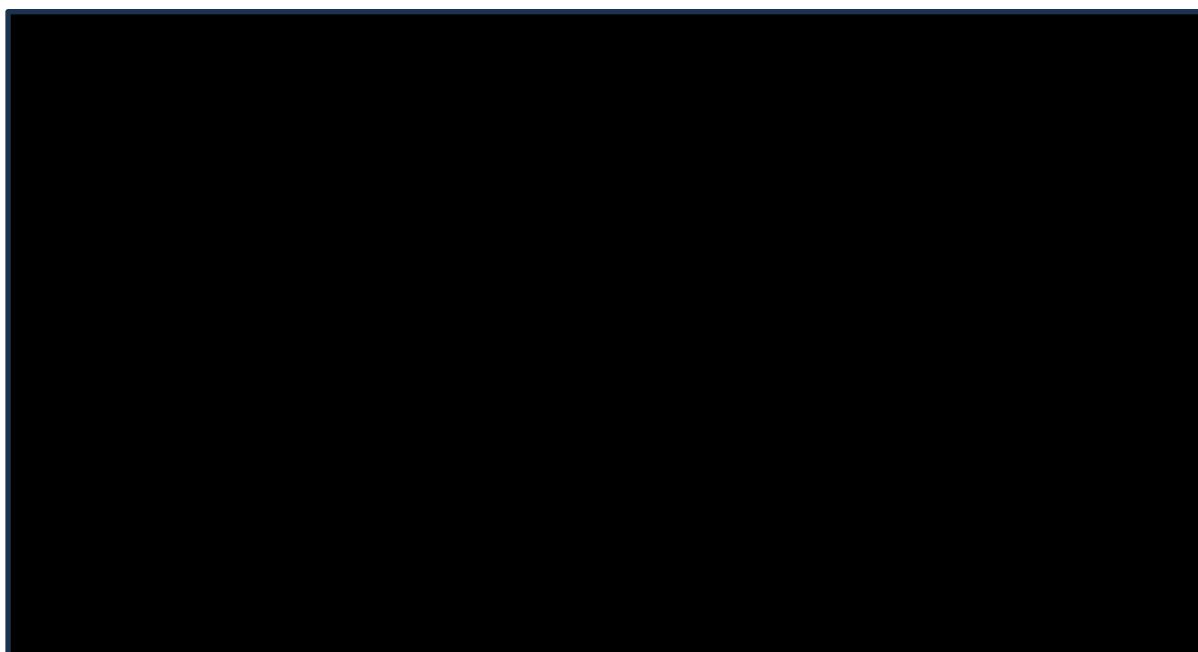
In their clarification response, the company presented a corrected tornado diagram using incremental net monetary benefit (INMB) as the measure of cost-effectiveness. The INMB was calculated by assuming that each QALY is worth £51,000, with the value of a QALY calculated as the upper limit of NICE's typical threshold range (£30,000) multiplied by a 1.7 severity modifier (see Section 4.6). All of the deterministic sensitivity analyses (DSA) provided in the tornado diagram show that B-VEC dominates BSC and BBE (Figure 17 and Figure 18).

Figure 16: Tornado diagram for deterministic sensitivity analyses (B-VEC versus BSC)



Threshold for NMB (£) = 51,000

Figure 17: Tornado diagram for deterministic sensitivity analyses (B-VEC versus BBE)



Threshold for NMB (£) = 51,000

4.2.10 Company's scenario analyses

Most of the deterministic scenario analyses provided by the company had a ICER below £0 (dominant) when compared with BSC (Table 44). Two ITC scenarios (ITC scenarios 2 and 4) showed B-VEC to be more effective but also more costly than BSC, yielding ICERs of £[REDACTED] and £[REDACTED]. In scenarios

involving assumptions on wound closure rate and treatment duration, B-VEC incurred higher costs compared with BSC.

Otherwise, all of the deterministic scenario analyses provided by the company had a ICER below £0 (dominant) when compared with BBE.

Table 44: Company's scenario analyses, deterministic versus BSC (adapted from clarification response, Table 13)

Scenario	B-VEC vs BSC		
	ΔQALYs	ΔCosts (£)	ICER (£)
Updated company base case	22.47	████████	dominant
B-VEC vial optimization: 9 syringes per two vials (maximum of 4 syringes per patient).	22.47	████████	dominant
Proportion of patients to consider for vial optimization: 90%	22.47	████████	dominant
Proportion of patients to consider for vial optimization: 70%	22.47	████████	dominant
B-VEC discontinuation: 9.68% per year in the first year, then 1% per year onwards	19.36	████████	dominant
Utility values for patients: BBE NICE submission	14.27	████████	dominant
Discounting for costs and outcomes set to 1.5%	36.75	████████	dominant
████ compliance	22.42	████████	dominant
Inclusion of utility decrements for clinical manifestations	23.16	████████	dominant
ITC scenario 1 - Baseline health-state distribution derived from Bruckner <i>et al.</i>; - BBE transitions through Bucher ITC - B-VEC and BSC transitions from the patient-level simulation	22.47	████████	dominant
ITC scenario 2 - Baseline health-state distribution derived from Bruckner <i>et al.</i>; - BBE and BSC health-state transitions from the replicated HST28 model. - B-VEC transitions through Bucher ITC	20.56	████████	████████
ITC scenario 3 - Baseline health-state distributions based on HST28 model; - BBE transitions through Bucher ITC - B-VEC and BSC transitions from the patient-level simulation	18.77	████████	dominant
ITC scenario 4 - Baseline health-state distributions based on HST28 model; - BBE and BSC health-state transitions from the replicated HST28 model. - B-VEC transitions through Bucher ITC	18.96	████████	████████
5.75% weekly reduction in open area treated with placebo	22.52	████████	dominant
5.75% weekly reduction in open area treated with placebo and 33.53% weekly reduction in open area treated with B-VEC	22.06	████████	████████
B-VEC duration of closure: 240 days	22.47	████████	dominant

Scenario	B-VEC vs BSC		
	ΔQALYs	ΔCosts (£)	ICER (£)
Updated company base case	22.47		dominant
B-VEC duration of closure: 345 days	22.48		dominant
B-VEC duration of closure: 103 days	22.43		
B-VEC duration of closure: 150 days	22.46		

Table 45: Company's scenario analyses, deterministic versus BBE (adapted from clarification response, Table 13)

Scenario	B-VEC vs BBE		
	ΔQALYs	ΔCosts (£)	ICER (£)
Updated company base case	16.43		dominant
B-VEC vial optimization: 9 syringes per two vials (maximum of 4 syringes per patient).	16.43		dominant
Proportion of patients to consider for vial optimization: 90%	16.43		dominant
Proportion of patients to consider for vial optimization: 70%	16.43		dominant
B-VEC discontinuation: 9.68% per year in the first year, then 1% per year onwards	13.32		dominant
Utility values for patients: BBE NICE submission	7.24		dominant
Discounting for costs and outcomes set to 1.5%	26.65		dominant
compliance	16.37		dominant
Inclusion of utility decrements for clinical manifestations	16.97		dominant
ITC scenario 1 - Baseline health-state distribution derived from Bruckner <i>et al.</i>; - BBE transitions through Bucher ITC - B-VEC and BSC transitions from the patient-level simulation	20.23		dominant
ITC scenario 2 - Baseline health-state distribution derived from Bruckner <i>et al.</i>; - BBE and BSC health-state transitions from the replicated HST28 model. - B-VEC transitions through Bucher ITC	16.59		dominant
ITC scenario 3 - Baseline health-state distributions based on HST28 model; - BBE transitions through Bucher ITC - B-VEC and BSC transitions from the patient-level simulation	15.07		dominant
ITC scenario 4 - Baseline health-state distributions based on HST28 model; - BBE and BSC health-state transitions from the replicated HST28 model. - B-VEC transitions through Bucher ITC	14.74		dominant
5.75% weekly reduction in open area treated with placebo	16.44		dominant
5.75% weekly reduction in open area treated with placebo and 33.53% weekly reduction in open area treated with B-VEC	15.98		dominant
B-VEC duration of closure: 240 days	16.43		dominant
B-VEC duration of closure: 345 days	16.44		dominant
B-VEC duration of closure: 103 days	16.40		dominant
B-VEC duration of closure: 150 days	16.42		dominant

4.3 Critique of company's submitted economic evaluation by the EAG

4.3.1 Model verification

The EAG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying assumptions upon which this was based. These included:

- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the EAG.
- Examination of the correspondence between the company's executable models and their description in the CS and the company's clarification response.
- Replication of the base-case results, PSA, DSAs and scenario analyses presented within the CS using the company's executable model.
- Where possible, checking the parameter values used in the company's model against their original data sources.
- Comparison of the model structure and data sources against the model used to inform HST28.
- The use of expert clinical input to judge the credibility of the company's economic evaluation and the assumptions underpinning the model.

A few minor errors in the post-clarification updated model were identified by the EAG. These are described in Section 4.3.3.1. The EAG considers the company's updated version of the model to be generally well programmed despite these errors, however the version of the model used by the EAG was different as explained in Section 4.4.2.

4.3.2 Adherence of the company's model to the NICE reference case

The extent to which the company's submission adhere to the NICE Reference Case is summarised in Table 46.

Table 46: Adherence of the company's economic analyses to the NICE Reference Case

Element	Reference case	EAG comments (a ✓ denotes the company's analyses are in line with the reference case)
Population	The scope developed by NICE	✓
Intervention	As listed in the scope developed by NICE	✓
Comparator(s)	As listed in the scope developed by NICE	✓
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	✓
Perspective on costs	NHS and PSS	✓

Element	Reference case	EAG comments (a ✓ denotes the company's analyses are in line with the reference case)
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	✓
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	✓
Synthesis of evidence on health effects	Based on systematic review	The company conducted a systematic review and identified relevant studies for both interventions and comparator, but the B-VEC studies did not provide the data required to populate the model and instead the company simulated the outcomes needed to estimate health effects for B-VEC versus BSC.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	✓ But the utility source preferred by the company was based on a general population sample providing EQ-5D scores for a set of vignettes. The EAG disagrees that it is appropriate to use these estimates from vignettes given that EQ-5D data are available from the EASE OLE study.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	A severity weighting of 1.7 has been applied.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	✓
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	✓

4.3.3 EAG Critique of the modelling performed by the company

Box 1 summarises the main issues identified within the EAG's critical appraisal of the company's economic analyses.

Box 1 Summary of the main issues identified within the company's health economic model

- (1) Errors identified in the implementation of the model
- (2) Choice of utility data source (Key Issue 3)
- (3) Methods used in the company's utility vignette study (related to Key Issue 3)
- (4) PLS reliance on GEM-1 (Key Issue 4)
- (5) Validity of PLS outputs and related assumptions (Key Issues 4 and 5)
- (6) Validity of mapping algorithm between the different state structures (Key Issue 6)
- (7) ITC implementation in the model (related to Key Issues 2 and 6)
- (8) B-VEC impact on clinical manifestation (Key Issue 7)
- (9) Mortality extrapolations (Key Issue 7)
- (10) B-VEC vial optimisation (Key Issue 9)
- (11) Concomitant medications
- (12) Health states following discontinuation of B-VEC or BBE (Key Issue 8)
- (13) Clinical plausibility of assuming a "near cure" status
- (14) The appropriate baseline distribution of the cohort across the health states

4.3.3.1 Errors identified in the implementation of the model

The EAG identified a number of implementation errors in the updated model version post-clarification:

- Bruckner *et al.* reported results for 31 DDEB and 53 RDEB cases in total (sum of 33 patients and 51 carers). However, the company's model double counted the number of patients to end up with a total of 117 cases.
- In the PLS, the company used the SE instead of the SD to characterise the normal distribution of the size of a reopened wound.
- When age-adjusting the utilities for carers, the utility should be multiplied by a factor equal to the utility of general population for the carers current age divided by the utility of general population for the carers age at the start of the model. However, the calculation refers to the utility for carers at the start of the model for both numerator and denominator resulting in no age-adjustment of carer utility. This was corrected in the EAG version of the economic model.

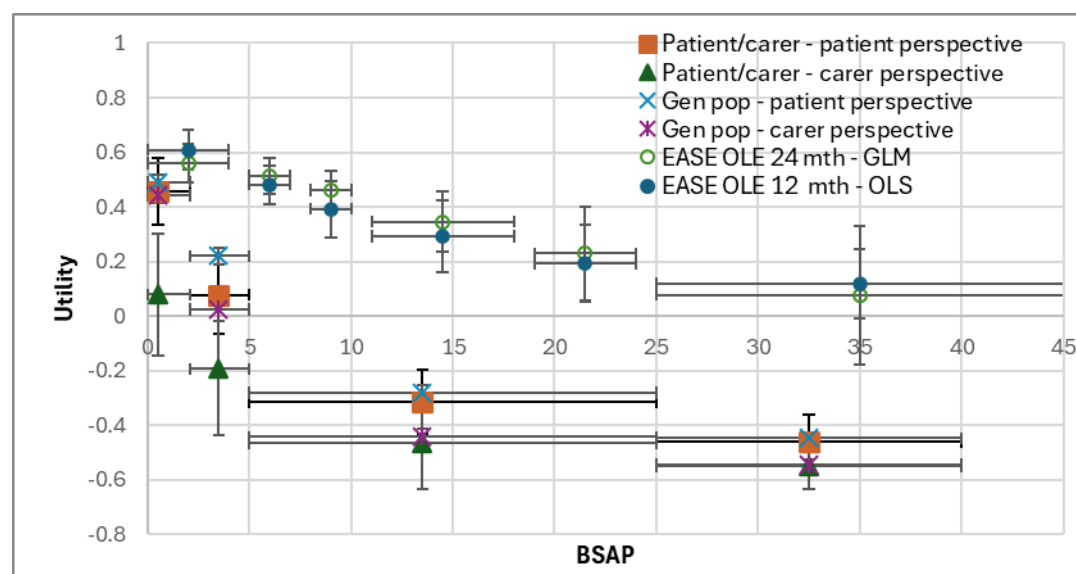
4.3.3.2 Choice of utility data source

The hierarchy reported in the NICE methods guide and the supporting NICE Decision Support Unit (DSU) report by Rowen *et al.* clearly state that vignettes studies should only be used in situations where suitable EQ-5D estimates obtained from a relevant patient sample are not available or the EQ-5D is not suitable.^{55, 56} The CS makes no claim that the EQ-5D is not suitable in this case and has used the EQ-5D-3L within the vignette study suggesting that it considers it suitable in this population. Therefore, the

only rationale for using a vignette study would be that EQ-5D data measured in a relevant cohort of patients are either not available or the available data are insufficient for some reason. This does not appear to be a reasonable argument given the availability of EQ-5D estimates from the EASE OLE, and their acceptance by the appraising committee in HST28. The CS only presents EQ-5D estimates from the EASE OLE for the 6 states used in the HST28 economic model, and then proceeds to apply a mapping technique to obtain estimates that relate to the four health states in the company's economic model. However, the utility values in HST28 were generated using regression modelling meaning that the company could determine relevant utility values for any BSAP score. This negates any argument that the available EQ-5D data are insufficient due to the definition of the health states not being aligned. The EAG therefore considers that the vignette study conducted by the company is not justified given the estimates available from the EASE OLE study. The EAG has a strong preference for using the estimates from the EASE OLE study as these comply with the NICE reference case, ensuring comparability across appraisals, and these estimates would take precedence over vignette-based estimates based on the hierarchy presented in the NICE manual.

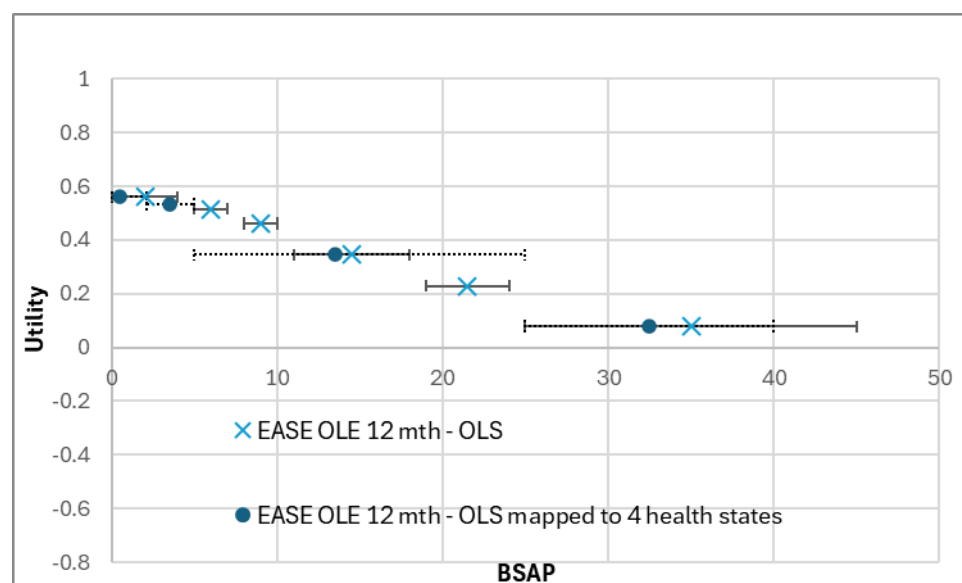
Figure 19 allows a comparison between the values from the company's vignette study and the values obtained from the sample of patients recruited to the EASE OLE. The range of BSAP scores falling within the six health states used in HST28 is shown using horizontal error bars. The exact upper limit of health state 6 is not known as it is described as BSAP >25%. It has been represented as ranging from 25% to 45% in this figure as the plots of utility against BSAP provided in the committee papers for HST28 suggest that BSAP values went up to maximum of around 45%. It can be seen from Figure 19 that the estimates from the EASE OLE study are higher than those obtained in the company's vignette. Although the company presents one set of EQ-5D data from the EASE OLE which they applied in a scenario analysis (CS, Table 3.22), the EAG notes that this is only one of several sets of utility estimates presented in the committee papers for HST28. The EAG for HST28 preferred an alternative set of utility estimates obtained by applying a Generalised Linear Model (GLM) model to the 24-month data from the EASE OLE, which was later accepted by the company in HST28 as a more appropriate source during technical engagement and was later endorsed by the committee. The values obtained from the 12-month OLS and 24-month GLM regression are presented in Figure 19 for comparison.

Figure 18: Utility values for the four health states in the company's vignette and the 6 health states in HST28 estimated from the EASE OLE



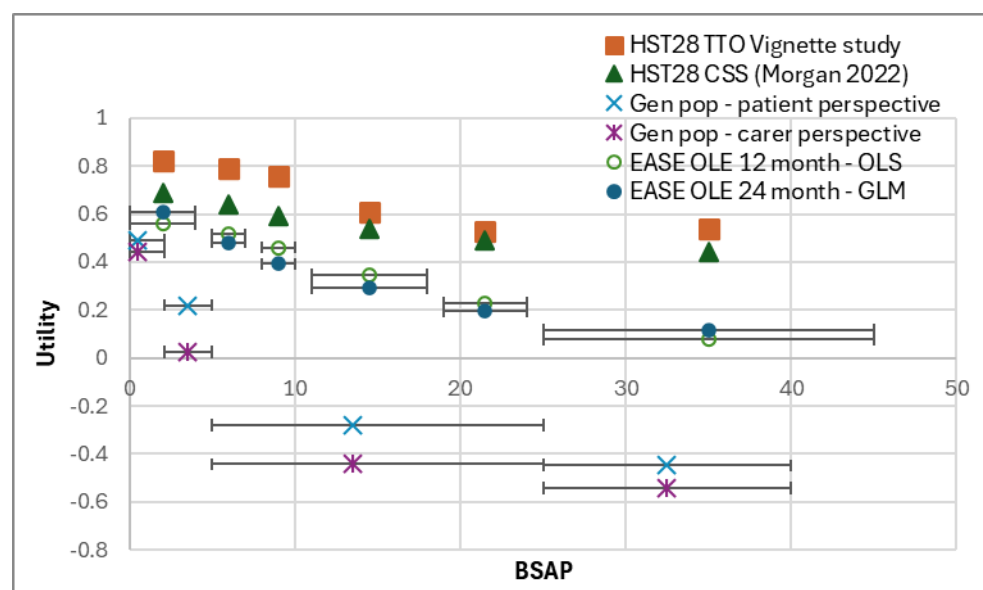
In order to apply the estimates from the EASE OLE in the company's four health state model, the company applied a mapping to determine the proportion of patients from each of the six HST28 health states falling within each of the company's four health states. However, this mapping was not based on any presumed distribution of BSAP and instead relied on obtaining estimates by trial and error that gave equivalent cost-effectiveness results (see Table 32). Figure 20 shows the original utility values for the HST28 health states and the mapped values applied by the company when using the data from HST28 in a scenario analysis. It can be seen that the BSAP range for the moderate health state spans the BSAP range for health states 2 to 5 from HST28. However, the mapping (see Table 32) assumes 0% occupation of HS2 and similar non-zero proportions are assumed to fall in health states 3 to 5. This means that the average utility applied in the moderate state (BSAP 5% to 25%) is similar to the utility for health state 4 in HST28 (BSAP 11% to 18%). Figure 19 demonstrates that the company's four state model does not distinguish between any utility differences that may occur within a BSAP range of 5% to 25%, whilst the HST28 six health state model has a substantial range of utility falling within the same BSAP range.

Figure 19 Utility values from EASE OLE and the mapped values applied as a scenario analysis in the company's four health state model



The company does not mention two other sources of utility data described in the committee papers for HST28. These were unpublished data available from a cross-sectional study, which has since been reported in abstract form by Morgan *et al.*,⁵⁷ and an unpublished vignette study sponsored by the company for BBE, although the company does rely on the HST28 vignette study when later obtaining estimate for carers. The EAG is concerned that the company's systematic review of utility studies did not identify the abstract by Morgan *et al.* and the poor reporting of this review makes it difficult to identify the reason for this omission. The company stated that 22 of the 37 studies included in the non-clinical SLR, reported data on HRQoL or utility but only three publications were considered directly relevant to the decision problem. However, no further details are provided on why the remaining papers were considered not directly related. Therefore, the EAG cannot verify if the Morgan *et al.* abstract was identified but classified as not relevant to the decision problem or if the search strategy was not comprehensive enough to identify this abstract. The EAG cannot therefore be confident that the company's SLR of utilities has comprehensively identified all relevant published sources of utility. The EAG notes that the alternative utility values from cross-sectional study reported by Morgan *et al.* and the vignette study conducted by the company in HST28, both provide estimates of utility for the six HST28 health states that are higher than those estimated from the EASE OLE data (see Figure 21). In addition, the estimates of utility based on EQ-5D-5L responses in patients with DEB and their carers from the survey conducted by DEBRA UK, which were 0.601 for current health and 0.141 when asked to recall a day when the disease was at its worst, are more consistent with the range of utility values provided by the EASE OLE study.⁸

Figure 20: Comparison of utility values in the company's base case and those provided by the company in HST28



Overall, based on the hierarchy of utility sources presented in the NICE methods guide, the EAG would prefer the company's economic analysis to use estimate of utility obtained from the EASE OLE 24-month data set with values being taken from the GLM regression for the BSAP range falling within the relevant health state. This negates the need to rely on the arbitrary mapping from 6 to 4 health states.

4.3.3.3 Methods used in the company's utility vignette study

In addition to considering the vignettes unnecessary given the availability of EQ-5D estimates from the EASE OLE study population, the EAG also had significant concerns regarding the conduct of the vignette study. The adult and child vignettes are summarised in Table 47. The adolescent vignette is not presented as it was only used for 2 participants in the patient/carers sample, but it followed a similar pattern of severity levels for itch, pain and wound management, with the fruit-based imagery adjusted to account for the larger BSA for adolescents versus children.

The vignettes themselves do not state the BSA of the individual or the percentage of BSA affected by wounds. Instead, the vignette describes the number of wounds and the average wound size using fruit-based imagery. An example of the type of statement used to describe wounds is as follows, "You have fourteen recurrent wounds, each covering an area of your body that is about the size of three oranges." In the case of the paediatric vignettes, it is unclear whether the participants knew how old the child was supposed to be. But the descriptions of wound size using fruit-based imagery have been estimated for a specific age and a specific BSA. Based on the estimates provided, the EAG believes that these have been calculated using the BSA for a 6-year-old, but this is not clearly stated within the vignettes. It is

unclear whether the people, who were asked to imagine a child, would have imagined a child of the correct size for the wound size descriptions to be relevant. For example, if the intended age was 6 years, and the person imagined a 14-year-old then the BSAP would have been around half of what was intended, whereas the opposite would have been true if the person had imagined a younger child with half the BSA of the intended age. It is possible that this information was provided in introductory materials not provided to the EAG, but ideally it should be stated clearly within the wording of each vignette, especially if the study participants are being expected to imagine a child of a particular size with a wound of a particular size.

Table 47: Summary of severity levels in the adult and child vignettes*

	Adult (BSA = 17,000 cm²)				Child (BSA = 8,050 cm² for age 6)**			
Severity level	Very mild	Mild	Moderate	Severe	Very mild	Mild	Moderate	Severe
Recurrent wounds								
- BSAP	0.50%	3.00%	8.00%	17.50%	0.50%	3.00%	8.00%	17.50%
- Number of wounds	2	8	14	20	2	8	14	20
- Size per wound in cm ²	43	64	97	149	20	30	46	70
- Fruit based imagery (size per wound)***	1- 2 oranges each	2 oranges each	3 oranges each	2 melons each	3 grapes each	1 orange each	1 -2 oranges each	1 melon each
Chronic wounds								
- BSAP	0.00%	0.50%	5.50%	15.00%	0.00%	0.50%	5.50%	15.00%
- Number of wounds	0	2	4	6	0	2	4	6
- Size per wound in cm ²	0	43	234	425	0	20	111	210
- Fruit based imagery (size per wound)	0	1-2 oranges each	3 melons each	5 melons each	0	3 grapes each	1-2 melons each	3 melons
Non-wound aspects of vignettes								
General pain	2 “Hurts little bit”	4 “Hurts little more”	8 “Hurts whole lot”	10 “Hurts worst”	2 “Hurts little bit”	4 “Hurts little more”	8 “Hurts whole lot”	10 “Hurts worst”
Itch	2 “Itches little bit”	4 “Itches little more”	8 “Itches whole lot”	10 “Itches worst”	2 “Itches little bit”	4 “Itches little more”	8 “Itches whole lot”	10 “Itches worst”
Hours of wound management per day	1 hour	2 hours	3 hours	4 hours	1 hour	2 hours	3 hours	4 hours
Dressing change pain	2 “Hurts little bit”	4 “Hurts little more”	8 “Hurts whole lot”	10 “Hurts worst”	2 “Hurts little bit”	4 “Hurts little more”	8 “Hurts whole lot”	10 “Hurts worst”

* Set of vignettes also provided for adolescent patients from the patient perspective but these were only used for adolescents in the patient sample and the number was small (N=2/31)

** Lewis *et al.* provide BSA estimates for three ages (6, 14, and 35 years) and the EAG believes the wound surface areas described in the child vignette align with those for a 6-year-old but the age is not explicitly stated in the vignette.

*** pictures appear to indicate that grapes are 3cm diameter, oranges are 6 cm, and melons are 10cm

Rowen *et al.* provide recommendations on best practice for vignette development. This includes obtaining high-quality evidence to inform vignette development from sources such as published literature and/or original qualitative studies with patients, carers or clinical experts. They also describe the need to validate and refine vignettes using input from clinical experts and patients or carers. The vignettes used by the company are described by Lewis *et al.* as being based on a targeted literature review, but no details are provided regarding the scope or methods for this review. Lewis *et al.* reported conducting a focus group to obtain feedback on the vignettes. They reported minimal feedback and state that they concluded that the vignettes were valid. The research report by Lewis *et al.* states, “*All materials employed were validated by patients, patient representatives and clinicians through focus groups and survey ranking tasks to ensure content validity before commencing data collection.*” The focus group to validate the vignettes is described as including patients and patient representatives affiliated with the DEBRA UK and CureEB patient groups, however, the involvement of clinical experts was not explicitly stated. Whereas for the DCE study, the stakeholder group used for validation is described as consisting of 7 clinicians and 1 patient representative. Based on these statements, the EAG is unclear if the vignettes were validated by both patients and clinical experts and whether either of these groups were involved in the development of the vignettes prior to their validation. The EAG is therefore unclear whether best practice was followed within the vignette study.

Because the vignettes say that the person should imagine that they or their child have EB, the people in the patient/carers sample may have implicitly assumed other EB symptoms are present based on their experience of EB, whereas those in the general population may not have any knowledge of other symptoms that are relevant to EB so may presume only the symptoms described are relevant. This may account for the lower scores in the patient/carers sample. The CS is also somewhat contradictory when describing how comprehensive the vignettes are. For example, when describing the DCE design, Lewis *et al.* state that, “*Disease characteristics that were not included in the vignette study were considered,*” suggesting that the DCE was intended to capture aspects of the condition not included in the vignettes. However, in response to clarification question B12, the company stated that the health state descriptions already integrated, “*the typical clinical and functional burden associated with each severity level of DEB (e.g., wound area, pain, disability, infection risk),*” and therefore, including utility decrements for key clinical manifestations would risk introducing some double counting. The EAG can see how some disease aspects included in the DCE, such as loss of independence or fatigue, may be inferred from the vignette descriptions, which include phrases such as, “*the pain makes regular activities difficult such*

as sleeping or taking a bath or shower.” However, the vignettes are not prescriptive about the presence or absence of other disease manifestations such as mitten deformity or SCC. Given that once these complications occur, they may continue to impact HRQoL even if the patient moves to a state with a lower wound burden, their presence or absence should have been explicitly stated within the vignettes.

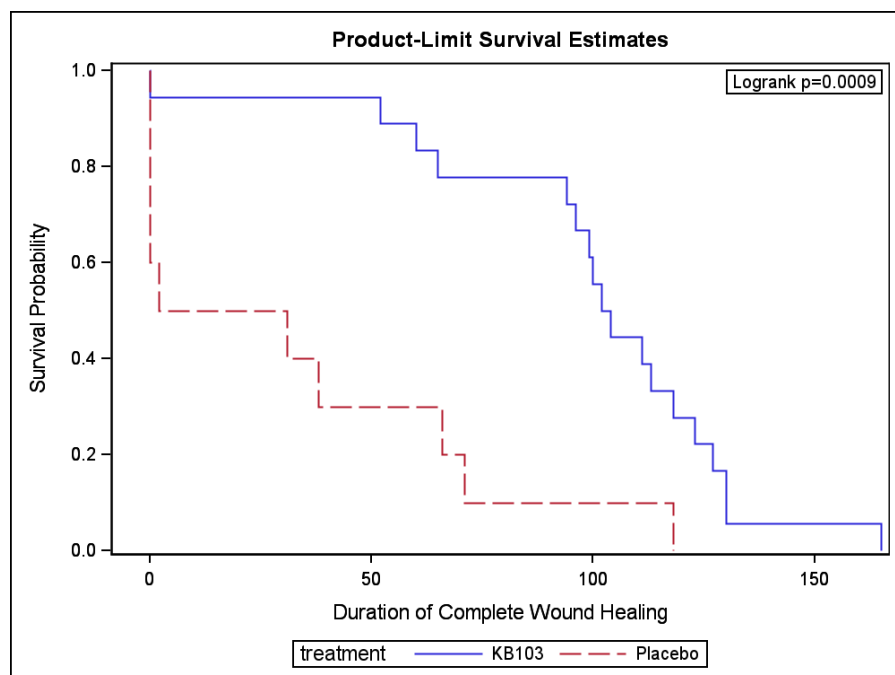
The recommendation by Rowen *et al.* is that when conducting vignette studies, estimates from a sample of patients are generally preferred to estimate from a general population sample, as patients have a greater understanding of the impact of the condition on the dimensions of quality of life. The CS notes that the estimates from the general population sample are less uncertain than those from the patient/carer sample due to the larger sample size. In addition, the EAG notes that the general population sample estimates are not subject to any adaptation bias, whereby a patient (or their carer) underestimates the impact of a condition on activities of daily living because they have adapted to living with the condition. Rowen *et al.* notes that this bias can go in either direction resulting in utilities generated by patients that are higher or lower than those obtained from general population samples. However, given the EAG’s concerns regarding the methods used to describe the health states within the vignettes, and the large discrepancies between the values obtained in the vignette study and the alternative estimates available from HST28, the EAG would prefer not to use the patient/carer sample valuations in this case due to their lack of face validity. Of particular note is the fact that the lower limit of the 95% CI for the severe health state in the carer perspective valued by the patient/carer sample (-0.635) falls below minimum value (-0.594) that can be achieved using the EQ-5D-3L UK valuation set.⁵⁸ Therefore, using these estimates to quantify uncertainty in the utility parameters would clearly lack face validity. Although the estimates from the general population, preferred by the company are higher than those obtained from the patient/carer sample, the EAG is still cautious about their face validity and prefers the estimates from the EASE OLE for the reasons previously discussed.

Given its preference for using the EQ-5D data from the EASE OLE study, the EAG does not consider it necessary to include additional utility decrements for clinical manifestations as these would have been present at the typical prevalence within the cohort evaluated in the EASE OLE study. For those disease manifestations that track with the severity of the skin manifestations, the estimates from the EASE OLE study should already reflect the average prevalence of clinical manifestations within each health state. The EAG notes that using the utility data from the EASE OLE study may be potentially favourable to treatments which lower wound burden, as patients moving to a health state with a lower wound burden will benefit from a health utility that reflects a health state where clinical manifestation are less likely to be present, even though they may have already experienced irreversible clinical manifestations such as mitten deformity before starting treatment.

4.3.3.4 PLS reliance on GEM-1

As discussed in Section 4.2.5.1.1, the company utilised GEM-1 data as these provided weekly wound-level healing trajectories which was more granular compared to the data available from GEM-3. These data included rates of wound closure for both arms, duration of wound closure in the BSC arm, and size and increase in size of reopened wounds. However, the EAG notes that such granularity was not always used in the model. For example, the duration of closure was based solely on the median value which is just one point in time. This median duration of closure was then used to estimate the weekly probability of a wound reopening assuming a constant hazard over time. In response to clarification question A25, the company provided the KM plots for time to reopening in GEM-1 (Figure 22) showing that the hazards are not constant, and that assuming an exponential distribution based on the median value is a strong assumption.

Figure 21: Kaplan-Meier plot for time to reopening in GEM-1 (replicated from Figure 2 of the clarification response)



Regarding the increase in size of the reopened wound for patients on BSC, the PLS applies that as a one-off to avoid added complexity to the model, which also clashes with the primary aim of preferring GEM-1 data over GEM-3 for its granularity of weekly tracking of outcomes.

In addition, the company stated the following in their response to clarification question B19 when discussing alternative sources for data on the duration of closure for the B-VEC arm “*Considering the differences in study design between the GEM-1/2 and GEM-3 studies, it is not adequate to directly compare the duration of closure observed in the GEM-1/2 study and our analysis that combines the*

GEM-3 and OLE studies,” because “the phase 1/2 study consisted of various dosing regimens and treatment cycles alternating with observation periods over the course of approximately 12 weeks.” It seems contradictory that the company considers it unreasonable to use data from the GEM-1 study to estimate the duration of closure, because the dosing regimen differed from dosing in GEM-3 which reflects the licensed dose, but the company also considers it acceptable to use GEM-1 to estimate transition probabilities related to wound closure.

Due to the different dosing regimen applied in the GEM-1 trial, the EAG views GEM-1 as an unsuitable source of data, and it considers that GEM-3 data should have been used to parameterise treatment effectiveness for B-VEC in the model. Although wound outcomes were collected less frequently in GEM-3, they were available at 3 and 6 months, which seems a reasonable starting point to populate a model with a 3-month cycle length.

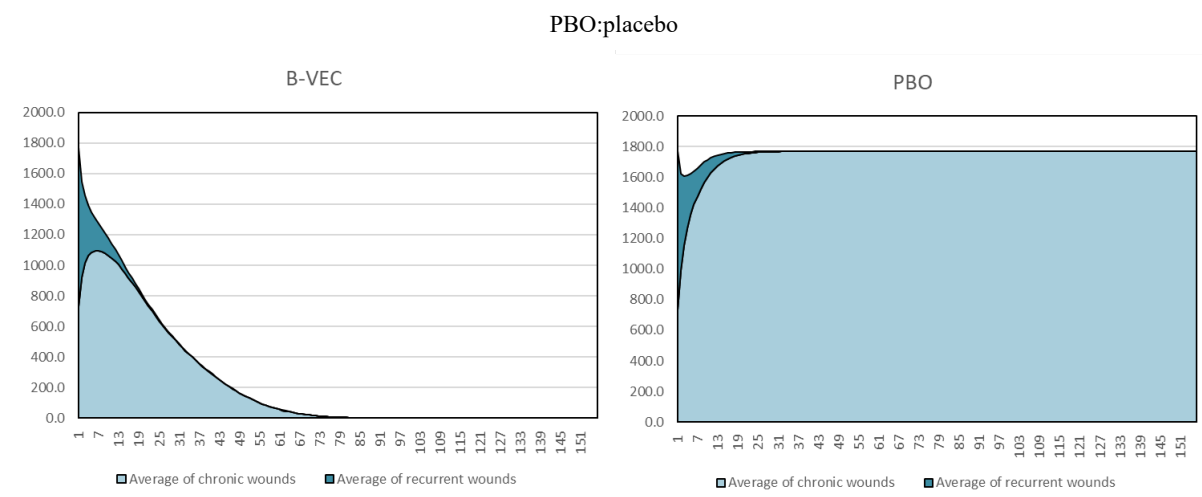
4.3.3.5 Validity of PLS outputs and related assumptions

Figure 23 shows the progression of open wound area across the modelled time horizon of the PLS. The EAG notes several issues with such extrapolations. First, it shows that B-VEC achieves a “near cure” status by an average of 70 weeks from treatment start (See Section 4.3.3.13 for a critique of the underlying assumptions of the very mild state). After achieving this status, B-VEC is only used to treat reopened wounds where its action is immediate hence BSAP plateaus at zero. The EAG views this as implausible and contradicts the findings from the OLE phase after GEM-3. These report that rollover subjects with complete wound closure ranged from 61.1% to 89.5% and never reached 100%. Moreover, these rates were comparable to the rates observed at months 3 and 6 in GEM-3 (Table 39). Though this relates to number of closed wounds rather than the BSAP, the EAG believes that based on the data of rollover subjects from the OLE, it is unlikely the BSAP would drop from 17% to ~1% after a year on B-VEC as the PLS suggests.

Second, the PLS assumes that chronic wounds close as quickly as recurrent wounds on B-VEC which differs from the assumption applied for BSC (which is assumed to have no effect on chronic wounds). This is even though in the GEM-1 trial, all the wounds treated with placebo were recurrent and no data were available for chronic wounds. This is further complicated by the fact that conversion rates from recurrent to chronic wounds dominate the dynamics in the PLS beyond eight weeks. This is most likely because the proportion of wound area not healed at 8 weeks is being applied in the model as the probability of conversion from recurrent to chronic each and every week in the PLS. Although this erroneous assumption applies in both arms, the probability is much higher in the BSC arm and there is also no probability of healing for chronic wounds in the BSC arm. These assumptions combine to result in a situation in the PLS whereby recurrent wounds convert to chronic ones for patients on BSC, and

these are assumed to never heal, whereas all recurrent and chronic wounds for patients on B-VEC are healed, as shown in Figure 23.

Figure 22: Modelled BSA opened by recurrent and chronic wounds (PLS outputs)



Note: x-axis (time in weeks) vs y-axis (BSAP)

Table 48: Summary of responders with complete wound closure for primary wounds previously treated with B-VEC during GEM-3 (adapted from OLE CSR)

Visit	Responders (%)
Month 3 (GEM-3)	13/19 (68.4)
Month 6 (GEM-3)	14/19 (73.7)
Week 1 (OLE)	17/19 (89.5)
3 months (OLE)	16/19 (84.2)
6 months (OLE)	11/18 (61.1)
9 months (OLE)	14/17 (82.4)
12 months (OLE)	10/16 (62.5)
Abbreviations: OLE - open label extension	

Third, PLS outputs misalign with the definition of the health states as described in the CS where very mild had BSAP of 0-2% for recurrent and 0-0.1% for chronic wounds, mild (2-4% recurrent, 0.1-1% chronic), moderate (4-15% recurrent, 1-10% chronic), and severe ($\geq 15\%$ recurrent, $\geq 10\%$ chronic). The company's definition of the health states, which were validated with clinical experts, assumes that within any health state a certain proportion of the BSA affected will be chronic and the rest will be recurrent. The proportion that is chronic is assumed to be higher in more severe health states, as shown in Table 34. However, the PLS does not maintain this ratio of chronic to recurrent wounds. Instead, the dynamics in the PLS simulation result in an increasing ratio of chronic to recurrent wounds in both

treatment arms as shown in Figure 18. Even if treatment with B-VEC was able to impact the ratio of chronic to recurrent wounds, the ratio in the BSC arm should continue to reflect the definition of the health states which were validated with clinician experts as being reflective of the prevalence of chronic and recurrent wounds for patients receiving BSC. If the rate of conversion from recurrent to chronic under BSC is as high as suggested in the PLS, then the starting distribution of chronic and recurrent wounds would not reflect what is observed in current clinical practice. The EAG's clinical expert described how it can be difficult to categorise wounds as either recurrent or chronic as some wounds may have a 'tidal edge' and it is unclear if these should be labelled as recurrent wounds because they experience some healing or chronic wounds because they do not close completely. They noted that wounds were more likely to be chronic in older patients, but the PLS applies the same risk of wounds becoming chronic in all age groups.

Fourth, vial consumption outputs in terms of mean number of vials used per cycle is believed to be implausible and contradicts results reported in the OLE. In the B-VEC exposure data from the OLE, the rollover patients received a mean of 62.1 doses over 86 weeks (clarification response A29), suggesting on average 0.72 doses per week. For naïve patients the equivalent figure was similar at 0.71 doses per week. The EAG believes that a 'dose' in the context of the GEM-3 and OLE study refers to a patient receiving one or more syringes of B-VEC in a given week as the CSR for GEM-3 describes 26 doses being expected over 26 weeks. Given that the minimum number of syringes that can be used per dose is 1 syringe, the OLE data suggest that the expected number of syringes would be at least 9 per 13-week period. However, the PLS predicts between [REDACTED] and [REDACTED] vials per 13 weeks for patients in the very mild state (see Table 49). This would equate to [REDACTED] to [REDACTED] syringes across 13 weeks, which is much lower than the minimum of 9 syringes per 13 weeks predicted by the OLE data. Furthermore, the upper limit for the very mild state across years 2 and 3, once patients have been stabilised on B-VEC, is [REDACTED] vials, equivalent to only [REDACTED] syringes per 13 weeks. These estimates suggest a dosing rate which is much lower than the 0.7 doses per week observed in the OLE study. As such, the EAG is concerned that the PLS is underestimating the number of vials required to maintain patients in the very mild state.

The EAG notes that the publication by Gurevich *et al.*, which describes the GEM-1 study, reports that the expected duration of wound closure during after treatment with B-VEC is 12 weeks, based on a 2-month cutaneous half-life of COL7 and a 4-8 week epidermis turnover rate. This study also employed a 3-month washout period between the treatments in phases 2a and 2b, suggesting that at the point the GEM-1 study was designed, treatment effects were not expected to persist more than 3 months after stopping treatment. This would imply that any wound that achieved closure through treatment with B-VEC is likely to need re-treating around 3 months later if treatment stops once closure is achieved. If the BSA affected by wounds in an individual is greater than the area that can be treated at one time (200

cm²), then the treatment would need to be rotated across all affected areas over a 3-month period. For example, CS Table 3.2 reports that the BSA for the average child aged 0 to 6 years with RDEB is 5,129 cm². This means that one syringe can be used to treat approximately 1% of the child's BSA. If the child has a 12% BSA affected by wounds, consistent with being in the moderate health state, then only 4% could be treated at any one time. Even if it takes only 2 weeks of treatment to achieve complete wound healing (median time to complete closure being 13.5 days in GEM-1) then it would require 6 weeks of treatment, using 24 syringes (6 vials), to achieve complete wound healing across a 12% BSA. Whilst the PLS may allocate this patient to the very mild state, as they have a 0% BSA at 12 weeks, if the duration of wound closure is 3 months, then the first 4% BSA area treated is expected to reopen shortly after 3 months, with the next 4% BSA expected to reopen 2 weeks later and so on. Therefore, the EAG would expect the same usage of vials over the second 3-month period as required over the initial 3-month period if the wound healing duration based on the COL7 half-life is only 3-months. However, the PLS does not force the whole BSA affected originally to reopen when untreated over a time frame that represents the expected half-life of COL7 within the skin. Instead it uses estimates of wound closure duration for B-VEC that rely on making assumptions regarding whether wounds remained closed between the GEM-3 and OLE studies. The estimate of wound closure duration from the GEM-1 study where treatment was not continued during the follow-up period was 103 days, which is much closer to the 3-month expectation expressed when the GEM-1 study was designed, but the estimate of wound closure duration applied in the PLS was ■■■ days. This could explain why the vial usage predicted by the PLS does not tally with the treatment exposure data from the OLE.

Table 49: B-VEC vial consumption per 13-week model cycle as predicted by the PLS

	Very mild	Mild	Moderate	Severe
Year 1, children	■■■	■■■	■■■	■■■
Year 2, children	■■■	NA	NA	NA
Year 3, children	■■■	NA	NA	NA
Year 1, adolescents	■■■	■■■	■■■	■■■
Year 2, adolescents	■■■	■■■	■■■	NA
Year 3, adolescents	■■■	NA	NA	NA
Year 1, adults	■■■	■■■	■■■	■■■
Year 2, adults	■■■	■■■	■■■	■■■
Year 3, adults	■■■	NA	NA	NA
Note that some cells were not available as there was no patients on this health state for the corresponding time.				

The behaviour in the PLS whereby patients on B-VEC are modelled to achieve a “near cure” status quickly with a corresponding low consumption of treatment vials, is being driven by the estimated

duration of wound closure. However, this estimate is dependent on the company's assumption that wounds remained closed between completion of the GEM-3 trial and enrolment in the OLE study (median of [REDACTED]). In response to clarification question B19, the company cites the decision by Haute Autorité de Santé in France, in which wounds were assumed to remain closed for 12 months, however this is not backed up by any trial evidence and seems incongruous to both the half-life of COL7 cited in Gurevich *et al.* and the estimates of doses received in the OLE study. The company's response to clarification question B19 demonstrates that a wide range of values for duration of wound closure can be estimated from the available trial data (103 days to [REDACTED] days) suggesting that this parameter is highly uncertain.

Finally, in response to clarification question B5 the company stated the importance of maintenance treatment with B-VEC as it *"is required to keep patients in the very mild health state and ensure that patients receive optimal benefit"*, however this contradicts what is modelled where patients remain in the very mild state on BSC after discontinuing B-VEC (see Section 4.3.3.13).

4.3.3.6 Validity of mapping algorithm between the different state structures

The mapping from six to four disease severity states adds an extra layer of structural uncertainty as there is not a logical relationship between the BSAP for the states that are assumed to overlap according to the mapping algorithm. As discussed in Section 4.2.4, the company agrees that the mapping algorithm has issues but could not find other possible solutions to make the algorithm converge. The EAG considers that the impact of such a misalignment is too heavy to ignore as the mapping lack face validity and has only been selected because it happens to produce approximately matching costs and QALYs.

First, as shown in Figure 19, the four states are not offering enough granularity in the range of 5-25% BSAP. The moderate state includes four different categories of BSAP (which are health states 2 to 5 from the HST28 model), each with a different QoL that was captured in the six-state structure of the HST28 model. Within the company's four state model, these are all condensed into a single state with the same costs and utilities.

Secondly, as presented in Table 28, the algorithm resulted in lower total QALYs in the HST28 replicated model compared to the original six-state structure for BBE and BSC. The reason is that the six-state structure allowed the patients on BBE to reside in the health states 1 to 4 where BSAP ranges between 0 to 18%. However, the four-state structure unnecessarily constrains the population in two states (mild and moderate) where BSAP open ranges between 2.1 to 25% with no patients allowed in the very mild state. A similar trend was observed with BSC where instead of being distributed between states 2 to 4, the majority is confined to the moderate state. Figure 24 and Figure 25 shows the

differences in health state occupancy between the four- and six-state structures for BBE and BSC respectively.

Figure 23: Markov trace of the 6-state and 4-state structures in the HST28 replicated model – BBE arm

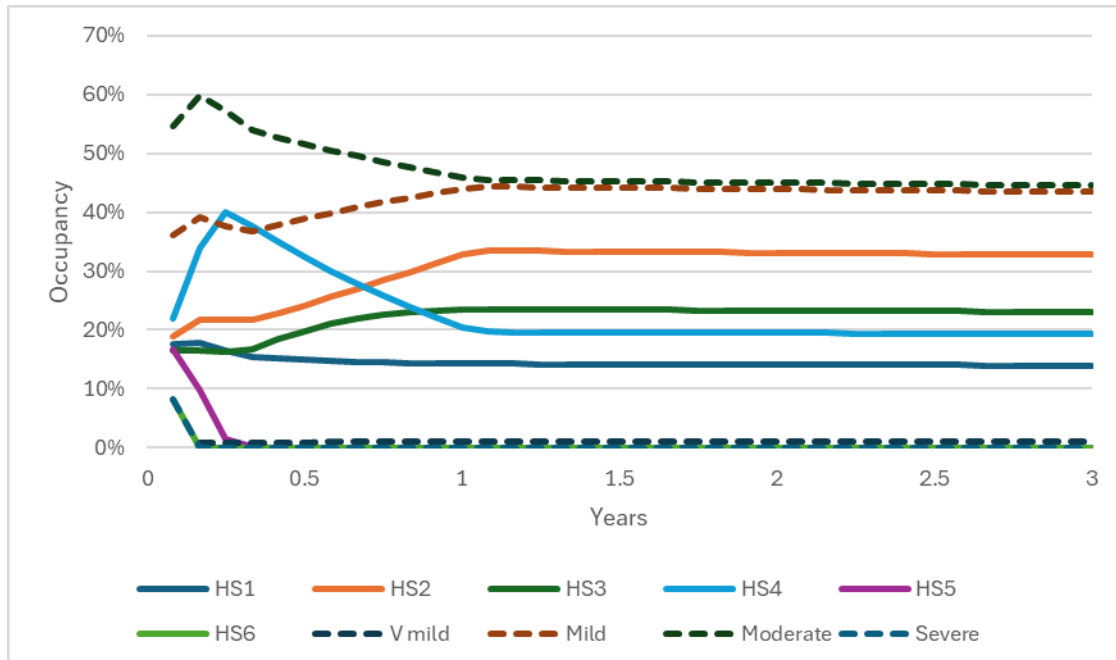
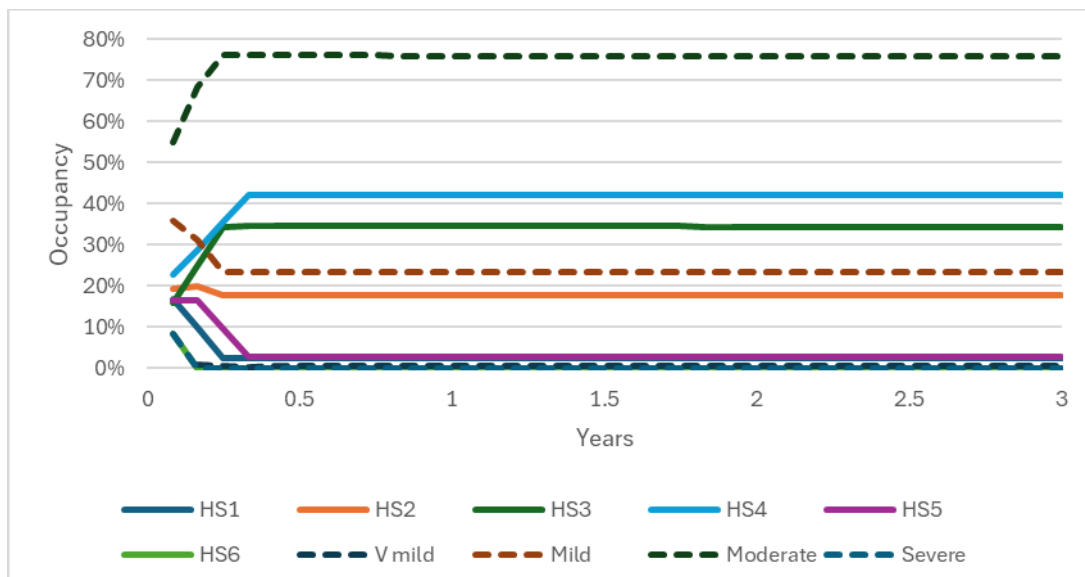


Figure 24: Markov trace of the 6-state and 4-state structures in the HST28 replicated model – BSC arm



Overall, the EAG thinks that the current four-state structure lacks granularity in the range of 5-25% BSAP and that the constituting states may need redefining for better convergence of results. The EAG is convinced the six-state structure is better to address and avoid this issue.

4.3.3.7 Company's model-based ITC and its implementation in the cost-effectiveness scenario analyses

In response to clarification question B15, the company conducted an ITC using the Bucher method for the health state's occupancy (i.e., the proportion of cohort in each health state over time).[39] The company conducted its model-based ITC using both the six-state replication of the HST28 model, which was based on the original transition probabilities for BBE and BSC reported in HST28, and the health state occupancies for BBE and BSC for the four-state structure generated during its mapping exercise. In both cases, the data used to inform the B-VEC, and its associated placebo arm was based on the health state's occupancy from the PLS of the wound outcomes expected if patients received either B-VEC or BSC across all eligible wounds. The company's original PLS used its preferred four health-states, but in response to clarification, the company also provided a version of the PLS that provided outcomes for the six health states used in HST28. The TP matrices for B-VEC and BSC from the PLS were averaged according to the weight for each age group to provide a single estimate of health state occupancy across all age categories as the replicated HST28 model did not track age subgroups separately.

The company conducted the Bucher analysis separately for each health state and each model cycle. The results for the full ITC across all health states and model cycles are presented in Table 51 for the four-state model and Table 52 for the six-state model. However, as the process used to conduct the ITC was unusual, we illustrate the process in more detail below using the four-state model, very mild health state from baseline to month 3 as an example.

Firstly, the company estimated the occupancy of each health state relative to the previous cycle using a ratio. Table 50 shows the health state occupancy for B-VEC and BSC at baseline and month 3. The occupancy for the very mild state on B-VEC increased from 0.8% to [REDACTED] (equivalent to [REDACTED] relative increase) compared to [REDACTED] in the proportion occupying the very mild state on BSC (equivalent to [REDACTED] relative change). These estimates of the ratios of health state occupancy between baseline and 90 days are shown in row 1 in the first two columns of Table 51. An equivalent calculation was then conducted for the health state occupancy of BBE and BSC to give ratios of 1.16 and 0.67 for BBE and BSC.

Secondly, the absolute difference in these ratios between treatment (B-VEC/BBE) and BSC was estimated (e.g., [REDACTED] for B-VEC versus BSC and $1.16-0.67=0.49$ for BBE versus BSC). This was used as the measure of treatment effect within each comparison (i.e. B-VEC versus BSC and BBE versus BSC), presented in columns 3 and 6 of Table 49.

Finally, the difference in these differences was presented as the ITC measure of treatment effect between B-VEC and BBE (i.e. $[REDACTED]-0.49 = [REDACTED]$ for B-VEC versus BBE).

Table 50: Health state occupancy at baseline and month 3 according to the TP matrices estimated from the PLS average weighted by the split of patient population across the three age groups

Time since model start	B-VEC				BSC			
	V mild	Mild	Moderate	Severe	V mild	Mild	Moderate	Severe
Baseline	0.8%	33.0%	49.5%	16.7%	0.8%	33.0%	49.5%	16.7%
Month 3	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

The ITC results from the adapted HST28 model with four health states (Table 51) differ markedly from those of the replicated HST28 model with six health states (Table 52). In the four-state model, there is a single large gain in occupancy for B-VEC from baseline to day 90 in the very mild health state. No such noticeable difference was observed in the results from the six-state model.

The EAG has serious concerns about the ITC conducted by the company. The reported relative effect in terms of health state occupancy does not provide a meaningful indication of treatment effect. For example, for the mild health state from baseline to day 90, the treatment effect appears to favour BBE. However, this does not imply that BBE is more effective than B-VEC in treating patients in this health state, as it is unclear where patients transitioned to in each treatment arm to result in this difference in occupancy. A more meaningful measure would be the estimation of relative risk based on transition probability matrices. The ITC based on the six-state model structure has the advantage that it avoids a reliance on the company's mapping from four to six states for BBE outcomes. The fact that the ITC produces differing results for the four-state model compared with the six-state model raises further concerns regarding the validity of the mapping algorithm to convert BBE outcomes from six states to four states. In addition, both ITC analyses rely on the PLS for predictions of the wound outcomes for B-VEC and BSC. The EAG has additional concerns regarding the data sources used for the PLS, as well as the validity of the simulation outputs and associated assumptions as discussed previously (see Sections 4.3.3.4 and 4.3.3.5).

Table 51: Bucher adjusted indirect comparison between B-VEC and BBE on the difference in the relative change in proportion of patients in each health-state over time using the adapted HST28 model with 4 health states (adapted from response to clarification question B15)

	Relative change in proportion of patients in health-state over two consecutive model cycles						
	Health state's occupancy from PLS based on GEM-1, GEM-3 and OLE in adapted HST28 model with 4 health states			Health state's occupancy from EASE in adapted HST28 model with 4 health states			Bucher ITC
	B-VEC	Placebo (BSC)	B-VEC vs placebo mean, SE ^a (95%CI ^c)	BBE	Placebo (CCM)	BBE vs placebo mean, SE ^a (95%CI ^c)	B-VEC vs BBE mean, SE ^b (95%CI ^c) p-value
Very mild health-state							
Baseline to day 90	■*	■*	■	1.16	0.67	0.49, 0.05 (0.4, 0.59)	■
Day 90 to day 180	■	■	■	1.07	1.00	0.07, 0.01 (0.06, 0.08)	■
Day 180 to day 270	■	■	■	1.08	1.00	0.08, 0.01 (0.06, 0.09)	■
Day 270 to day 360	■	■	■	1.06	1.00	0.06, 0.01 (0.05, 0.07)	■
Mild health-state							
Baseline to day 90	■	■	■	1.20	0.71	0.49, 0.05 (0.39, 0.59)	■
Day 90 to day 180	■	■	■	1.09	1.00	0.09, 0.01 (0.07, 0.11)	■
Day 180 to day 270	■	■	■	1.07	1.00	0.07, 0.01 (0.06, 0.08)	■
Day 270 to day 360	■	■	■	1.06	1.00	0.06, 0.01 (0.05, 0.07)	■
Moderate health-state							
Baseline to day 90	■	■	■	1.20	1.54	-0.33, 0.03 (-0.4, -0.27)	■
Day 90 to day 180	■	■	■	0.94	1.00	-0.06, 0.01 (-0.07, -0.05)	■
Day 180 to day 270	■	■	■	0.94	1.00	-0.06, 0.01 (-0.07, -0.04)	■
Day 270 to day 360	■	■	■	0.95	1.00	-0.05, 0.01 (-0.06, -0.04)	■
Severe health-state							
Baseline to day 90	■	■	■	0.00	0.00	0, 0 (0, 0)	■

	Relative change in proportion of patients in health-state over two consecutive model cycles						
	Health state's occupancy from PLS based on GEM-1, GEM-3 and OLE in adapted HST28 model with 4 health states			Health state's occupancy from EASE in adapted HST28 model with 4 health states			Bucher ITC
	B-VEC	Placebo (BSC)	B-VEC vs placebo mean, SE ^a (95%CI ^c)	BBE	Placebo (CCM)	BBE vs placebo mean, SE ^a (95%CI ^c)	B-VEC vs BBE mean, SE ^b (95%CI ^c) p-value
Day 90 to day 180	■	■	■	0.00	0.00	0, 0 (0, 0)	■
Day 180 to day 270	■	■	■	0.00	0.00	0, 0 (0, 0)	■
Day 270 to day 360	■	■	■	0.00	0.00	0, 0 (0, 0)	■

B-VEC=beremagene geperpavec; BBE=birch bark extract; BSC=best supportive care; CCM=current clinical management; CI: confidence interval, ITC=indirect treatment comparison; OLE=open-label extension; SE=standard error; PLS=patient-level simulation.

*These numbers indicate the change in health state occupancy. For example, the very mild state occupancy increased ■ times from baseline to day 90 for patients on B-VEC compared to ■ for BSC (Day 90 had ■ times its occupancy from baseline).

Notes: Bold p-value indicates statistical significance. a) SE was calculated assuming 10% of mean difference. b) the SE was calculated as square root of the sum of SEB-VEC vs placebo² and SEBBE vs placebo². c) The 95% CI was calculated assuming a normal distribution

Table 52: Bucher adjusted indirect comparison between B-VEC and BBE on the difference in the relative change in proportion of patients in each health-state over time using the replicated HST28 model with 6 health states (adapted from response to clarification question B15)

	Relative change in proportion of patients in health-state over two consecutive model cycles						
	Transitions from PLS based on GEM-1, GEM-3 and OLE in replicated HST28 model with 6 health states			Transitions from EASE in replicated HST28 model with 6 health states			Bucher ITC
	B-VEC	Placebo (BSC)	B-VEC vs placebo mean, SE ^a (95%CI ^c)	BBE	Placebo (CCM)	BBE vs placebo mean, SE ^a (95%CI ^c)	B-VEC vs BBE mean, SE ^b (95%CI ^c) p-value
Health state 1							
Baseline to Month 1	■	■	■	■	■	■	■

	Relative change in proportion of patients in health-state over two consecutive model cycles						
	Transitions from PLS based on GEM-1, GEM-3 and OLE in replicated HST28 model with 6 health states			Transitions from EASE in replicated HST28 model with 6 health states			Bucher ITC
	B-VEC	Placebo (BSC)	B-VEC vs placebo mean, SE ^a (95%CI ^c)	BBE	Placebo (CCM)	BBE vs placebo mean, SE ^a (95%CI ^c)	B-VEC vs BBE mean, SE ^b (95%CI ^c) p-value
Month 1 to Month 2	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 2 to Month 3	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 3 to Month 4	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 4 to Month 5	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 5 to Month 6	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 6 to Month 7	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 7 to Month 8	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 8 to Month 9	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 9 to Month 10	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 10 to Month 11	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 11 to Month 12	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
<i>Health state 2</i>							
Baseline to Month 1	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 1 to Month 2	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 2 to Month 3	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 3 to Month 4	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 4 to Month 5	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 5 to Month 6	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 6 to Month 7	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■

	Relative change in proportion of patients in health-state over two consecutive model cycles						
	Transitions from PLS based on GEM-1, GEM-3 and OLE in replicated HST28 model with 6 health states			Transitions from EASE in replicated HST28 model with 6 health states			Bucher ITC
	B-VEC	Placebo (BSC)	B-VEC vs placebo mean, SE ^a (95%CI ^c)	BBE	Placebo (CCM)	BBE vs placebo mean, SE ^a (95%CI ^c)	B-VEC vs BBE mean, SE ^b (95%CI ^c) p-value
Month 7 to Month 8	■	■	■	■	■	■	■
Month 8 to Month 9	■	■	■	■	■	■	■
Month 9 to Month 10	■	■	■	■	■	■	■
Month 10 to Month 11	■	■	■	■	■	■	■
Month 11 to Month 12	■	■	■	■	■	■	■
<i>Health state 3</i>							
Baseline to Month 1	■	■	■	■	■	■	■
Month 1 to Month 2	■	■	■	■	■	■	■
Month 2 to Month 3	■	■	■	■	■	■	■
Month 3 to Month 4	■	■	■	■	■	■	■
Month 4 to Month 5	■	■	■	■	■	■	■
Month 5 to Month 6	■	■	■	■	■	■	■
Month 6 to Month 7	■	■	■	■	■	■	■
Month 7 to Month 8	■	■	■	■	■	■	■
Month 8 to Month 9	■	■	■	■	■	■	■
Month 9 to Month 10	■	■	■	■	■	■	■
Month 10 to Month 11	■	■	■	■	■	■	■
Month 11 to Month 12	■	■	■	■	■	■	■
<i>Health state 4</i>							

	Relative change in proportion of patients in health-state over two consecutive model cycles						
	Transitions from PLS based on GEM-1, GEM-3 and OLE in replicated HST28 model with 6 health states			Transitions from EASE in replicated HST28 model with 6 health states			Bucher ITC
	B-VEC	Placebo (BSC)	B-VEC vs placebo mean, SE ^a (95%CI ^c)	BBE	Placebo (CCM)	BBE vs placebo mean, SE ^a (95%CI ^c)	B-VEC vs BBE mean, SE ^b (95%CI ^c) p-value
Baseline to Month 1	■	■	■	■	■	■	■
Month 1 to Month 2	■	■	■	■	■	■	■
Month 2 to Month 3	■	■	■	■	■	■	■
Month 3 to Month 4	■	■	■	■	■	■	■
Month 4 to Month 5	■	■	■	■	■	■	■
Month 5 to Month 6	■	■	■	■	■	■	■
Month 6 to Month 7	■	■	■	■	■	■	■
Month 7 to Month 8	■	■	■	■	■	■	■
Month 8 to Month 9	■	■	■	■	■	■	■
Month 9 to Month 10	■	■	■	■	■	■	■
Month 10 to Month 11	■	■	■	■	■	■	■
Month 11 to Month 12	■	■	■	■	■	■	■
<i>Health state 5</i>							
Baseline to Month 1	■	■	■	■	■	■	■
Month 1 to Month 2	■	■	■	■	■	■	■
Month 2 to Month 3	■	■	■	■	■	■	■
Month 3 to Month 4	■	■	■	■	■	■	■
Month 4 to Month 5	■	■	■	■	■	■	■
Month 5 to Month 6	■	■	■	■	■	■	■

	Relative change in proportion of patients in health-state over two consecutive model cycles						
	Transitions from PLS based on GEM-1, GEM-3 and OLE in replicated HST28 model with 6 health states			Transitions from EASE in replicated HST28 model with 6 health states			Bucher ITC
	B-VEC	Placebo (BSC)	B-VEC vs placebo mean, SE ^a (95%CI ^c)	BBE	Placebo (CCM)	BBE vs placebo mean, SE ^a (95%CI ^c)	B-VEC vs BBE mean, SE ^b (95%CI ^c) p-value
Month 6 to Month 7	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 7 to Month 8	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 8 to Month 9	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 9 to Month 10	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 10 to Month 11	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 11 to Month 12	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
<i>Health state 6</i>							
Baseline to Month 1	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 1 to Month 2	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 2 to Month 3	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 3 to Month 4	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 4 to Month 5	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 5 to Month 6	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 6 to Month 7	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 7 to Month 8	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 8 to Month 9	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 9 to Month 10	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 10 to Month 11	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■
Month 11 to Month 12	■	■	■■■■■■■■■■	■	■	■■■■■■■■■■	■■■■■■■■■■

B-VEC=beremagene geperpavec; BBE=birch bark extract; BSC=best supportive care; CCM=current clinical management; CI: confidence interval, ITC=indirect treatment comparison; OLE=open-label extension; SE=standard error; PLS=patient-level simulation.

Notes: Bold p-value indicates statistical significance. a) SE was calculated assuming 10% of mean difference. b) the SE was calculated as square root of the sum of $SE_{B-VEC \text{ vs placebo}}^2$ and $SE_{BBE \text{ vs placebo}}^2$. c) The 95% CI was calculated assuming a normal distribution

The company also went on to apply the ITC estimates within its own four-state Markov model to present cost-effectiveness estimates that incorporated the ITC. The company took the relative treatment effects from the Bucher ITC and applied them twice; once to estimate the patient flow for B-VEC through ITC estimates versus BBE(scenarios 2 and 4 in Table 44 and 45). However, the other to estimate the patient flow for BBE using the same estimates but applied inversely to give BBE versus B-VEC (scenarios 1 and 3 in Table 44 and 45). However, in both cases, adaptations were needed to ensure that health state occupancy did not become negative and to ensure that the total health state occupancy across all states summed to one. The company used different approaches in each case as shown in Table 53 and Table 54 for B-VEC and BBE respectively.

Table 53: Patient flow for B-VEC as estimated from ITC (calculations provided here are for Month 3, same calculations carry forward)

	Very mild	Mild	Moderate	Severe
Baseline	0.0%	21.6%	29.0%	49.3%
Month 3	██████████	██████████	██████████	██████████
Month 6	██████████	██████████	██████████	██████████
Month 9	██████████	██████████	██████████	██████████
Month 12	██████████	██████████	██████████	██████████

Table 54: Patient flow for BBE as estimated from ITC (calculations provided here are for Month 3, same calculations carry forward)

	Very mild	Mild	Moderate	Severe
Baseline	0.0%	21.6%	29.0%	49.3%
Month 3	██████████	██████████	██████████	██████████
Month 6	██████████	██████████	██████████	██████████
Month 9	██████████	██████████	██████████	██████████
Month 12	██████████	██████████	██████████	██████████

The EAG views this methodology as inaccurate and unreliable as it inherently introduces different assumptions for both arms and had to introduce the boundaries to avoid implausible results (i.e., negative health state occupancy). For example, in estimating the patient proportion for B-VEC in the mild state using ITC for month 3 (Table 53), the company applied the relative treatment effect (██████████) to the relative change in proportions occupying the mild state on BBE as reported in Table 54 (1.2).

This led to a negative occupancy level which required the company to introduce a fix using the MAX function. In addition, patient flow differed massively when the ITC was used as shown in Table 55. The EAG does not believe that the differences in BSC, which is the anchoring arm, were sufficiently great to warrant such a difference. These differences led to quite different cost-effectiveness estimates when comparing scenario 1 and 3 to scenario 2 and 4. Overall, the EAG did not have confidence in the methods used to incorporate the ITC results within the company's cost-effectiveness analysis to generate the scenario analyses presented by the company.

Table 55: Patient flow for B-VEC and BBE with and without using the ITC relative treatment effect estimates

	B-VEC				BBE			
	V mild	Mild	Moderate	Severe	V mild	Mild	Moderate	Severe
	Estimated through PLS				Estimated through HST28 transition matrices			
Baseline	0.0%	21.6%	29.0%	49.3%	0.0%	21.6%	29.0%	49.3%
Month 3	████	████	████	████	0.6%	26.0%	73.4%	0.0%
Month 6	████	████	████	████	0.7%	31.5%	67.8%	0.0%
Month 9	████	████	████	████	0.9%	36.2%	63.0%	0.0%
Month 12	████	████	████	████	1.0%	40.2%	58.8%	0.0%
	Estimated through applying ITC to BBE				Estimated through applying ITC to B-VEC			
Baseline	0.0%	21.6%	29.0%	49.3%	0.0%	21.6%	29.0%	49.3%
Month 3	████████	████	████████	████████	████	████████	████████	████████
Month 6	████████	████	████████	████████	████	████████	████████	████████
Month 9	████████	████	████████	████	████	████████	████████	████████
Month 12	████████	████	████████	████	████	████████	████████	████████
Each arrow represents a difference of 10%								

4.3.3.8 B-VEC impact on clinical manifestations

The company's base case assumes a difference in clinical manifestations and mortality based on the health state at any given cycle. This translates into higher prevalence or rates of such manifestations and higher death probabilities for more severe states compared to the mild ones. The rationale provided by the company in responding to clarification questions B10 and B18 is that *"In the study by Eng et al., 2021, the self-reported disease severity was significantly correlated with occurrence of extracutaneous manifestations such as anaemia, complete or partial mitten deformity of foot, use of gastrostomy tube, infections, osteoporosis and SCC"* and that *"The study by Eng et al. 2021 provides evidence supporting a correlation between larger wound burden and increased clinical manifestations."*

The EAG notes that Eng *et al.* used patient self-report to classify severity which was the “*impact on performing activities of daily living and need for treatment.*” This classification differs from how the severity is defined in the current model structure (i.e., based solely on BSAP). The EAG highlights that although the study suggests that larger wound burden correlates with higher disease severity, this does not mean that lowering wound burden would decrease all the aspects of disease severity. There was no evidence presented to support that disease severity as described in Eng *et al.* would reduce by wound healing.

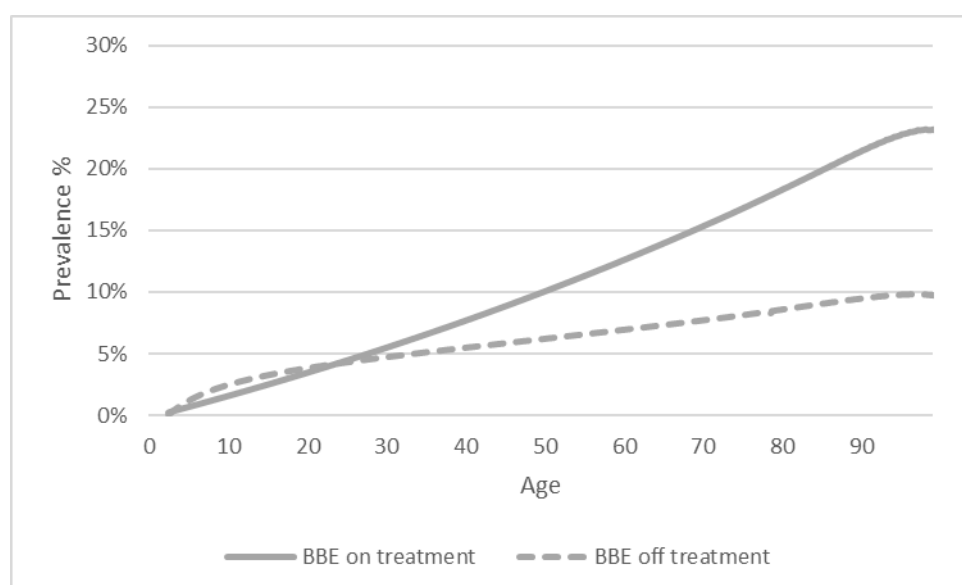
This was further supported by the clinical validation report of economic model assumptions submitted by the company where two out of the three clinical experts consulted disagreed with the company’s assumption of no clinical manifestations for the very mild health state. One of the consulted clinicians stated that “*Treatment that is not systemic will not eradicate complications outside the skin completely/at all. Even if treatment healed all skin, mucosal complications, for example, would still be an issue.*” The experts also “*noted that non-skin-related complications such as mucosal or renal manifestations would not be addressed by B-VEC, and chronic complications such as mitten deformity or scarring would persist*” with one expert specifying “*that local skin infections may still occur in mild patients.*” This relates to B-VEC “*localised mechanism of action and absence of systemic distribution upon B-VEC exposure*” as stated by the company in response to clarification question A18. The EAG’s clinical expert advised that whilst an effective topical treatment for wounds which significantly lowered the wound burden may have some systemic benefit from lowering the level of systemic inflammation, it would not address all non-cutaneous manifestations.

It is worth mentioning that the HST28 which evaluated BBE, which also possesses a localised mechanism of action, did not apply assumptions around mortality or clinical manifestations that differed by health state. The company manufacturing BBE could not find evidence on an association between BSAP or other wound burden measures and QALY gains that were not captured in the HST28 model, “*from additional utility, cost and mortality benefits of reduced complications such as SCC.*”

An additional issue that was noted in the company’s model was the overly complex formulae used to estimate the prevalence of irreversible manifestations leading to implausible prevalence^a results. The EAG could identify two examples of such cases. First, as shown in Figure 21, in the long-term the prevalence of SCC for patients on BBE was higher compared to their counterparts who discontinued treatment; this lacks face validity given BBE superiority over BSC in transitioning patients to less severe states.

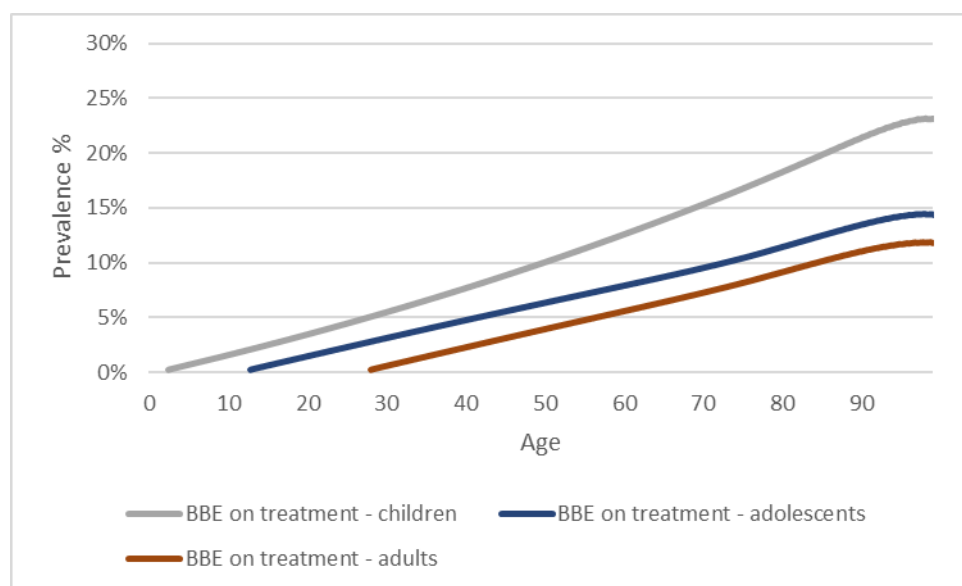
^a Prevalence was defined as total cases (as explained by the company’s response to clarification question B51) divided by patients alive for that cohort at any given cycle.

Figure 25: Prevalence of SCC in the modelled children group in the BBE arm



The second case is shown in Figure 27 where the prevalence is assumed to be 0% for all age groups at model start. This also lacks face validity as a proportion of older patients could have already developed these manifestations by the time they start treatment.

Figure 26: Prevalence of SCC in for the different age groups in the BBE arm



Overall, the EAG is not convinced that mortality and non-cutaneous manifestations should differ by health state due to lack of supporting evidence, and it does not agree with the way the rates of irreversible manifestations were implemented in the model.

4.3.3.9 Mortality extrapolations

The mortality assumptions provided in CS, Section 3.3.5.1 and summarised here in Section 4.2.5.4 are arbitrary, and are not backed by any evidence. In particular, the EAG could not find any evidence that mortality risks could differ according to BSAP. Although the data reported by Petrof *et al.* show that patients with the severe subtype of RDEB have markedly lower survival than those with non-severe RDEB, it is unclear whether reducing the wound burden of a patient with severe RDEB to a level consistent with that experienced by patients with non-severe RDEB will produce a corresponding change in their mortality risk. Non-cutaneous manifestations of DEB, such as oesophageal strictures and oral mucosal involvement, which contribute to poor nutrition and restricted growth in DEB, are not expected to resolve with B-VEC treatment. Therefore, any increased mortality associated with non-cutaneous manifestations may not be affected by B-VEC treatment.

The EAG notes that the risks of SCC and death from SCC are much higher in patients with severe RDEB as quantified by Fine *et al.*⁵⁹ (see Section 2.1). Fine *et al.* comment that whilst the increased risk of SCC in DEB may be analogous to the increased risk in other conditions which result in recurrent or chronic wounds, *“the presence of chronic scar tissue in EB patients cannot by itself fully explain this phenomenon, since SCCs arising in the [other] conditions are not typically as biologically aggressive as those which arise in RDEB skin, suggesting the presence of other contributing factors or mechanisms in the setting of RDEB.”* As the mechanism for the high prevalence and biological aggressiveness of SCC in RDEB is not fully understood, it may therefore not follow that the risk of death from SCC in a patient classified as having severe RDEB will be reduced to the risk seen in patients with non-severe RDEB or DDEB through a treatment that reduces wound burden. The EAG acknowledges that a reduction in SCC due to a lower wound burden is a plausible mechanism via which B-VEC could potentially reduce mortality in patients with severe RDEB, although there is currently no long-term data demonstrating this potential benefit. The EAG therefore prefers to make alternative assumptions regarding the association between BSAP affected by wounds and mortality (see Section 4.4).

Additionally, the EAG disagrees with the company’s rationale for choosing an exponential distribution to model survival for RDEB severe cases. This was that *“As patients enter the model at a later age (depending on the age subgroup), it would not be appropriate to use a parametric curve that does not represent a constant hazard of death.”* The EAG highlights that for any selected curve, hazards at any timepoint could be used to model survival regardless of when the patients started in the model.

Moreover, as shown in Table 15 of the response to clarification question B8, the Weibull, Gompertz and Generalised Gamma models offered significantly better statistical fits based on the BIC scores (833, 830, 830 respectively) than the exponential distribution (868). The EAG considered that the Gompertz model provided a better fit to the observed mortality data for severe RDEB than the company’s preferred

exponential model. For the mortality curve for patients with non-severe RDEB, all of the models fitted by the company gave fairly similar predictions, but the EAG preferred the Gompertz model to provide consistency with the model choice for the severe population..

4.3.3.10 B-VEC vial optimisation

The CS base case assumes that vial optimisation applies for 80% of the patients/vials. This is purely an assumption and has no supporting evidence, and it greatly impacts on the costs associated with B-VEC consumption. The EAG notes that EB is a rare disease, therefore a single treatment centre could struggle to get a patient cohort size sufficient to make vial sharing feasible. In addition, the company acknowledges that the currently approved in-use storage times range from 24 hours under non-aseptic conditions to 7 days when mixed under aseptic conditions and then stored in a refrigerator. The CS mentions that a 30-day stability period is anticipated if B-VEC is mixed under aseptic conditions and then frozen, but this approach would require an update to the SmPC. As the PLS predicts that patients would be in the very mild state most of their journey on B-VEC, this means that four patients are needed per vial. If syringe preparation occurred within a limited number of specialist centres then this may make vial sharing more feasible. However, this would mean either patients having to travel a long distance for treatment at the specialist centre, or coordination of refrigerated transport of syringes to multiple sites if administration is expected to happen at local hospitals or in patients' homes.

Based on this, the EAG thinks that drug wastage could be higher than what is assumed in the CS base case.

4.3.3.11 Concomitant medications

The company used data from Eng *et al.* to estimate varying use of concomitant medications across the four health states included in the company's model. However, the EAG notes that Eng *et al.* only reported a statistically significant difference in concomitant medications between patients reporting themselves as having severe and mild disease for a minority of the medications examined: opiates, gabapentin and Medihoney. Eng *et al.* also reported no significant trend between disease severity and use of medications for itch, constipation or skin infections. The EAG does not consider it reasonable to assume zero usage of concomitant medications in patients with very mild disease when no data were reported for this group by Eng *et al.* and only a minority of medications were found to have a significant association with disease severity. However, as concomitant medications were not a significant driver of cost in the company's model, the EAG has not attempted to amend the company's implementation of concomitant medications in the company's model or include concomitant medications in its preferred base-case scenario.

4.3.3.12 Health states following discontinuation of B-VEC or BBE

In the company's base case model, patients who discontinue treatment after 3 months were modelled using the BSC transition probabilities rather than those associated with the active treatment. However, this had the limitation that after 3 months patients discontinuing treatment were assumed to remain in the same health state until death as the cohort of patients in the BSC arm were assumed to be in steady state after 3 months with no movement between health states. Therefore, patients who discontinued either of the two active treatments, may have a better health state for the rest of their lives compared to those who had never received it. The EAG believes that this is implausible, and it would have preferred to distribute patients who discontinue treatment in accordance with the BSC steady state distribution as happened in HST28 and accepted by the company and the committee.

4.3.3.13 Clinical plausibility of assuming a "near cure" status

In its base case, the company assumed the following for the very mild state:

- All RDEB patients in the very mild state have the average of general population and non-severe RDEB mortality.
- Whilst the utility value for the very mild state is poor relative to general population values (0.49 for adults with very mild DEB versus 0.93 for 18 year olds in the general population) the very low utility for patients with severe DEB (-0.45) means that there is a large utility gain of 0.99 associated with moving adults from the severe to the very mild health states; the gain in children is similarly large at 0.94.
- No irreversible clinical manifestations or osteoporosis would occur.
- Cost of bandage changes is half of what it should be based on the costs calculated as reported in Section 4.2.5.8.5.
- No concomitant medications of any type are needed.
- The health states implemented are described as being based on the severity levels described by Eng *et al.* but none of the patients in the cohort described by Eng *et al.* reported having very mild disease as participants were only allowed to self-declare as mild, moderate or severe. Due to this lack of data, the company made the assumption that patients in the very mild state would not experience irreversible clinical manifestations or osteoporosis. However, as previously discussed in Section 4.3.3.8, two out of three of the clinical experts involved in the company's model validation exercise did not agree with an assumption of zero clinical manifestations for patients in the very mild state.

These assumptions describe someone who is nearly cured from EB. The EAG did not see any supporting evidence of such a claim. Moreover, HST28 did not use differential mortality between health state 1 and the other states, nor did it assume improvements in non-cutaneous manifestations for more mild

states. Also, the EAG could not identify any precedents of different health states of the same disease where the utility difference was 0.99. The EAG disagrees with the description of the very mild state and views it as overly optimistic.

4.3.3.14 The appropriate baseline distribution of the cohort across the health states

In its base case, the company derived the baseline distribution of the cohort at model start as explained in Table 55. However, the definitions from Bruckner *et al.* do not fully align with the health state definitions in the company's model. For example, assuming a uniform distribution per state, half of Bruckner's mild population (<10%), whose BSAP >5%, should be considered moderate as per the company's model definitions of health states.

Table 56: Baseline distribution of the cohort at model start by BSAP

Health state	Definition according to Bruckner <i>et al.</i>	Range suggested by experts	% of patients (RDEB)	% of patients (DDEB)
Very mild	—	0.0-2.1%	0%	0%
Mild	<10.0%	2.1-5.0%	11.1% (6/53)	35.4% (12/31)
Moderate	10.0-30.0%	5.0-25.0%	29.0% (15/53)	29.0% (9/31)
Severe	>30%	25.0-40.0%	59.8% (32/53)	32.6% (10/31)
Abbreviations: DDEB - dominant dystrophic epidermolysis bullosa, RDEB - recessive dystrophic epidermolysis bullosa				

4.4 Exploratory analyses undertaken by the EAG

4.4.1 Overview of EAG's exploratory analyses

The exploratory analyses performed by the EAG are described in Section 4.4.2. The results of the EAG's analyses are provided in Section 4.4.3.

4.4.2 EAG's exploratory analyses - methods

The EAG requested from the company a model version where the six-health state structure is explored, however the company rejected to provide this for the reasons critiqued in Sections 4.3.3.2, 4.3.3.6, 4.3.3.8 and 4.3.3.9 and repeated below.

The EAG would have preferred to adapt the company's model; however, due to time constraints, the EAG used the replicated HST28 model in its base case as this already adopted the six-health state structure. The EAG-adapted HST28 replicated model deviates from the company's base case model mainly in the aspects discussed in exploratory analysis (EA) 1-7 in addition to the following exclusions:

- It does not include reversible and irreversible clinical manifestations. However as explained in Section 4.3.3.8, the EAG prefers to exclude clinical manifestations from the model.
- It does not involve the mapping algorithm from six states to four states, avoiding the associated structural uncertainty introduced by the algorithm as explained in Section 4.3.3.6.

Table 58 below provides a comparison of the assumptions and parameters for the following models: the model from HST28 with the committee's preferences, the CS model for B-VEC using their preferred four-state structure, the company's replication of the six-state HST28 model, and the EAG adaptation of that replicated model. It should be noted that the company's replication of the HST28 model aimed to reflect the first model presented in the CS for HST28 and this is why it differs from the committee preferred model from HST28 which reflects later adaptations made by the company and EAG during the clarification and technical engagement stages of HST28. Where possible the EAG has attempted to incorporate data and assumptions preferred by the committee in HST28, except where these are superseded by more data or assumptions that are more appropriate to the current appraisal.

Table 57: Comparison of the modelling approaches employed by the company and the EAG against those preferred by the committee in HST28

	HST28 model with committee preferences	CS model for B-VEC	Company's HST28 replicated model	EAG adaptation of replicated HST28 model
Markov Model structure	Six-health state	Four-health state with transformation of HST28 inputs from six-states to four-states via a mapping algorithm	Six-health state replication of HST28 but only includes BBE and BSC arms	Six-state state replication of HST28 with B-VEC arm added and additional adaptations
Time horizon	Lifetime	Lifetime	50 years	Lifetime
Baseline characteristics (starting age and male %)	EASE - starting age of 16.7 years - 60% male	GEM-3 - Weighted average age of 17 years^a - 64.5% male	EASE - starting age 6 years^b - 60% male	GEM-3 - 16 years - 64.5% male
Distribution of EB types	Petrof <i>et al.</i> - 49.10% DDEB - 21.83% RDEB (non-severe) - 2.43% RDEB (severe) - 26.65% JEB [only RDEB (severe) % influences outputs]	Bruckner <i>et al.</i> - 38.5% DDEB - 61.5% RDEB	Petrof <i>et al.</i> - 49.10% DDEB - 21.83% RDEB (non-severe) - 2.43% RDEB (severe) - 26.65% JEB [only RDEB (severe) % influences outputs]	EAG corrected values for Bruckner <i>et al.</i> - 36.9% DDEB - 63.1% RDEB
Starting distribution of the cohort across the severity states	EASE	Bruckner <i>et al.</i>	Equal distribution across six states	EASE

	HST28 model with committee preferences	CS model for B-VEC	Company's HST28 replicated model	EAG adaptation of replicated HST28 model
Transition probabilities	BSC – EASE ^c , BBE – EASE ^c ,	BSC - PLS BBE - EASE B-VEC – PLS	BSC – EASE ^d BBE – EASE ^d	BSC – EASE ^d BBE – EASE ^d B-VEC - RR from EAG ITC applied to BBE transitions
State distribution upon BBE/B-VEC discontinuation	Redistributed according to the steady state associated with BSC	Continue on the same state when discontinuation occurs	Continue on the same state when discontinuation occurs	Redistributed according to the steady state associated with BSC
Mortality	Independent of disease severity, 2.4% get RDEB-S associated mortality with rest following GP mortality	Dependent on disease severity as explained in Table 38	Independent of disease severity, 2.4% get RDEB-S associated mortality with rest following GP mortality	Dependent on disease severity; DDEB patients follow GP mortality, RDEB patients (HS1-4) follow RDEB-NS, while RDEB patients (HS5-6) follow RDEB-S associated mortality
Life tables	2018-2020	2020-2022	2018-2020	2020-2022
Clinical manifestations	Excluded	Included	Excluded	Excluded
Utility values (patients)	Generalised linear model fitted to EASE 24-month EQ-5D data	Vignette study	OLS model fitted to 12-month EQ-5D data	Generalised linear model fitted to EASE 24-month EQ-5D data

	HST28 model with committee preferences	CS model for B-VEC	Company's HST28 replicated model	EAG adaptation of replicated HST28 model
Age-adjusted utilities for patients	Excluded	Included	Excluded	Included
Age-adjusted utilities for carers	Excluded	Excluded due to error in implementation	Excluded	Included
Proportion of utility loss for second caregiver	77%	77%	100%	77%
Concomitant medications	Excluded	Included	Excluded	Excluded
Cost inflation	Inflated to 2021 prices	Inflated to 2023 prices	Inflated to 2021 prices	Inflated to 2023 prices
Abbreviations: BBE - birch bark extract; BSC - best supportive care, GP - general population, HS - health state, HST - Highly Specialised Technology, PLS - patient-level simulation, RDEB - recessive dystrophic epidermolysis bullosa, RR - relative risk ^a Weighted average across 3 age subgroups: 12.9% aged 2.25 years, 48.4% aged 12.62 years and 38.7% aged 27.99 years ^b this appears to be an error as the original CS model in HST28 used a starting age of 6 months not 6 years ^c the committee preferred the transition probabilities based on transitions directly observed in the EASE study, however these were redacted in the committee papers for HST28 and were therefore not available for use in the replicated model ^d transition probabilities generated using the approximation method used by Amryt Pharmaceuticals (the company for birch bark extract) in the original CS for HST28				

The EAG's base case analysis is comprised of several changes applied to the adapted HST28 replicated model. The impact of individual changes on incremental costs, incremental QALYs and ICER for BBE versus BSC are presented in Table 58. The adapted HST28 replicated model started with redesigning the Markov traces to build in the capacity to handle discontinued patients separately and allow for the potential for differential mortality by health state. This had a minimal impact on the ICER as shown in Table 59 (an increase of 0.6%). The table lists other changes which needed to be included in the HST28 replicated model to reflect the company's preferences which are; adopting a lifetime horizon, changing starting age and male % to reflect GEM-3, using 2020-2022 life tables, age-adjusting utilities for patients, applying only 77% of utility loss to a second caregiver, and inflating costs to 2023 prices. Results presented use the list price for BBE.

Table 58: Changes applied to the EAG adaptation of the HST28 replicated model and their individual impact on the cost-effectiveness results for BBE vs BSC compared to the adapted model (without any PAS for BBE)

	Incremental costs	Incremental patient QALYs	Incremental carer QALYs	ICER
HST28 replicated model submitted by the company to reflect the HST28 CS as explained in the Appendix				
	£1,561,915	1.15	1.02	720,969
HST28 replicated model submitted by the company to reflect the HST28 CS, where the Markov traces were redesigned by the EAG to reflect the CS model for B-VEC (EAG-adapted replicated HST28 model)				
	£1,558,050	1.15	1.00	725,579
Changes made to the EAG-adapted replicated HST28 model to reflect company's preferences reflected in their preferred four-state model that the EAG agreed with				
Changing time horizon from 50 years to lifetime	£1,662,794	1.28	1.12	691,682
Changing male % from 60% to 65% to reflect GEM-3	£1,557,834	1.15	1.00	725,605
Changing starting age from 6 to 16 years old to reflect GEM-3	£1,546,090	1.14	0.99	726,946
Using 2020-2022 life tables	£1,557,804	1.15	1.00	725,623
Age-adjusting utilities for patients	£1,558,050	1.13	1.00	731,171
Applying only 77% of utility loss to a second caregiver	£1,558,050	1.15	0.97	736,339
Inflate costs to 2023 prices	£1,515,139	1.15	1.00	705,595
Impact of all changes listed above which were made to the EAG-adapted replicated HST28 model to reflect company's preferences reflected in their preferred four-state model that the EAG agreed with				
	£1,575,388	1.18	1.04	708,527
Abbreviations: BBE - birch bark extract, CS - company's submission; EA - exploratory analysis, EAG - Evidence Assessment Group, GLM - generalised linear model, HST - Highly Specialised Technology, ICER - incremental cost-effectiveness ratio, QALY - quality-adjusted life year				

The EAG's base-case analysis is comprised of six main amendments to the company's model: EAG EAs 1-7; these are detailed below. These were applied to the EAG-adapted replicated HST28 model after applying the changes listed in Table 59. EA3 involved estimating outcomes for B-VEC using the EAG's ITC for wound closure outcomes. EA5 details how vial usage was estimated for B-VEC. These two changes were therefore necessary to generate results for B-VEC and therefore these methods are implemented across all of the EAG exploratory analyses including the EAG's preferred base-case scenario.

EA1: Correcting programming and implementation errors in the company's economic model

The EAG corrected the company's implementation errors mentioned in Section 4.3.3.1 as follows:

- The DDEB/RDEB split was amended to 36.9% (31/84) of DDEB versus 63.1% (53/84) RDEB patients.
- The utility of carers was age-adjusted to factor in the current age of carers at a model cycle.
- The PLS was corrected to include the correct SD for size of reopened wounds (■■■■ instead of ■■■■). This impacted the estimates of vial usage from the PLS incorporated in EA4.

EA2: Using the utility values from HST28

For the reasons described in Sections 4.3.3.2 and 4.3.3.3, the EAG considers that the values from the vignette study lack face validity, and it prefers to use the values from HST28 which are centred on the six-state structure and were estimated from applying a GLM model to the 24-month HRQoL data from the EASE trial. These values were 0.609, 0.482, 0.392, 0.293, 0.194, and 0.118 for HS1, HS2, HS3, HS4, HS5, and HS6 respectively.

EA3: ITC implementation in the model using RR value for complete wound closure to derive the transitions for B-VEC

The EAG implemented the RR value calculated from the EAG ITC in Section 3.10 and applied it to the TP matrices of BBE from the HST28 model. In the EAG's base case, this RR was assumed to affect all the transitions to better states (i.e. the RR value for complete wound closure was assumed equal to the RR value of moving to better states). This was implemented through three steps:

- 1- All the transitions from any state to better ones for BBE were converted into rates using this formula:

$$Rate = -\ln(1 - probability)$$

- 2- These rates were multiplied by 3.12, and converted back to probabilities using this formula:

$$Probability = 1 - e^{-rate}$$

- 3- The remaining transitions per row were multiplied by a constant factor so that the sum of transitions equals to 1.

EA4: Mortality assumptions preferred by the EAG

The mortality risk for RDEB patients is assumed to follow a parametric survival curve fitted to the data for RDEB (non-severe) for health states 1 to 4, and a curve fitted to the data for RDEB-Severe for states 5-6. As explained in Sections 4.3.3.10, the EAG prefers the Gompertz distributions for both fits.

EA5: PLS assumptions preferred by the EAG

The EAG only used the PLS to estimate B-VEC vial consumption as follows:

- Use the R code adapted for the six-health state structure and submitted by the company for the clarification process in the EAG's base case.
- Corrected the SD used in the PLS to characterise the normal distribution for the size of a reopened wound as mentioned in EA1
- The EAG used 80% vial optimisation in its base case and explored 50% and 0% in a scenario analysis.

The vial usage predicted by the PLS for the six health states specified in the HST28 model, when correcting the distribution used to sample the size of reopened wounds is given in Table 59.

Table 59: Vial usage predicted by the PLS for the six-health states used in HST28

	HS1	HS2	HS3	HS4	HS5	HS6
Year 1, adults	■	■	■	■	■	■
Year 2, adults	■	■	■	■	■	■
Year 3, adults	■	■	■	■	■	■
Note that some cells were not available as there was no patients on this health state for the corresponding time.						

EA6: Health states following discontinuation of B-VEC or BBE

The EAG prefers to distribute patients who discontinue B-VEC or BBE treatment according to the steady state distribution for BSC. This was 3%, 18%, 34%, 42%, 3% and 0% for HS1, HS2, HS3, HS4, HS5, and HS6 respectively.

EA7: Baseline distribution across the health states

The EAG prefers not to include the baseline distribution at the model start from Bruckner *et al.* as explained in Section 4.3.3.14. Instead, the EAG preferred to use the starting distribution from the EASE trial which was available from the committee papers for HST28. This was 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 following additional sensitivity analyses (ASA) were undertaken using the EAG's base case as the starting point.

ASA1: Applying the RR value for complete wound closure only to the transitions to HS1

This used the same methods as explained in EA2 except that the RR value was applied only to the BBE transitions to HS1 to estimate the TP matrices for B-VEC.

ASA2: Assuming a vial optimisation of 50%

The EAG ran this scenario analysis to measure the impact of changing this parameter on the resulting ICERs.

ASA3: Assuming a vial optimisation of 0%

The EAG ran this scenario analysis to measure the impact of assuming no vial sharing for B-VEC on the resulting ICERs.

ASA4: Assuming a minimum consumption of B-VEC equivalent to one syringe per week

The EAG ran this scenario analysis by setting the number of vials presented in Table 61 to a minimum of one vial every model cycle (4 weeks) which is equivalent to one syringe per week.

The EAG ran also a subgroup analysis for RDEB population by reducing the proportion who have DDEB to 0%. This analysis assumes that the estimates of treatment effect from the EASE and GEM-3 studies are transferable to the RDEB subgroup. This seemed a reasonable assumption given that the RDEB subgroup made up 78.5% of the EASE trial population and 97% of the GEM-3 trial population.

4.4.3 EAG's exploratory analyses – results

The results of the EAG's preferred analyses are shown in Table 63. EA3 and EA5 are both incorporated for all analyses presented as these allow clinical effectiveness and vial usage to be estimated for B-VEC. The EAG's EA 1 implements the corrections described in Section 4.4.2.1. This is followed by implementing individual changes using the EAG-adapted replicated HST28 model after applying the changes listed in Table 59 as the starting point, which are described as EAG EAs 1, 2, 4, 6, and 7. These are then combined in an EAG base case, for which a deterministic result is presented. Due to time constraints, the EAG could not produce a probabilistic version of the HST28 replicated model, however it notes from the HST28 committee papers that results of the probabilistic and deterministic versions of the HST28 model were similar. Deterministic scenario analyses are presented using the EAG base case as the starting point. One subgroup analysis is also presented for the RDEB population.

4.4.3.1 Impact of individual changes

The ICERs substantially increased upon using the EAG-adapted HST28 replicated model compared to the CS model, where B-VEC shifted from being [REDACTED] to generating ICERs around [REDACTED] and [REDACTED] versus BBE and BSC respectively. The next largest change in the ICER was seen when correcting model errors, particularly the correction for the SD of reopened wound area which increased B-VEC consumption (ICERs increased to around [REDACTED] and [REDACTED] versus BBE and BSC respectively). Similar increases were observed when patients were redistributed according to the steady state associated with BSC after B-VEC/BBE discontinuation. The implementation of the EAG's preferred mortality assumptions had marginal impact on the ICERs. Using the baseline distribution from EASE decreased both incremental costs and incremental QALYs but as these both decreased to a similar extent, the impact on the ICERs was not significant. Implementing the utility values estimated from applying a GLM model to the 24-month HRQoL data from the EASE OLE instead of the utility values fitted to 12-month data from the EASE OLE notably decreased the ICERs to approximately [REDACTED] and [REDACTED] versus BBE and BSC respectively.

When including all the changes preferred by the EAG, the deterministic ICERs were [REDACTED] and [REDACTED] versus BBE and BSC respectively. ASA1 in which the relative efficacy of B-VEC was limited to transitions to HS1 resulted in a substantial increase in the ICERs. All of the ASAs assuming increased vial consumption increased the ICERs substantially relative to the EAG base case. The subgroup analysis in which the proportion with DDEB was reduced to 0% to provide an estimate of cost-effectiveness for the RDEB subgroup resulted in minimal change to the ICERs.

The EAG used the Schneider *et al.* tool to calculate the expected QALYs in the general population for a starting age of 16 years assuming 65% of the cohort are male to match the age and sex distribution in its modelled base case.⁵⁴ This gave a figure of 23.30 expected discounted QALYs for people in the general population without DEB. This means that the absolute QALY shortfall in the EAG basecase is >12 QALYs when using either BBE or BSC to reflect the current standard, suggesting that the relevant QALY multiplier is 1.2.

Table 60: EAG exploratory analysis results

Option	Absolute outcomes by treatment arm			Incremental			ICER of B-VEC versus comparator (£/QALY)
	Costs (£)	QALYs (patients)	QALYs (carers)	Costs (£)	QALYs (patients)	QALYs (carers)	
Company’s base case – post-clarification (Deterministic)							
B-VEC		10.97	40.37				
BBE	3,042,222	-2.07	36.98		13.04	3.39	Dominant
BSC	2,011,845	-4.87	33.74		15.84	6.63	Dominant
The EAG-adapted HST28 replicated model (Table 59) including EA3 and EA5 to incorporate B-VEC arm							
B-VEC		12.95	40.74				
BBE	2,711,026	11.42	39.54		1.53	1.19	
BSC	1,135,638	10.24	38.50		2.71	2.23	
EAG EA1: Correction of model errors							
B-VEC		12.95	37.44				
BBE	2,711,026	11.42	36.36		1.53	1.08	
BSC	1,135,638	10.24	35.41		2.71	2.03	
EAG EA2: Using the HST28 utility values estimated from applying a GLM model to the 24-month HRQoL data from the EASE trial							
B-VEC		13.14	40.74				
BBE	2,711,026	10.62	39.54		2.52	1.19	
BSC	1,135,638	8.96	38.50		4.18	2.23	
EAG EA4: Mortality assumptions preferred by the EAG							
B-VEC		12.97	40.81				
BBE	2,713,374	11.44	39.61		1.53	1.19	
BSC	1,109,188	10.19	38.51		2.78	2.29	
EAG EA6: Patients redistributed according to the steady state associated with BSC after B-VEC/BBE discontinuation							
B-VEC		12.48	40.34				
BBE	2,776,919	11.18	39.30		1.31	1.03	
BSC	1,135,638	10.24	38.50		2.25	1.83	
EAG EA7: Assuming the same baseline distribution from EASE							
B-VEC		13.07	40.79				
BBE	2,611,036	11.80	39.87		1.27	0.92	
BSC	1,034,384	10.67	38.72		2.40	2.07	
EAG base case applying EAs 1+2+4+6+7							

Option	Absolute outcomes by treatment arm			Incremental			ICER of B-VEC versus comparator (£/QALY)
	Costs (£)	QALYs (patients)	QALYs (carers)	Costs (£)	QALYs (patients)	QALYs (carers)	
B-VEC		12.74	37.24				
BBE	2,674,622	10.81	36.49		1.93	0.75	
BSC	1,013,844	9.40	35.63		3.35	1.60	
EAG ASA1: EAG base case + estimating the transitions for B-VEC by applying the RR value for complete wound closure only to the transitions to HS1							
B-VEC		11.92	36.77				
BBE	2,674,622	10.81	36.49		1.11	0.28	
BSC	1,013,844	9.40	35.63		2.53	1.13	
EAG ASA2: EAG base case + assuming vial optimisation for B-VEC of 50%							
B-VEC		12.74	37.24				
BBE	2,674,622	10.81	36.49		1.93	0.75	
BSC	1,013,844	9.40	35.63		3.35	1.60	
EAG ASA3: EAG base case + assuming vial optimisation for B-VEC of 0%							
B-VEC		12.74	37.24				
BBE	2,674,622	10.81	36.49		1.93	0.75	
BSC	1,013,844	9.40	35.63		3.35	1.60	
EAG ASA4: EAG base case + assuming a minimum of one vial per cycle							
B-VEC		12.74	37.24				
BBE	2,674,622	10.81	36.49		1.93	0.75	
BSC	1,013,844	9.40	35.63		3.35	1.60	
EAG base case: Subgroup analysis of RDEB population							
B-VEC		12.64	37.17				
BBE	2,652,436	10.73	36.43		1.91	0.74	
BSC	1,000,255	9.31	35.59		3.33	1.58	

Abbreviations: ASA - additional sensitivity analysis; B-VEC - beremagene geperpavec; BBE - birch bark extract; BSC - best supportive care; EA - exploratory analysis; GLM - generalised linear model; ICER - incremental cost-effectiveness ratio; QALY - quality-adjusted life year

4.4.4 The EAG's estimate of the ICER

The exploratory analyses conducted by the EAG at Section 4.4.3, indicate that there are plausible changes to parameter values which would considerably increase the company's estimate of the ICER. The EAG is fairly confident about the best way to correct some of the issues identified in the company's base-case, such as adopting the six-health state structure, including the EQ-5d utility values from the EASE OLE and redistributing patients according to the steady state associated with BSC. However,

there is more uncertainty associated with other issues, such as the vial sharing assumptions and the relative treatment efficacy for B-VEC compared to BBE and BSC.

In the company's base case, estimated total costs associated with B-VEC were considerably lower because the data and assumptions informing the PLS resulted in it predicting that all patients on B-VEC would move rapidly to the "near cure" very mild health-state, where patients are assumed to consume little to no treatment and where they accrue significantly more QALYs, and cost less compared to the other states. In addition, the company's assumption that patients continue indefinitely in this state regardless of treatment continuation is particularly favourable and contradicts the preferences expressed by the committee in HST28. The EAG did not consider that the company's rationale for preferring the four-state model structure was sufficiently strong to warrant all the assumptions necessary to implement the analysis within the four-state structure. It also had significant concerns regarding the validity of the PLS on which the all of the company's modelling of B-VEC effectiveness and costs relied. Therefore, the EAG preferred to use the company's replicated HST28 model as a starting point for its base case, and adopt the ITC explained in Section 3.10 and other modelling assumptions similar to the HST28 committee preferences.

4.5 Discussion

The model submitted by the company was implemented to a good standard, but the EAG could not adapt it to its base case to accommodate its preferences. This was mainly because the company's model centred around a four-health state structure and a mapping algorithm to convert parameters and assumptions from the HST28 six-health state structure. The EAG asked the company for a version of the company's model in the six-health state structure, but the company declined to provide one.

Another key issue was the intra-patient design of the GEM trials which meant that the company's estimates of BSAP for patients treated with B-VEC were based on the outputs of the PLS which the EAG considered lacked validity. The PLS itself was heavily reliant on data from the GEM-1 study which did not match the weekly dosing regimen used in the GEM-3 trial and described in the EMA's SmPC.

Although the company attempted to conduct a model-based ITC between B-VEC and BBE, this was also dependent on the outputs of the PLS for B-VEC. In addition, the model-based ITC was based on the relative change in a given health state occupancy between two consecutive time points, and did not account for the fact that the occupancy of the different states should be correlated through the transition matrix.

Given the EAG's major concerns regarding both the mapping of BBE outcomes from the four state model to the six state model and the estimates of B-VEC outcomes from the PLS, the EAG preferred to simply apply the RR of complete wound closure estimated from an ITC between GEM-3 and EASE to the six state transition matrices available for BBE from HST28. The ITC had its own limitations; however, these were considered less concerning than the limitations associated with the company's approach.

Other differences implemented in the EAG base case were the exclusion of clinical manifestations where the EAG was uncertain about the impact of treating skin wounds on the incidence of clinical manifestations, particularly the non-cutaneous ones such as anaemia and osteoporosis. The EAG acknowledges there may be some reduction in mitten deformity and SCC if patients are treated young and can avoid irreversible scarring by achieving a lower wound burden, however the formulae implemented by the company to incorporate clinical manifestation in their model gave face validity issues. The EAG was therefore reluctant to replicate the company's approach within its adaption of replicated HST28 model and did not have sufficient time to explore alternative approaches.

The EAG base case preferences led to ICERs in the range of [REDACTED] and [REDACTED] for B-VEC when compared to BBE and BSC respectively. The EAG's scenario analyses demonstrate that these ICERs could increase further if applying the RR from the ITC to fewer transitions or if less favourable assumptions were made regarding vial sharing or minimum vial usage per week.

5. OVERALL CONCLUSIONS

The decision problem presented in the CS compared B-VEC versus BBE and B-VEC versus BSC for treating skin wounds in patients with DEB. The EAG notes that the CS adheres to the final NICE scope except for outcomes and subgroups to be considered. Two of the main outcomes used in the modelling, namely BSAP and duration of wound closure, were not pre-specified trial outcomes in GEM-3. Further, GEM-3 did not assess BSAP and the company had to design a PLS to simulate the change in total body wound burden across time for B-VEC and BSC. Also, the GEM trials recruited few patients with DDEB, thus the efficacy of B-VEC for this subgroup remains unknown.

The key evidence for clinical effectiveness of B-VEC within the CS comprised one double-blind phase 3 RCT (GEM-3) and one open-label phase 1/2 RCT (GEM-1). Both compared B-VEC versus placebo within an intra-patient design. The dosing used for B-VEC in GEM-3 aligns with the dosing regimen described in the EMA's SmPC, but various dosing regimens were applied in the different phases of GEM-1 and none of these aligned with the dosing regimen in GEM-3. B-VEC treated wounds achieved higher rates of wound closure at 3 and 6 months compared with placebo treated wounds, with a relatively better response in younger age groups.

Given the open-label design of the GEM-1 trial, the small sample size, and the presence of uncontrolled potential confounding factors (including wound size, wound duration, and the use of a non-licensed dose) the EAG assessed the overall risk of bias in GEM-1 to be high and deemed it unsuitable for informing clinical effectiveness in the economic model. Although the EAG assessed the overall risk of bias in GEM-3 to be low to moderate, the EAG notes that many of the secondary endpoint data from GEM-3, such as measures of HRQoL, cannot distinguish between the effect of B-VEC or placebo given the intra-patient design of the trial.

The principal uncertainty in terms of the clinical effectiveness evidence concerns the absence of any direct head-to-head comparison between B-VEC and BBE. The company presented a model-based ITC based on health state occupancy during the clarification stage. However, the EAG considered this analysis not meaningful for assessing treatment effect, as it was unclear how patients transitioned between health states in each treatment arm, leading to the observed differences in occupancy. The EAG's exploratory analysis suggests that patients receiving B-VEC were 3.12 times more likely to have complete wound closure at 3 months compared to those receiving BBE, but the result was not statistically significant (RR: 3.12 with 95% CI 0.66 to 14.82).

The model submitted by the company was implemented to a good standard, but the EAG was concerned about the validity of the model because it relied on a mapping algorithm to estimate clinical outcomes

for BBE for the company's preferred four-state structure. This mapping algorithm was required to convert the clinical outcomes reported for BBE using the six-state model structure from HST28 into outcomes relevant to the company's preferred four-state structure. The EAG preferred to avoid this mapping algorithm by using the six-state model structure from HST28 as its starting point. However, the company declined to submit a model version in line with the HST28 model structure. Within the timeframe, the EAG adapted another model version submitted by the company. This was the replication of the HST28 model that was used to generate the mapping algorithm to convert parameters from the six-state to four-state structure. The EAG redesigned the company's replicated six-state HST28 model to combine the HST28 committee preferences with the current parameters and assumptions relative to the decision problem in hand. This generated ICERs in the range of [REDACTED] and [REDACTED] when compared to BBE and BSC respectively. Higher ICERs were obtained when accommodating different assumptions for vial sharing and B-VEC efficacy. Several factors contribute the different ICERs obtained by the EAG and the company. Although the different model structures employed makes it difficult to assess the exact contribution of each factor, the EAG believes that the key differences include: the EAG's preference to estimate B-VEC outcomes using its ITC for wound closure; use of the EQ-5D data from EASE in preference to the company's vignette utility estimates, the assumption that patients discontinuing treatment are redistributed according to the steady state occupancy of BSC treated patients and the use of alternative assumptions to capture the reduction mortality that can be achieved by reduced wound burden.

The EAG acknowledges there remain some unresolvable uncertainties where available evidence is lacking and where further long-term data from real world studies would allow the cost-effectiveness estimates to be refined. These include the impact of wound burden on clinical manifestations, mortality, and concomitant treatment. Further real world evidence on vial usage when patients are treated with B-VEC across all eligible wounds would be beneficial as would further information on the feasibility of vial sharing within NHS clinical practice. In addition, further evidence is needed to demonstrate B-VEC efficacy in the DDEB population.

6. REFERENCES

1. Krystal Biotech. Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]: Company evidence submission. London, UK: National Institute for Health and Care Excellence; 2025.
2. Has C, Bauer JW, Bodemer C, Bolling MC, Bruckner-Tuderman L, Diem A, *et al.* Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. *Br J Dermatol* 2020;183:614-27.
3. Tang JY, Marinkovich MP, Lucas E, Gorell E, Chiou A, Lu Y, *et al.* A systematic literature review of the disease burden in patients with recessive dystrophic epidermolysis bullosa. *Orphanet J Rare Dis* 2021;16:175.
4. Fine JD, Johnson LB, Weiner M, Stein A, Cash S, Deleoz J, *et al.* Eye involvement in inherited epidermolysis bullosa: experience of the National Epidermolysis Bullosa Registry. *Am J Ophthalmol* 2004;138:254-62.
5. Fine JD, Johnson LB, Weiner M, Li KP, Suchindran C. Epidermolysis bullosa and the risk of life-threatening cancers: the National EB Registry experience, 1986-2006. *J Am Acad Dermatol* 2009;60:203-11.
6. Fine JD. Inherited epidermolysis bullosa. *Orphanet J Rare Dis* 2010;5:12.
7. Petrof G, Papanikolaou M, Martinez AE, Mellerio JE, McGrath JA, Bardhan A, *et al.* The epidemiology of epidermolysis bullosa in England and Wales: data from the national epidermolysis bullosa database. *Br J Dermatol* 2022;186:843-8.
8. DEBRA UK. Epidermolysis bullosa patient insights. Quantitative research presentation. June 2023/JN4286; 2023.
9. British Association of Dermatologists. Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]: Professional organisation submission. London, UK: National Institute for Health and Care Excellence; 2025.
10. National Institute for Health and Care Excellence (NICE). Birch bark extract for treating epidermolysis bullosa: final draft guidance. In; 2023.
11. National Institute for Health and Care Excellence (NICE). Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]. Committee papers; 2023.
12. European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP) assessment report: Filsuvez. 2022. <https://www.ema.europa.eu/en/medicines/human/EPAR/filsuvez> (Accessed 4 December).
13. National Institute for Health and Care Excellence. Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa: Final scope. London, UK: National Institute for Health and Care Excellence; 2025.
14. Krystal Biotech. Summary of product characteristics: Vyjuvek (beremagene geperpavec). In. Amsterdam, Netherlands: Krystal Biotech Netherlands, B.V.; 2023.
15. Bruckner-Tuderman L, Has C. Molecular Heterogeneity of Blistering Disorders: The Paradigm of Epidermolysis Bullosa. *Journal of Investigative Dermatology* 2012;132:E2-E5.
16. Medicines and Healthcare products Regulatory Agency (MHRA). Filsuvez Gel Summary of Product Characteristics. 2022. <https://www.medicines.org.uk/emc/product/13971/smpc/print> (Accessed 3 April).
17. Joint Formulary Committee. The British National Formulary. London, UK; 2025.

18. Krystal Biotech Inc. GEM-3 Clinical Study Report. A Phase 3 Efficacy and Safety Study of Beremagene Geperpavec (B-VEC, Previously KB103) for the Treatment of Dystrophic Epidermolysis Bullosa (DEB); 2022.
19. Krystal Biotech Inc. GEM-1 Clinical Study Report: A Phase 1/2 Study of B-VEC, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB); 2022.
20. Kern JS, Schwieger-Briel A, Lowe S, Sumeray M, Davis C, Martinez AE. Oleogel-S10 Phase 3 study "EASE" for epidermolysis bullosa: study design and rationale. *Trials* 2019;20:350.
21. UK D. Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]: Patient organisation submission; 2025.
22. Guide SV, Gonzalez ME, Bagci IS, Agostini B, Chen H, Feeney G, *et al.* Trial of beremagene geperpavec (B-VEC) for dystrophic epidermolysis bullosa. *N Engl J Med* 2022;387:2211-9.
23. Krystal Biotech Inc. OLE Clinical Study Report: Open label treatment of beremagene geperpavec (B-VEC). B-VEC-EX-02; 2023.
24. ClinicalTrials.gov. NCT04491604: Ph 3 Efficacy and Safety of B-VEC for the Treatment of DEB (GEM-3). 2023. <https://clinicaltrials.gov/ct2/show/NCT04491604> (Accessed 3 April).
25. Gurevich I, Agarwal P, Zhang P, Dolorito JA, Oliver S, Liu H, *et al.* In vivo topical gene therapy for recessive dystrophic epidermolysis bullosa: a phase 1 and 2 trial. *Nat Med* 2022;28:780-8.
26. ClinicalTrials.gov. NCT03536143: A Phase I/II Study of KB103, a Topical HSV1-COL7, on DEB Patients (GEM-1). 2023. <https://clinicaltrials.gov/ct2/show/NCT03536143> (Accessed 3 April).
27. Kern JS, Sprecher E, Fernandez MF, Schauer F, Bodemer C, Cunningham T, *et al.* Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa - results from the phase 3, randomised, double-blind phase of the 'EASE' study. *British Journal of Dermatology* 2022; 10.1093/bjd/ljac001/6763699.
28. RCT / CCT - MEDLINE, Embase. In: Canada's Drug Agency Search Filters Database. Ottawa: Canada's Drug Agency; 2025: <https://searchfilters.cda-amc.ca/link/122>. Accessed 2025-05-29.
29. Stansfield C, Dickson K, Bangpan M. Exploring issues in the conduct of website searching and other online sources for systematic reviews: how can we be systematic? *Systematic Reviews* 2016;5:191.
30. Cochrane. Cochrane Handbook for Systematic Reviews of Interventions, version 6.5 (updated August 2024). 2024. www.training.cochrane.org/handbook (Accessed
31. Krystal Biotech. Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]. Clarification Response. 2025.
32. Schwieger-Briel A, Kiritsi D, Schempp C, Has C, Schumann H. Betulin-Based Oleogel to Improve Wound Healing in Dystrophic Epidermolysis Bullosa: A Prospective Controlled Proof-of-Concept Study. *Dermatol Res Pract* 2017;2017:5068969.
33. Eng VA, Solis DC, Gorell ES, Choi S, Nazarov J, Li S, *et al.* Patient-reported outcomes and quality of life in recessive dystrophic epidermolysis bullosa: A global cross-sectional survey. *J Am Acad Dermatol* 2021;85:1161-7.
34. Solis D, Teng C, Gorell E, Barriga M, Nazarov J, Li S, *et al.* Classification of 2 distinct wound types in recessive dystrophic epidermolysis bullosa: A retrospective and cohort natural history study. *J Am Acad Dermatol* 2021;85:1296-8.
35. Murrell D, L. Bruckner A, Sprecher E, Kiritsi D, Maher L, Cunningham T, *et al.* BG04 Oleogel-S10 (birch triterpenes) in the treatment of epidermolysis bullosa wounds: 24-month efficacy and safety data from the EASE study. *Br J Dermatol* 2023;188.

36. Murrell D, Bruckner A, Kern J, Maher L, Cunningham T. Safety and efficacy of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: Results of a 12-month interim analysis from the open label phase of the phase 3 study 'EASE'. *Pediatric Dermatology* 2023;40:35 EP - 6.
37. Malviya S, Voepel-Lewis T, Burke C, Merkel S, Tait A. The revised FLACC observational pain tool: improved reliability and validity for pain assessment in children with cognitive impairment. *Paediatr Anaesth* 2006;16:258-65.
38. Kern JS, Sprecher E, Fernandez MF, Schauer F, Bodemer C, Cunningham T, *et al.* Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: results from the phase III randomized double-blind phase of the EASE study. *Br J Dermatol* 2022;188:12-21.
39. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *J Clin Epidemiol* 1997;50:683-91.
40. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;313:275-83.
41. Reimer A, Hess M, Schwieger-Briel A, Kiritsi D, Schauer F, Schumann H, *et al.* Natural history of growth and anaemia in children with epidermolysis bullosa: a retrospective cohort study. *Br J Dermatol* 2020;182:1437-48.
42. Bruckner AL, Losow M, Wisk J, Patel N, Reha A, Lagast H, *et al.* The challenges of living with and managing epidermolysis bullosa: insights from patients and caregivers. *Orphanet J Rare Dis* 2020;15:1.
43. Marinkovich MP, Gonzales ME, Guide S, Bageci IS, Chitra S, Agostini B, *et al.* GEM-3: A phase 3 study of beremagene geperpavec (B-VEC), an investigational, topical gene therapy, for the treatment of dystrophic epidermolysis bullosa (DEB). [Abstract presented at the American Academy of Dermatology Annual Meeting 2022, March 25-29, 2022; Boston, MA]. abstract no. 12.
44. Bardhan A, Bruckner-Tuderman L, Chapple ILC, Fine JD, Harper N, Has C, *et al.* Epidermolysis bullosa. *Nat Rev Dis Primers* 2020;6:78.
45. Office for National Statistics. National life tables – life expectancy in England and Wales: 2021 to 2023. 2024. <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2021to2023> (Accessed 2/7/25)
46. York Health Economics Consortium. Administration Cost of Beremagene Geperpavec: Final Report; 2025.
47. NHS England. National Cost Collection for the NHS. 2024. <https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/> (Accessed 2/7/25)
48. Jones KWH, Birch, S., Castelli, A., Chalkley, M., Dargan, A., Findlay, D., Forder, J., Gao, M., Hinde, S., Markham, S. Premji, S. Teo, H., . Unit Costs of Health and Social Care 2023. In. Kent, UK: Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York); 2024.
49. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. *Nutrition* 1989;5:303-11; discussion 12-3.
50. National Center for Health Statistics. Downloadable Charts - growthcharts. 2024. <https://www.cdc.gov/growthcharts/who-charts.html> (Accessed 2/7/25)
51. Royal College of Paediatrics and Child Health (RCPCH). UK-WHO Growth chart - 2-18 years. 2012. <https://www.rcpch.ac.uk/resources/uk-who-growth-charts-2-18-years> (Accessed 2/7/25)

52. York Health Economics Consortium. Eliciting Health State Utility Values for Dystrophic Epidermolysis: Final Report. 08 December 2023.
53. Pillay E.I. JE, Martinez A.E., Mellerio J.E., McGrath J., Bisquera A., Robertson S. Treatment costs for individuals with recessive dystrophic epidermolysis bullosa (RDEB): Findings of the pebles study. 1st World Congress on Epidermolysis Bullosa, EB 2020; London United Kingdom, abstract no. 65, p. 58.
54. Schneider P, McNamara S, Love-Koh J, Doran T, Gutacker N. QALY Shortfall Calculator. 2021. <https://shiny.york.ac.uk/shortfall/#> (Accessed February 2025).
55. Rowen D, Brazier J, Wong R, Wailoo A. Measuring and valuing health-related quality of life when sufficient EQ-5D data is not available. NICE DSU Report. 2020.
56. NICE. Guide to the methods of technology appraisal 2022 [PMG36]. NICE; 2022. <https://www.nice.org.uk/process/pmg36> (Accessed 29 November 2024).
57. Morgan G, Back E, Rosa D, Irwin J, Ferguson S, Carr E. PCR240 A Cross-Sectional Study of Disease Severity and Health Related Quality of Life in Epidermolysis Bullosa. *Value in Health* 2022;25:S436.
58. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. *Health Economics* 2018;27:7-22.
59. Fine JD, Mellerio JE. Extracutaneous manifestations and complications of inherited epidermolysis bullosa: part II. Other organs. *J Am Acad Dermatol* 2009;61:387-402; quiz 3-4.

7. Appendix

The transition matrices used for B-VEC and BSC in the company's base case

Transition probabilities associated with B-VEC using the company's post-clarification PLS model (formatted as children/adolescents/adults if any differences are present). Note that matrices were assumed to stabilise (i.e., patients remain in their state once the count of patients for a row equals zero).

Week 0 to 13				
	Very mild	Mild	Moderate	Severe
Very mild	■	■	■	■
Mild	■	■	■	■
Moderate	■	■	■	■
Severe	■	■	■	■
Week 13 to 26				
	Very mild	Mild	Moderate	Severe
Very mild	■	■	■	■
Mild	■	■	■	■
Moderate	■	■	■	■
Severe	■	■	■	■
Week 26 to 39				
	Very mild	Mild	Moderate	Severe
Very mild	■	■	■	■
Mild	■	■	■	■
Moderate	■	■	■	■
Severe	■	■	■	■
Week 39 to 52				
	Very mild	Mild	Moderate	Severe
Very mild	■	■	■	■
Mild	■	■	■	■
Moderate	■	■	■	■
Severe	■	■	■	■
Week 52 to 65				
	Very mild	Mild	Moderate	Severe
Very mild	■	■	■	■
Mild	■	■	■	■
Moderate	■	■	■	■
Severe	■	■	■	■
Week 65 to 78				
	Very mild	Mild	Moderate	Severe
Very mild	■	■	■	■
Mild	■	■	■	■
Moderate	■	■	■	■
Severe	■	■	■	■
Week 78 to 91				
	Very mild	Mild	Moderate	Severe
Very mild	■	■	■	■
Mild	■	■	■	■
Moderate	■	■	■	■
Severe	■	■	■	■
Week 91 to 104				
	Very mild	Mild	Moderate	Severe
Very mild	■	■	■	■
Mild	■	■	■	■
Moderate	■	■	■	■
Severe	■	■	■	■

	Very mild	Mild	Moderate	Severe
Very mild				
Mild				
Moderate				
Severe				

Transition probabilities associated with BSC using the company's post-clarification PLS model (formatted as children/adolescents/adults if any differences are present). Note that matrices were assumed to stabilise (i.e., patients remain in their state once the count of patients for a row equals zero).

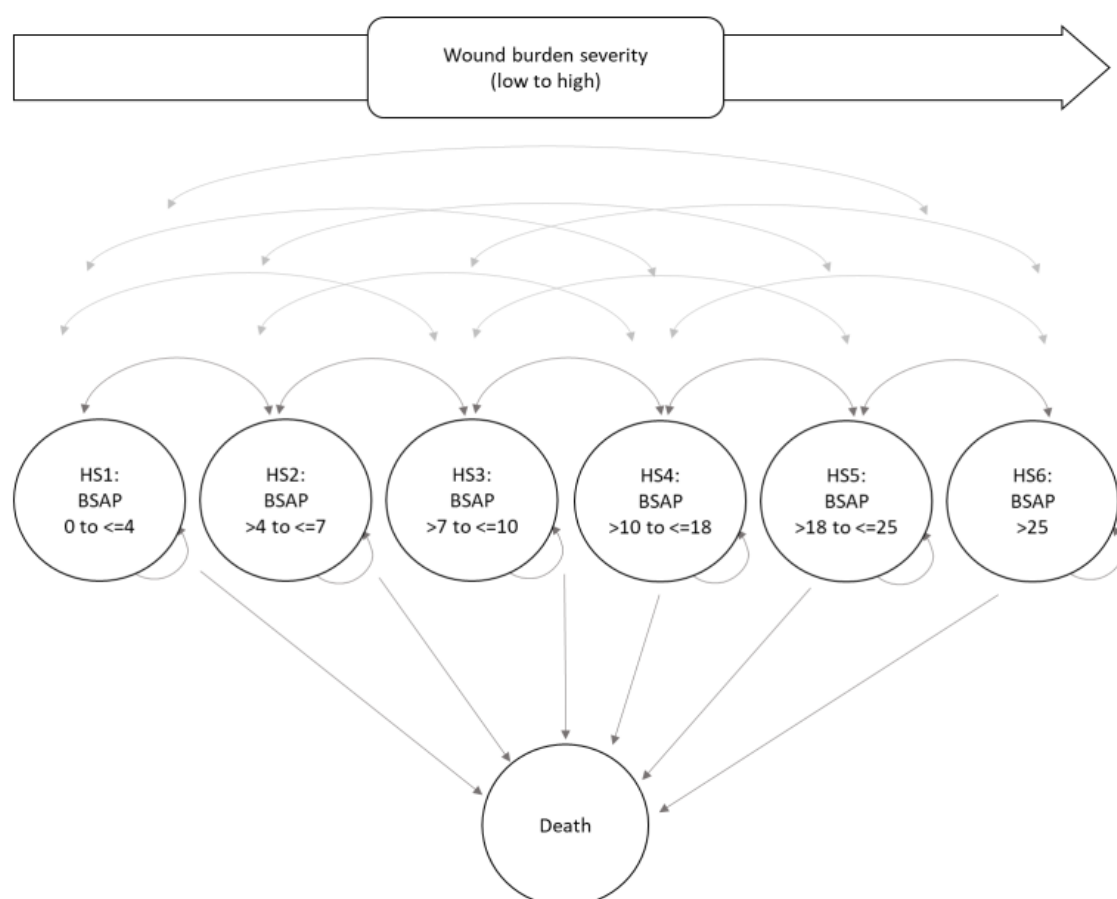
Week 0 to 13				
	Very mild	Mild	Moderate	Severe
Very mild				
Mild				
Moderate				
Severe				
Week 13 to 26				
	Very mild	Mild	Moderate	Severe
Very mild				
Mild				
Moderate				
Severe				
Week 26 to 39				
	Very mild	Mild	Moderate	Severe
Very mild				
Mild				
Moderate				
Severe				
Week 39 to 52				
	Very mild	Mild	Moderate	Severe
Very mild				
Mild				
Moderate				
Severe				
Week 52 to 65				
	Very mild	Mild	Moderate	Severe
Very mild				
Mild				
Moderate				
Severe				
Week 65 to 78				
	Very mild	Mild	Moderate	Severe
Very mild				
Mild				
Moderate				
Severe				
Week 78 to 91				
	Very mild	Mild	Moderate	Severe
Very mild				
Mild				

Moderate					
Severe					
Week 91 to 104					
	Very mild	Mild	Moderate	Severe	
Very mild					
Mild					
Moderate					
Severe					

Description of the replicated HST28 model

The HST28 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 28. The HST28 replication uses a 50-year time horizon, a cycle length of 30 days, and half-cycle correction was employed. Both costs and benefits are discounted at 3.5% per annum.

Figure 27: The HST28 model structure (reproduced from Figure 14 of the HST28 CS)



All patients are assumed to enter the model at 6 months old, although the replicated version inaccurately uses 6 years old. This had minimal impact on the estimated ICERs however. The starting population was equally distributed between the health states.

The HST28 transition probabilities used in the CS for BBE and BSC, assuming no discontinuations or deaths, are reported in Table 61 and Table 62 respectively.

Table 61: Transition probabilities associated with BBE used at the CS of HST28

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 62: Transition probabilities associated with BSC used at the CS of the HST28

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: HS, health state

After 90 days, the HST28 CS base case assumed that the cohort of patients receiving BSC 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 until 12 months before assuming steady state, it's assumed that patients would not discontinue treatment.

The HST28 CS base case assumed that 8.3% discontinue BBE at 90 days and then that 1% would discontinue per annum. When patients discontinue treatment, they are assumed to use the transition probabilities associated with BSC, which, if the patient discontinued after 90 days, would mean that the patient stayed within the same health state, as the patients in BSC were assumed to have reached steady state.

For the HRQoL associated with patients, each health state in the model has an associated HRQoL which decreased as the severity of the condition worsened. These were estimated using an ordinary least squares regression approach using 12-month data from the EASE study and are provided in Table 63.

Table 63: Estimated patient utility by model health state in the HST28 company's base case

	EASE 12-month data: Using an OLS Mean (95% CI) Company Base Case
HS1 (BSAP 0 to ≤4%)	0.560 (0.488 – 0.631)
HS 2 (BSAP 5-7%)	0.515 (0.448 – 0.581)
HS3 (BSAP 8-10%)	0.461 (0.389 – 0.533)
HS4 (BSAP 11-18%)	0.345 (0.234 – 0.456)
HS5 (BSAP 19-24%)	0.229 (0.056 – 0.402)
HS6 (BSAP ≥25%)	0.077 (-0.177 – 0.332)

For carers, the modelling in HST28 assumed that there would be 1.78 carers per patient in the two most severe health states, one carer for states 3 and 4, with 0.50 assumed for health states 1 and 2. Table 64 presents the number of carers per patient with the estimated carer utility applied in the company's base case for HST28.

Table 64: Estimated carer utility by model health state in the HST28 company's base case

	Mean of utility estimate with (standard deviation)	Assumed number of caregivers per patient in each health state
HS1 and 2 (BSAP 0 to 7%)	0.85 (0.21)	0.50
HS 3 and 4 (BSAP 8-18%)	0.76 (0.23)	1.00
HS5 and 6 (BSAP ≥19%)	0.64 (0.27)	1.78

The HST28 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.

To model the patients' mortality, the general population mortality was used for DDEB and RDEB-NS. For RDEB-S (representing 2.4% of the modelled population regardless of the modelled disease severity), the modelling in HST28 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. Hence, no differential mortality was assumed between both treatment arms.

For BBE acquisition costs, the HST28 replicated model uses the list price a 23.4g tube of BBE gel is £275.33; however, there is a confidential PAS in place. The mean number of tubes used per month was 29.67 based on the DBP of EASE. Usage was lower in OLP; however, this was not reported. So, the HST28 replicated model assumed 29.67 tubes would be used monthly for all patients on treatment. No administration costs were assumed, and no drug costs were associated with BSC.

Medical resource use and costs associated with each health state were estimated as explained here in Sections 4.2.5.8.4 and 4.2.5.8.5. Total annual costs related to outpatient visits and dressing changes are detailed in Table 65.

Table 65: Annual costs associated with dressing changes and outpatient visits in the HST28 company's base case

Health State	Base Case Costs (Applied to both arms)
Health state 1 (BSAP $\leq 4\%$)	£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 $\geq 25\%$)	£108,569.11
<i>Abbreviations: BSAP, body surface area percentage</i>	

Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

“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 the end of **22 July 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Abbreviations

Abbreviation	Definition
BBE	birch bark extract
B-VEC	beremagene geperpavec
BSA	body surface area
BSAP	body surface area percentage
CI	confidence interval
COL7	collagen type VII
CS	company submission
DDEB	dominant dystrophic epidermolysis bullosa
DEB	dystrophic epidermolysis bullosa
EAG	Evidence Assessment Group
EB	epidermolysis bullosa
EMA	European Medicines Agency
FDA	Food and Drug Administration
HAS	Haute Autorité de santé
HS	health state
HST	highlight specialised technology
INMB	incremental net monetary benefit
ITC	indirect treatment comparison
ITT	intention to treat
MHRA	Medicines and Healthcare products Regulatory Agency
OLE	open label extension
OR	odds ratio
PLS	patient level simulation
RDEB	recessive dystrophic epidermolysis bullosa
SCC	squamous cell carcinoma
SLR	systematic literature review
UK	United Kingdom
USA	United States of America

Issue 1 Limited data available on clinical effectiveness of B-VEC in patients with dominant DEB

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 26: “Given that the marketing authorisation for B-VEC is not restricted to severe RDEB, the EAG would have preferred the company to have presented a more balance set of data on complications and mortality that cover severe RDEB, intermediate RDEB and DDEB” Page 39: “The EAG’s clinical expert also noted that there is a good biological rationale to expect treatment effectiveness might differ in DDEB compared with RDEB due to patients with DDEB having one non-mutated copy of the COL7A1 gene. Therefore, it may not be appropriate to assume equivalent effectiveness in patients with DDEB, although anecdotal evidence from the USA suggests	The Company suggests the acknowledgement that, although data for patients with DDEB are limited, B-VEC is likely to provide benefits for these patients, as supported by the mechanism of action of B-VEC. Suggested wording: Page 26: “Given that the marketing authorisation for B-VEC is not restricted to severe RDEB, the EAG would have preferred the Company to have presented a more balanced set of data on complications and mortality that cover severe RDEB, intermediate RDEB and DDEB. However, we recognize that data on patients with intermediate RDEB and DDEB are limited.”	We agree that data specific to DDEB are limited. As demonstrated in the SLRs described in the CS, data specific to DDEB are scarce. However, this scarcity reflects the underlying rarity of the condition and should be interpreted in the context of substantial unmet medical need. Patients with DDEB experience significant clinical manifestations and currently have no curative or disease-modifying treatments available. In this context, restricting access to B-VEC on the basis of limited trial numbers risks excluding a population with high unmet need from a therapy with a strong	This is not a matter of factual accuracy. No changes have been made.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
DDEB patients do experience some benefit.”	Page 39: “Data on the efficacy of B-VEC in patients with DDEB are limited and are available from only one patient in GEM-3 and an additional patient in GEM-3 OLE. The EAG’s clinical expert noted that there is a good biological rationale to expect treatment effectiveness might differ in DDEB compared with RDEB due to patients with DDEB having one non-mutated copy of the COL7A1 gene. However, anecdotal evidence from the USA suggests DDEB patients do experience some benefit. Therefore, it is plausible to expect that B-VEC would be beneficial for patients with DDEB.”	mechanistic rationale for benefit. The mechanism of action of B-VEC (topical delivery of COL7A1 via HSV-1 vectors) is expected to be effective in both RDEB and DDEB, as the fundamental pathology in both involves loss of functional type VII collagen and compromised dermal-epidermal adhesion. While patients with DDEB may retain one non-mutated allele of COL7A1, this does not obviate the pathophysiological potential for B-VEC to enhance wound healing. This is supported by anecdotal evidence from clinical use in the USA, where DDEB patients have demonstrated clinical responses to B-VEC. Further supporting the unmet need in the DDEB population, the EAG noted, on Page 80, "there were no differences	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		between BBE and control gel in patients with DDEB (OR 1.25, 95% CI 0.15, 10.7).” Although BBE was recommended for both RDEB and DDEB subtypes, the pivotal EASE trial did not show differences between BBE and control gel in the latter patient group. In GEM-3, one patient with DDEB (Subject 01-07) achieved complete closure of the B-VEC-treated wound by Month 6, meeting the primary endpoint for multiple consecutive assessments (Weeks 22, 24, and 26), despite the placebo-treated wound failing to heal. OLE follow-up of this patient showed continued durable responses at treated wound sites. In addition, a second	

		DDEB patient enrolled in the GEM-3 OLE (Subject 05-02) demonstrated repeated complete closures at multiple wound sites during follow-up. Although the sample size is small, these consistent individual patient results provide direct evidence of clinical benefit in the DDEB population. Furthermore, the pivotal EASE trial assessing BBE (the comparator), which enrolled both RDEB and DDEB patients, showed no statistically significant differences in wound closure outcomes between the subgroups. This finding provides indirect comparative evidence that treatment efficacy is not materially different between the two DEB subtypes. Taken together, the mechanistic rationale,	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		supportive anecdotal experience, direct individual patient evidence from GEM-3 and OLE, and the absence of any observed efficacy differential in comparator data, all support the plausibility that B-VEC will provide meaningful benefit in DDEB. In the context of unmet need, this justifies maintaining DDEB patients within the modelled licensed population.	
Page 33 “Therefore, across the GEM-1, GEM-3 and GEM-3 OLE, only 2 DDEB patients were recruited making subgroup analysis by DEB type unfeasible. “ “The company’s economic analysis is conducted assuming a mixed population of DDEB and RDEB... but subgroup analyses	The Company suggests acknowledgement of the efficacy of B-VEC in the two patients with DDEB participating in the GEM-3 and GEM-3 OLE. Suggested wording: “Therefore, across the GEM-1, GEM-3 and GEM-3 OLE, only 2 DDEB patients were recruited making subgroup analysis by	As stated above, the Company agree that data in DDEB patients are limited, making subgroup analyses difficult. However, this does not underplay the unmet need in this population and the efficacy of B-VEC in the few patients with DDEB that participated in GEM-3 and its OLE.	This is not a matter of factual accuracy. No changes have been made.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
by DEB subtype or age category are not reported for the cost-effectiveness analysis.”	DEB type unfeasible. However, in both patients with DDEB enrolled across GEM-3 and the GEM-3 OLE, B-VEC achieved clinically meaningful wound closure.”	A patient with DDEB (Subject 01-07) showed complete healing of the B-VEC treated wound, but not the placebo-treated wound, by Month 6, with sustained closure confirmed across multiple timepoints in GEM-3. A second patient (Subject 05-02) also benefited from B-VEC at several wound sites during the OLE of GEM-3. It is also important to note that the model differentiates between RDEB and DDEB in key aspects that affect both costs and outcomes. First, patients with RDEB often have reduced total BSA compared with the general population due to malnutrition, anaemia, and failure to thrive.¹ This directly affects predicted B-VEC consumption, as smaller	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		patients require fewer vials to treat an equivalent percentage of BSA. In contrast, patients with DDEB have a total BSA consistent with the general population (according to clinical expert opinion, as discussed in the CS). Second, the baseline distribution of severity differs between subtypes, with patients with RDEB more heavily weighted towards the severe health states, while patients with DDEB generally have less severe disease.² These differences are incorporated into the model structure and parameterisation, ensuring that the mixed-population approach reflects real-world biological and clinical differences between the subtypes.	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 24: “that the description of disease burden presented in the CS is biased towards data that represent the severe form of RDEB and that the CS does not present a balanced picture of disease severity across all groups covered by the marketing authorisation for B-VEC which includes DDEB and non-severe RDEB.”	The Company suggests acknowledgement that limited literature is available for mild cases of DEB. Suggested wording: “that the description of disease burden presented in the CS is biased towards data that represent the severe form of RDEB and that the CS does not present a balanced picture of disease severity across all groups covered by the marketing authorisation for B-VEC which includes DDEB and non-severe RDEB. However, the EAG acknowledges that limited literature is available for non-severe RDEB and DDEB.”	The Clinical and Non-Clinical SLRs described in the CS collectively identified only 11 publications³⁻¹⁴ out of 69 that reported separate data on patients with DDEB. In these publications, patients with RDEB often made up a larger component of the total sample size. For example, out of 412 patients included in Feinstein et al. (2022), which reported healthcare resource use in DEB patients, only 17 patients had DDEB, while 85 had RDEB.⁹	This is not a matter of factual accuracy. Although the EAG acknowledges that data may be more limited for DDEB, the EAG identified instances where data for severe RDEB were quoted from a study but corresponding data for DDEB from the same study were not quoted, hence its concern that the presentation of data were skewed towards data relating to severe RDEB.

Issue 2 An ITC between B-VEC and BBE based on a comparison of trial outcomes from the GEM-3 and EASE studies has not been provided

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 89, Table 28: the definition of Complete wound closure for EASE was “the proportion of participants with first complete closure of EB wound at 90 days.”	In the EASE trial, complete EB wound closure was defined as the proportion of patients with first target wound closure within 90±7 days (i.e., wound closure <u>by</u> 90 days).¹⁴ We suggest rewording the statement to reflect the correct definition, to “the proportion of participants with first complete closure of EB wound by 90 days”	The GEM-3 and EASE trials used fundamentally different definitions of wound healing, introducing structural heterogeneity and critical methodological inconsistencies that invalidated an indirect comparison. These discrepancies occur at two key levels: 1. Timing of Wound Closure Assessment:	The text is amended to “the proportion of participants with first complete closure of EB wound within 90±7 days.”
Page 89, Table 28 does not state a crucial difference in the definition of outcomes between the two trials. In GEM-3, wounds were only considered closed if they were fully closed during two consecutive visits, two weeks apart, while the primary analysis from EASE does not include confirmation of	In the Data column, “the percentage of wounds with complete closure at 3 months” should be changed to: “the percentage of wounds with complete closure at 3 months confirmed at two consecutive visits two weeks apart.”	GEM-3 defines wound healing as the number of wounds closed <u>at</u> 3 months, whereas EASE defines it as the number of wounds closed <u>by</u> 3 months. Assessing closure <u>at</u> 3 months is a more stringent criterion, potentially underestimating early healing, while assessing closure <u>by</u> 3 months allows	The text is amended as suggested. The EAG highlighted this issue in Section 3.9 under “Differences in definitions of endpoints”

wound closure, thus making it a less stringent criterion.		inclusion of any wound healing that occurred during the preceding period. This discrepancy may create a bias in favour of treatments assessed under the less stringent definition (i.e., BBE). 2. Confirmation of Wound Closure: In GEM-3, wound closure required confirmation after a two-week period, ensuring sustained healing rather than transient closure. In contrast, EASE did not include this confirmation step, counting wounds that may have reopened shortly after initial closure. The absence of confirmation introduces further inconsistency in outcome measurement and again biases results in favour of BBE. Given these methodological discrepancies, the EAG's use of a Bucher ITC, which	

		assumes comparability of endpoint definitions, is not methodologically robust. These are not minor protocol differences but represent fundamentally different outcome constructs. Combining them in a single treatment effect estimate risks, producing biased and misleading results. It is noteworthy that the EMA's assessment of BBE¹⁵ recognised this issue and included a scenario analysis where wound closure required confirmation after just one week, acknowledging the effect of changing closure definitions on results. Even under this more lenient adjustment, the outcome definition still does not align with GEM-3's more stringent, sustained-closure requirement. Additionally, results from the EASE trial showed that proportion of patients with complete closure of target	

		wound was not different between BBE (n=55/109) and control gel (n=50/114) up to Day 90, ¹⁴ highlighting the impact of duration of closure on clinical outcomes (i.e., change in BSA).	
Page 175 (EA3): the EAG's explanation of how the outcomes from their ITC were applied to the HST28 transition probabilities does not include some key assumptions.	The Company suggests adding an explanation of the following assumptions and limitations associated with the method applied by the EAG: • The average area treated is the same with B-VEC as with BBE • Patients can only move to the neighbouring health state (as was the case in the transition probabilities used for the BBE CS). • In the HST28 model, all patients starting in HS5 and HS6 move to a less severe state in the first cycle in both arms and do not return. This means there is no opportunity for B-VEC to demonstrate any	The EAG's explanation of how the outcomes from their ITC were applied to the HST28 transition probabilities omits key assumptions that materially disadvantage B-VEC. The EAG's application of HST28 transition probabilities removes the possibility for B-VEC to demonstrate any incremental benefit in patients starting in HS5 or HS6. Under the EAG's approach, all patients in these states move to a less severe state in the first cycle, in both arms, and never return. This is a structural artefact of the HST28 transition set, not a	This is not a matter of factual accuracy. No changes have been made to the report in response to this issue as none of the issues raised by the company are issues that are specific to the EAG's exploratory analysis. The EAG has assumed the same number of tubes of BBE as assumed by the company in their analysis. This was based on average usage in the EASE study. Usage of B-VEC is based on the company's PLS which

	incremental benefit for patients beginning treatment in these health states. • For costing, the EAG assumes the same maximum treatable area for B-VEC as for BBE (366 cm² from EASE trial data), despite this being smaller than the total BSA.	reflection of real-world outcomes, and it artificially erases potential treatment differences in the most severe patients. In addition, the EAG assumes the maximum treatable area for B-VEC is identical to that for BBE (366 cm², based on EASE trial data), despite this being less than the total BSA. If BBE were applied across the total BSA, costs would be significantly higher. It is inconsistent to assume lower efficacy for B-VEC while maintaining the same vial consumption as BBE. Both assumptions bias results against B-VEC: the first by removing clinical benefit in the most severe patients, the second by overstating costs. Together, these lead to an understatement of clinical	estimates usage per health state and the EAG used the company's PLS adapted for the 6 health states used in HST28. As the EAG used the baseline distribution from the EASE study, combining this with B-VEC usage by health state effectively estimates B-VEC usage for the EASE study population. The EAG highlights that HST28 transitions were trial-based and were also used in the company's CS model where these transitions were mapped to the 4-state structure to create total costs and QALYs for BBE. Therefore any limitation related to the transition probabilities from the EASE study

		value and an overestimation of costs. The EAG has assumed that the maximum treatable area for B-VEC is the same as that for BBE (366 cm², based on EASE trial data), despite this being less than the total BSA. It is inconsistent to assume limited efficacy for B-VEC, yet also maintain the same vial consumption. This results in an underestimation of clinical value and an overestimation of costs.	also applies to the company's model. The EAG disagrees that its approach leads to an underestimation of B-VEC's value and an overestimation of its costs and believe the opposite may be true. In its adaptation of the replicated HST28 model, the EAG uses the baseline distribution and the transitions from EASE. Therefore, cost data for BBE are correct for the EASE study population. On the other hand, the EAG notes that the maximum treatable area for B-VEC is 200 cm², so applying the RR from the ITC to the whole BSAP may significantly bias ICERs in favour of B-VEC if the BSA affected by wounds

			in the EASE population is higher than the maximum treatable surface area. This is because the costs have been scaled down to reflect the maximum treatable area but the efficacy from the target wound is assumed to scale up across the whole BSA affected by wounds. However, the EAG were unable to identify any information on average BSAP for the EASE population so it is unclear if this bias applies.
Page 183: “The EAG’s exploratory analysis suggests that patients receiving B-VEC were 3.12 times more likely to have complete wound closure at 3 months compared to those receiving BBE, but the result was not statistically significant	The Company suggests acknowledging the substantial statistical imprecision and noting that the ITC results are not suitable for decision-making. Suggested wording:	As noted in CS Section 2.9, a feasibility assessment concluded that an ITC between BBE and B-VEC was not possible due to fundamental	This is not a matter of factual accuracy. Limitations of the ITC analysis has been provided in Section 3.9.

(RR: 3.12 with 95% CI 0.66 to 14.82).”	“The EAG’s exploratory analysis suggests that patients receiving B-VEC were 3.12 times more likely to have complete wound closure at 3 months compared to those receiving BBE, but the result was not statistically significant (RR: 3.12 with 95% CI 0.66 to 14.82). However, given that the result was not statistically significant, and the substantial imprecision of the result (i.e., the estimate spans a wide range), results of this ITC are not suitable to inform decision-making.”	trial design and population differences. The exploratory analysis conducted by the EAG found that patients receiving B-VEC were 3.12 times more likely to achieve complete wound closure at 3 months compared with those receiving BBE, acknowledging that the result was not statistically significant (RR: 3.12; 95% CI 0.66 to 14.82). Given that this estimate spans a wide range, it is highly uncertain and supports the original conclusion that an ITC is not methodologically robust or suitable to inform decision-making. Further, the EAG’s Bucher ITC relies on an assumption of equivalence between the placebo arms in GEM-3 and EASE. Given the trial-level differences highlighted in the CS of why an ITC is not possible, this assumption is likely violated.¹⁶	

Issue 3 Validity of the company's patient level simulation as a source of effectiveness estimates

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 144: The EAG did not find it plausible that chronic wounds close as quickly as recurrent wounds when treated with B-VEC, and that wound dynamics are different between B-VEC and BSC arms. The EAG stated: "Although this erroneous assumption applies in both arms, the probability is much higher in the BSC arm and there is also no probability of healing for chronic wounds in the BSC arm."	The Company suggests that, in the second quoted statement, the EAG remove "erroneous".	There are no empirical data that track chronicity of transitions. Specifically, there are no clinical trials that systematically capture transition rates between recurrent and chronic wounds over time. As a result, all assumptions on chronic wounds (both from the Company and the EAG) will contain inherent uncertainty for this reason. The EAG's own clinical expert acknowledged that these wound categories can be difficult to define in practice. The EAG's "tidal edge" description highlights the significant overlap between recurrent and chronic wounds, reinforcing the difficulty of assigning wounds definitively to one group or another. This would be a caution point of any	The assumption was deemed erroneous because, as shown in Figure 23, it leads to most of the BSAP open being chronic after running the model for only several weeks (i.e. ratio between BSAP open with chronic versus recurrent wounds increases across time). This is in contrast with what CS, Table 3.6 suggests that the BSAPs open per each wound type are correlated.

		model that treats these ratios as constant. The Company's PLS adapts to individual wound area trajectories. The simulation dynamically tracks wound healing and reopening events, rather than assuming a static chronicity distribution. This is considered a more flexible approach, and is a more realistic representation of what patients are likely to experience. The EAG's criticism of the Company's assumption that chronic wounds do not heal under BSC is consistent with clinical expert opinion stating that without active intervention, chronic wounds rarely improve and often worsen. This is supported by the known efficacy limitations of standard of care in DEB and by expert consensus that chronic wounds represent a progressive, chronic condition.	

Page 147: “The estimate of wound closure duration from the GEM-1 study where treatment was not continued during the follow-up period was 103 days, which is much closer to the 3-month expectation expressed when the GEM-1 study was designed, but the estimate of wound closure duration applied in the PLS was [REDACTED]. This could explain why the vial usage predicted by the PLS does not tally with the treatment exposure data from the OLE.”	The Company suggests acknowledgement that the selection of the [REDACTED] closure duration is based on a clear rationale, including the fact that GEM-3 and the OLE provide the longest-term data available, as outlined in the CS. Suggested wording: “The estimate of wound closure duration from the GEM-1 study where treatment was not continued during the follow-up period was 103 days, which is much closer to the 3-month expectation expressed when the GEM-1 study was designed, but the estimate of wound closure duration applied in the PLS was [REDACTED]. This assumption was based on the data from the GEM-3 and OLE studies, which provided the longest-term data available.”	The Company explicitly tested alternate durations, including the 103-day closure duration based on GEM-1 data as cited by the EAG. The EAG relies on an early publication (Gurevich et al.),¹⁷ suggesting wound reopening at about 3 months, but this was based on preclinical data and assumptions prior to longer-term evidence became available from GEM-3 and the OLE. The OLE showed that a substantial proportion of wounds remained closed beyond 6 and 12 months, showing favourable outcomes beyond 6 months of treatment in children and adult patients with DEB,^{18,19} and supporting the Company’s longer median closure duration. The [REDACTED] duration was calculated from GEM-3 and OLE data, and further described on Page 97 of the CS. Furthermore, the French HTA body (HAS) accepted a 12-	This is not a matter of factual accuracy. The EAG already critiqued the HAS decision in page 148 where it <i>“is not backed up by any trial evidence and seems incongruous to both the half-life of COL7 cited in Gurevich et al. and the estimates of doses received in the OLE study.”</i>

		month assumption. While the Company agrees that cross-agency decisions are not binding for the EAG or NICE, the acceptance of a longer closure duration by HAS supports the reasonableness of the [REDACTED] assumption (i.e., approximately 10 months), especially when modelled and described transparently. Notably, HAS was a co-rapporteur at EMA, and thus their assessment is rigorous given that it is performed in a regulatory environment.	

Issue 4 Estimation of vial usage from the patient level simulation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG questioned the estimation of vial usage from the PLS. Page 144: “First, it shows that B-VEC achieves a ‘near cure’ status by an average of 70 weeks from treatment start”	The Company suggests acknowledging the clinical scenario of small wounds making up less than 1% of the BSAP. Suggested wording:	The Company acknowledges the EAG’s concern regarding the modelled decline in BSAP to ~0% by week 70 and its maintenance thereafter. However, describing this as a “near cure” misrepresents both	This is not a matter of factual accuracy. The EAG highlights the word ‘permanent’ was not used to describe the ‘near cure’ status.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	“First, it shows that B-VEC achieves a ‘near cure’ status by an average of 70 weeks from treatment start. This assumption is based on the clinical scenario of small wounds making up less than 1% of the BSAP.”	the clinical context and the modelling rationale. BSAP measures the total wound area, not the number of wounds. Clinically, it is possible for a small number of residual or recurrent wounds to remain yet collectively account for <1% of BSA. The OLE figures cited by the EAG (61.1%-89.5% of target wounds closed at various time points) refer to wound counts, not cumulative wound area, explaining the apparent discrepancy between wound closure rates and BSAP levels. Small, residual wounds, especially if <1% of BSA, have minimal impact on BSAP. Data from GEM-1 also support the durability of B-VEC, showing sustained closure of a median of 103 days (95% CI: 94–118). In the	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		Company's PLS, reopened wounds are rapidly retreated and managed, resulting in sustained low BSAP. ²⁰ This represents effective maintenance therapy, not a permanent "cure", and aligns with how B-VEC would be used in real-world clinical practice.	

Issue 5 The company's preferred four-state model structure is dependent on a mapping algorithm which the EAG considers lacks face validity

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 93: "Further justification is needed as to why the model was developed using four disease severity states, rather than the six levels of disease severity that was used in the previous appraisals of BBE (HST28)." Page 181: "The EAG asked the company for a version of the	The Company recommends rewording to the statement on Page 93 to: "The model was developed using four disease severity states, rather than the six levels of disease severity that was used in the previous appraisal of BBE (HST28).	The Company have provided rationale for the model structure that was submitted, both in the original CS and in the response to clarification questions B4 and B15. A six-health state model as used in HST28 may have facilitated an ITC with BBE; however, this	This is not a matter of factual accuracy. The EAG critique of the model structure was stated in Section 4.3.3.6.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
company's model in the six-health state structure, but the company declined to provide one"	The health states were developed in accordance with clinical experts and published data to reflect the most realistic clinical experience." Suggested wording for Page 181: "The EAG asked the company for a version of the company's model in the six-health state structure. The company provided a rationale as to why a six-health state model was not appropriate."	was not the primary consideration in developing the model for B-VEC. The six-state HST28 model was designed to reflect the clinical profile of BBE, a symptomatic topical with modest efficacy, no disease-modifying effect, a mechanism of action that is unknown, and an indication limited to partial-thickness wounds. Its structural assumptions and health state definitions were therefore tailored to a treatment that does not alter the underlying disease process. In contrast, B-VEC is the first topical, redosable gene therapy targeting the root cause of DEB by delivering COL7A1, restoring full-length COL7 expression, normalising anchoring fibrils, and enabling durable wound closure.	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		The development of the <i>de novo</i> model for B-VEC was therefore driven by its mechanism of action, which targets the root cause of the disease, and the model was structured to capture both the acceleration and maintenance of wound closure, as well as the downstream benefits of preventing or reversing the clinical complications associated with persistent open wounds. In summary, applying the HST28 six-state structure to B-VEC would misrepresent its clinical benefit profile and mechanism of action. This incompatibility is compounded by trial design and population differences between GEM-3 and EASE, as already acknowledged in the ITC feasibility assessment, which similarly, makes direct structural	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		comparison between the two models inappropriate.	

Page 148: “in response to clarification question B5 the company stated the importance of maintenance treatment with B-VEC as it “is required to keep patients in the very mild health state and ensure that patients receive optimal benefit”, however this contradicts what is modelled where patients remain in the very mild state on BSC after discontinuing B-VEC (see Section 4.3.3.13).” Page 149-150: “In response to clarification question B5, the company identified another anomaly where “BSC TP in the HST28 model result in the entire cohort in the severe health state transitioning out of that state after a single monthly cycle, with no return to the severe state over the remaining model time horizon. This pattern does not align with the observed distribution of patients by BSA with open wounds reported in Table 10 of	The Company recommends adding the following statement to Page 149-150: “With this response, the Company highlighted issues with the underlying transition probabilities as reported in the CS for HST28”	The issue raised by the Company in response to clarification question B5 was not referring to an issue with the mapping algorithm, but rather with the underlying transition probabilities reported in the CS for HST28, where, in both BBE and BSC arms (nearly) all patients left the respective health states 5 and 6 in the first month. This would mean that no patients are left in health state 6 after 1 month, but then in the subsequent month, there are again transition probabilities from health state 6 to health state 5. Table 55 of the EAG report further demonstrates this issue, where in the BBE arm (but this also applies to the BSC arm when using HST28 transition probabilities, as is shown from the steady state distribution in BSC as referred to under EA6 on page 176), ■ of patients are	The EAG agrees with the company that this is an inherent limitation of the TPs used for BSC in the BBE appraisal and deleted the indicated text in page 149-150.

the company submission (Page 46 of 173 of HST28 Committee Papers), where the proportion of patients with >25% BSA open wounds in the BSC arm remains relatively stable between the baseline double-blind and OLE phases of EASE". The company therefore appears to acknowledge that the mapping does not provide results which replicate the health state distribution for BBE from HST28."		left in Severe health state. This is not due to the mapping (which maps all patients from health state 6 to Severe), but due to the underlying transition probabilities from HST 28, as noted in the response to clarification question B5.	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 171, Table 57, column ‘HST28 model with committee preferences’ states that the transition probabilities that were used were based on EASE.	The Company recommends rewording to: “BSC – EASE, company approximation method BBE – EASE, company approximation method”	Regarding Table 57, although we agree that transition probabilities used in the HST model with committee preferences were based on the EASE trial, the statement implies that these are the same transition probabilities as the those used in the replicated HST28 model, which is not the case, as the committee for HST28 preferred the updated transition probabilities. The updated transition probabilities were marked confidential and could therefore not be used to inform the replicated HST28 model.	Footnotes have been added to Table 57 to clarify that the committee in HST28 preferred the EAG’s approach of using transition probabilities based on observed transitions in the EASE study, whereas the company’s replicated HST28 model (and the EAG’s adaptation of that replicated model) used the transition probabilities based on the company’s approximation method as these data were not redacted.
Page 148: “the four states are not offering enough granularity.” Page 150: “Overall, the EAG thinks that the current four-state structure lacks granularity...”	The Company recommends rewording to: Page 148: “the four states do not offer enough granularity in the range of 5-25% BSAP.”	Although the Company agrees that the four-health-state model may offer less granularity in the 5-25% BSAP range, it is deliberately more granular below 5% BSAP (the range	Text amended as suggested.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	Page 150: “Overall, the EAG thinks that the current four-state structure lacks granularity in the range of 5-25% BSAP.”	where B-VEC provides unique and substantial clinical benefits for patients). In a six-state HST28 structure, this sub-5% BSAP range would be merged into broader states, diluting the resolution in the area of maximum benefit for B-VEC. From a health-economic perspective, this would risk underestimating quality-of-life gains, overstating time spent in higher-burden states, and therefore biasing the ICER against B-VEC.	
Page 151: “In the four-state model, there is a single large gain in occupancy for B-VEC from baseline to day 90 in the very mild health state. No such noticeable difference was observed in the results from the six-state model.”	The Company recommends rewording to: “In the four-state model, there is a single large gain in occupancy for B-VEC from baseline to day 90 in the very mild health state, which reflects the capacity of B-VEC to durably heal wounds and thereby bring patients to a health state with only very few and/or small wounds.”	For this reason, alongside differences in mechanism of action and trial design between B-VEC and BBE, the HST28 six-state model is not structurally compatible with modelling B-VEC’s value. Based on the mechanism of action of B-VEC and results from GEM-3 OLE,¹⁹ B-VEC has	This is not a matter of factual accuracy. The EAG critique of the very mild state was stated in Section 4.3.3.13.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		the ability to durably close wounds, which can result in patients achieving a 'Very Mild' health state, where their BSAP is <2.1%. As BBE is only a symptomatic treatment, and wounds may reopen as quickly as with BSC,²¹ this additional health state towards the lower BSAP end (<2.1%) was not relevant for HST28, but it is relevant to the current one. Further details are provided in the follow-up clarification question B15. The reason for a large gain in occupancy for B-VEC from baseline to Day 90 in the Very Mild health state is that, in the six-health state model, HS1 includes both Mild and Very Mild health states from the four-health state model. Combining these two states results in the health state occupancy	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		increasing from [REDACTED] in the four-health state model.	

Issue 6 Half-life of collagen 7

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 13: “repeat treatment will be needed to maintain skin integrity in areas where wounds were previously present due to the half-life of COL7 being estimated at 2 months.”	The Company recommends rewording to: “repeat treatment in lower frequencies may be helpful to maintain skin integrity in areas where wounds were previously present due to the half-life of COL7 being estimated at 2 months in addition to cell turnover estimated at 4-8 weeks.”	Anchoring fibrils, containing COL7, engage with collagen in the dermis to anchoring it to the epidermis, providing critical structural support for skin integrity. Topical application of B-VEC delivers the COL7A1 gene to keratinocytes and fibroblasts, leading to the production of COL7 that assembles into anchoring fibrils, restoring dermal–epidermal adhesion. The durability of therapeutic effect reflects both the cell turnover rate and the half-life of COL7, and thus exceeds the ~2-month half-life of COL7 alone. While epidermal turnover occurs every ~28 days, dermal cells turn over more	The EAG has amended the text here to make it more consistent with the text on page 146. It now states, “...due to the half-life of COL7 being estimated at 2 months in addition to cell turn-over being estimated at 4-8 weeks”. The following sentence has also been amended to mention cell-turnover rates. However, the EAG notes that the durability data from the GEM-3 study and its OLE are not relevant here as durability in GEM-3 was based on whether wounds were healed at both 3 and

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		slowly, though exact rates are unclear. It is expected that COL7 expression persists as long as transduced cells remain, with functional protein continuing to support anchoring fibrils, for weeks to months after cell turnover. This is supported by durability of response data from the US OLE study.^{18,19} Furthermore, the GEM-3 trial has shown durability in wound closure after B-VEC administration (50% of wounds exposed to B-VEC and 7% of those exposed to placebo [difference, 43 percentage points; 95% CI, 23 to 63]).²² Collectively, the evidence indicates that B-VEC administration is not dependent solely on the pharmacokinetics of COL7, and therefore does not necessitate dosing at intervals based on its half-life.	6 months but any wounds reopening between those timepoints were retreated.

Issue 7 Data sources used for the model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 151: “The EAG has additional concerns regarding the data sources used for the PLS, as well as the validity of the simulation outputs and associated assumptions as discussed previously”	The Company asks that the EAG clarify the specific data sources they are referring to and the rationale of why they are not considered appropriate.	The EAG has not provided the specific data sources that they were concerned about. Additionally, the assumptions in the Company’s economic model were validated with clinical experts to reflect the most clinically realistic and plausible inputs. For example, for wound closure parameters, GEM-1 was the best available evidence, in spite of the limitations associated with the trial. However, for the duration of closure of wounds treated with B-VEC, better data were available in GEM-3 and were therefore used for the model base case. The Company aimed to implement the best quality available evidence for use in the economic model, which is why	This is not a matter of factual accuracy. Actually, the sentence quoted from the EAG report is not complete as it misses the reference to Sections 4.3.3.4 and 4.3.3.5 where for example GEM-1 was not judged by the EAG as an ‘unsuitable’ data source.

		both GEM-1 and GEM-3 were used.	

Issue 8 Incorrect description of the company model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 107: "in the simulation, very small wounds that are 2 cm ² or smaller, are assumed to close completely in a given week once treated."	The Company recommends rewording to: "In the patient level simulation, if a patient has a total area open of 2 cm ² or less, the open area is assumed to close completely in a given week once treated."	The EAG's assumption of complete closure only applies if the total area open for a simulated patient has a total of 2 cm ² or less. The proposed change would correctly reflect the Company's economic model.	Text amended as suggested.
Page 115: "It can be seen that in the moderate and severe health states the company intended to apply lower mortality risks for RDEB patients starting treatment aged under 6 years old (highlighted by italics in Table 36). However, the EAG identified during its model verification that the data specified for ages 6 and	The Company recommends rewording to: "In the Moderate and Severe health states, the Company applied lower mortality risks for RDEB patients under 6 years of age and starting treatment	In the Excel sheets containing the Markov model in the Company's economic model, the vlookup function for mortality (columns R to U) selects different columns from the Mortality sheet for patients in the Moderate and Severe health states who start the model between the ages 0-6 compared	The company's description is incorrect regarding this issue. The formulae used in columns T and U (for moderate and severe patients) pick the same mortality risk regardless of the age group. Separate columns per age group will

over were inadvertently applied to all age categories.”	(highlighted in italics in Table 36).”	to those who start the model at later ages. This is indicated by the grey numbers on Rows 9, 821 and 1633 of the sheets containing the Markov model.	be needed to capture the different mortality risks. No changes have been made as the EAG’s description of this issue is factually accurate.

Issue 9 Reporting of sensitivity analyses

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pages 127: “The scatter plot (Figure 16), generated by the EAG running the probabilistic analysis for the company’s base-case...”	The Company recommends rewording to: "The scatter plot, generated by the EAG running the probabilistic analysis for the company’s updated base-case received in the responses from the clarification questions”	The original text may imply that the Company did not provide a probabilistic analysis; however, it was included in the CS. If the EAG had to rerun the analysis, it was to update the analysis to align to the updated base case following the Company’s responses to the clarification questions.	This is not a matter of factual accuracy. The EAG mentioned at the start of Section 4.2 that <i>“Unless specified, the information presented here concerns the post-clarification models submitted by the company.”</i> Therefore, no changes have been made.
Page 129: "In their clarification response, the company presented a tornado diagram using incremental net monetary benefit (INMB)..."	The Company recommends rewording to: “In their clarification response, the company presented a corrected	The Company also presented a tornado diagram in the CS; however, it was updated in response to clarification questions. The original text may	Text amended as suggested.

	tornado diagram using incremental net monetary benefit (INMB)”	imply that the same tornado diagram as the Company Submission was provided in response to the clarification questions.	

Issue 10 Administration of B-VEC

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 28: “The CS does not explicitly state whether B-VEC will be provided at specialist centres, at local hospitals, within primary care settings or within the patient’s own home. Reference is made in the cost-effectiveness section to ‘home delivery’ as part of the costs of administration, suggesting that the intention is for B-VEC to be administered at home but this is not explicitly stated in the CS” Page 28: “However, the need for dressing changes to be done by a healthcare professional is not consistent with the CS	The Company understands that, while prescribing is expected to be under the purview of the four specialist centres, and an initiation visit is likely to be required, the Company is actively engaged in discussions with relevant stakeholders to explore and support home-based delivery models (already a key part of the EB National Service provision). The Company are committed to providing the most convenient patient access to people living with EB, especially in the context of only four specialist centres	The intent of the Company was not to be vague, but to allow for clinical discretion and system-level implementation, which is in conversation. The inclusion of home delivery in the economic model reflects a plausible and emerging route of administration, aligning with international experience (i.e., USA), as the EAG’s clinical expert has confirmed. Furthermore, the Company notes an inconsistency in the EAG’s commentary on Page 28. The EAG initially states that the CS does not specify the setting	This is not a matter of factual accuracy. The administration setting is not clear yet as the company confirmed there are active engagement in discussions with relevant stakeholders. Therefore, no changes have been made to the report in response to this issue.

stating that wound care is often performed by patients and carers in addition to specialised nurses, and it is unclear to the EAG whether patients routinely receive weekly dressing changes by nurses in current practice.” Page 29: “However, the BAD submission goes on to comment that at present B-VEC can only be dispensed by a hospital pharmacy and it requires 2 healthcare professionals to administer it in a hospital setting, taking 2- 4 hours per week per patient.” Page 29: “The EAG’s clinical expert also noted that B-VEC administration is routinely being undertaken by patients or their caregivers in the USA where it has been approved since May 2023.”	in England and the understanding that travel of any type for people living with DEB (and their carers) can be challenging.	in which B-VEC is administered. However, in a subsequent statement, the EAG acknowledges that the CS describes wound care as being undertaken by patients and carers in addition to specialised nurses. These observations appear contradictory, as the latter implies a degree of flexibility in the administration setting that addresses the concern raised in the former.	

Issue 11 Regulatory approval in the UK

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 35: “much of the company’s description of the intervention in the CS appears to rely on its EMA approved SmPC.”	The Company recommends rewording to: “With MHRA approval expected in May 2026, the description of the intervention in the CS is based on its EMA-approved SmPC. ”	The EMA-approved SmPC is used in lieu of an MHRA-approved SmPC. However, MHRA assessment for B-VEC is scheduled for November 2025, with approval expected in May 2026, and is expected to align with the EMA.	The following text is added, <i>“The EAG notes that the MHRA approval is expected in May 2026”</i>

Issue 12 Definition of wound closure in EASE

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 38: “For the EASE trial comparing BBE to placebo, complete wound closure was assessed as the proportion of patients with first complete closure of the target EB wound at 45 days”	The Company recommends rewording to: “For the EASE trial comparing BBE to placebo, complete wound closure was assessed as the proportion of patients with first complete closure of the target EB wound within 45 days.”	EASE defines wound closure as the number of wounds closed <u>within</u> 45 days, which is distinct from wounds that are closed <u>at</u> 45 days. Assessing closure at 45 days is a more stringent criterion, potentially underestimating early healing, while assessing closure within 45 days allows inclusion of any	Text amended to “ <i>within 45 days (+/-7 days)</i> ”

		wound healing that occurred during the preceding period.	

Issue 13 BBE was noted as not disease-modifying in the committee paper for HST28

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 27: “The CS states that the NICE committee concluded that BBE, “is not disease modifying or curative,” citing the committee papers for HST28. However, the EAG were unable to identify statements to this effect in the final appraisal document (FAD) for HST28, and this text appears to have been taken from the Summary of Information for Patients for HST28.”	The Company suggests amending this statement to reflect that this text was taken from Table 2 Key issues of the Technical engagement response form of the HST28 Committee Paper. Suggested Wording: “The CS states that the NICE committee concluded that BBE, “is not disease modifying or curative,” citing the committee papers for HST28. The statement appears in Table 2 of the Technical engagement response form of the HST28 Committee Papers.”	The Company has transparently provided the PDF for the HST28 committee paper, which included the Technical engagement response form, where the corresponding statement was taken from. The statement reads: “BBE does not appear to be disease-modifying, therefore, we agree that the EAG’s approach appears reasonable.”²¹	The text the company quotes here is taken from the British Association of Dermatologists’ response to the Technical Engagement report. It therefore does not reflect the conclusion of the committee. To reflect this additional information, we have deleted the following text: “However, the EAG were unable to identify statements to this effect in the final appraisal document (FAD) for HST28, and this text appears to have been taken from the Summary of

			Information for Patients for HST28.” We have also added the following text: “At the factual accuracy check, the company clarified that its statement was based on a statement made during Technical Engagement, however, the EAG notes that the statement was made by the British Association of Dermatologists and not by the Committee.”

Issue 14 Clinical trial errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 59: “the median wound size is relatively small (74% of wounds were <20cm ²)”	The Company recommends rewording to: “74% of wounds were <20cm ² in the B-VEC arm“	The median wound size in the EAG’s statement only applies to the B-VEC arm, while the value for the control group was 71%.	Text amended as suggested.
Page 60: “the median age was 19.5 and 20.1 years (range 10-	The Company recommends rewording to: “The median age was 19.5 and 21 years	The median age for the ITT population in the EAG’s	Text amended as suggested.

35 years) for the safety and ITT populations respectively”	(range 10-35 years) for the safety and ITT populations, respectively”	statement is incorrect and should be corrected to 21 years.	

Issue 15 Various typographical errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 135 , In Box 1: The numbers of key issues 8 and 9 are swapped and don’t reflect Table 1: <i>Overview of the EAG’s key issues</i> .	Main issue (10) “B-VEC vial optimisation (Key Issue 8)” should be amended to: “(10) B-VEC vial optimisation (Key Issue 9)”. Main issue (12) should be amended to: “(12) Health states following discontinuation of B-VEC or BBE (Key Issue 8)”	Key issues 8 and 9 have been swapped. The original text is not reflective of the numbering of key issues list of key issues in Table 1, Page 5.	Text amended as suggested.
Page 17 : “morality”	The word should be corrected to: “mortality”.	The original text has a typographical error.	Text amended as suggested.
Page 105, Table 29 : Total costs for BBE with 4 health states should also have an asterisk	Row 6, column 2: “1,300,037*”	A footnote is missing.	Footnote is added.

Page 103: “..age is incorporated”	The statement should be corrected to: “should be ‘BSA is incorporated’”.	The original text has incorrectly substituted a word.	Text amended as suggested.
Page 111: “percentage of total BSAP”	“Percentage of BSA” or “BSAP” should be corrected to either 1) “Percentage of BSA” or 2) “BSAP”.	The abbreviation, BSAP, is defined as body surface area percentage, therefore stating “percentage of total BSAP” is redundant.	Text amended to “ <i>total BSAP</i> ”
Page 141: “Because the vignettes say that the person should image that...”	The statement should be reworded to: “Because the vignettes say that the person should imagine that...”	The original text has a typographical error.	Text amended as suggested.
Page 164: “compnay’s”	The word should be corrected to: “company’s”.	The original text has a typographical error.	Text amended as suggested.
Page 183: “Both compared B-VEC versus BSC”	The statement should be corrected to: “Both compared B-VEC versus placebo”.	The GEM-1 and GEM-3 trials compared B-VEC with placebo, not with BSC.	Text amended as suggested.
Page 184: “compnay’s”	The word should be corrected to: “company’s”.	The original text has a typographical error.	Text amended as suggested.
Page 25: “the risk of blindness presented in CS, Table 1.4...”	The statement should be corrected to: “the risk of	The incorrect Table was referenced.	Text amended as suggested.

	blindness presented in CS, Table 1.5...”		
Page 68: “did not render redundant concealment of allocation redundant ”	The statement should be corrected to: “did not render concealment of allocation redundant ”	Redundant is stated twice in the sentence.	Text amended as suggested.

References

1. Tang JY, Marinkovich MP, Lucas E, et al. A systematic literature review of the disease burden in patients with recessive dystrophic epidermolysis bullosa. *Orphanet J Rare Dis*. 2021;16(1):175.
2. Petrof G, Papanikolaou M, Martinez AE, et al. The epidemiology of epidermolysis bullosa in England and Wales: data from the national epidermolysis bullosa database. *Br J Dermatol*. 2022;186(5):843-848.
3. Bishnoi A, Manjunath S, Kishore K, et al. Hindi translation and validation of quality of life score in Indian patients with epidermolysis bullosa; and its correlation with the clinical severity assessment scores: A cross-sectional study. *Indian journal of dermatology, venereology and leprology*. 2022;88(2):177-183.
4. Cestari T, Prati C, Menegon DB, et al. Translation, cross-cultural adaptation and validation of the Quality of Life Evaluation in Epidermolysis Bullosa instrument in Brazilian Portuguese. *Int J Dermatol*. 2016;55(2):e94-99.
5. Eismann EA, Lucky AW, Cornwall R. Hand function and quality of life in children with epidermolysis bullosa. *Pediatr Dermatol*. 2014;31(2):176-182.
6. Fulchand S, Harris N, Li S, et al. Patient-reported outcomes and quality of life in dominant dystrophic epidermolysis bullosa: A global cross-sectional survey. *Pediatr Dermatol*. 2021;38(5):1198-1201.
7. Kang M, Chen JSC, Radjenovic M, et al. An analysis of the prevalence of osteoporosis and osteopenia in patients with epidermolysis bullosa: A cross-sectional study. *Experimental dermatology*. 2021;30(11):1675-1685.
8. Dufresne H, Hadj-Rabia S, Bodemer C. Impact of a rare chronic genodermatosis on family daily life: the example of epidermolysis bullosa. *Br J Dermatol*. 2018;179(5):1177-1178.
9. Feinstein JA, Bruckner AL, Chastek B, et al. Clinical characteristics, healthcare use, and annual costs among patients with dystrophic epidermolysis bullosa. *Orphanet J Rare Dis*. 2022;17(1):367.
10. Frew JW, Martin LK, Nijsten T, Murrell DF. Quality of life evaluation in epidermolysis bullosa (EB) through the development of the QOLEB questionnaire: an EB-specific quality of life instrument. *Br J Dermatol*. 2009;161(6):1323-1330.
11. Frew JW, Cepeda Valdes R, Fortuna G, et al. Measuring quality of life in epidermolysis bullosa in Mexico: cross-cultural validation of the Hispanic version of the Quality of Life in Epidermolysis Bullosa questionnaire. *J Am Acad Dermatol*. 2013;69(4):652-653.
12. Hernandez ARV, Alonso FM, Marin AJA, de la Paz MP. Transcultural Validation of a Spanish Version of the Quality of Life in Epidermolysis Bullosa Questionnaire. *Int J Environ Res Public Health*. 2022;19(12):7059.
13. Yuen WY, Frew JW, Veerman K, et al. Health-related quality of life in epidermolysis bullosa: Validation of the Dutch QOLEB questionnaire and assessment in the Dutch population. *Acta dermato-venereologica*. 2014;94(4):442-447.

14. Kern JS, Sprecher E, Fernandez MF, et al. Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: results from the phase III randomized double-blind phase of the EASE study. *Br J Dermatol*. 2022;188(1):12-21.
15. European Medicines Agency. Assessment report Filsuvez. Amsterdam, The Netherlands 2022.
16. Phillippo D, Ades, T., Dias, S., Palmer, S., Abrams, K. R., & Welton, N. . NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. 2016.
17. Gurevich I, Agarwal P, Zhang P, et al. In vivo topical gene therapy for recessive dystrophic epidermolysis bullosa: a phase 1 and 2 trial. *Nat Med*. 2022;28(4):780-788.
18. Agostini B, Mailliard S, Parry T. J, et al. Long-Term Treatment of Large Chronic Wounds with B-VEC. Results in Durable Healing in DEB Patients. Presented at the Society for Pediatric Dermatology 2025, Seattle, Washington 2025.
19. Marinkovich MP, Paller AS, Guide SV, et al. Long-Term Safety and Tolerability of Beremagene Geperpavec-svdt (B-VEC) in an Open-Label Extension Study of Patients with Dystrophic Epidermolysis Bullosa. *American Journal of Clinical Dermatology*. 2025;26(4):623-635.
20. Krystal Biotech Inc. GEM-1 Clinical Study Report: A Phase 1/2 Study of B-VEC, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB). 24 May 2022.
21. National Institute for Health and Care Excellence (NICE). Highly Specialised Technology Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505] Committee Papers. 20 September 2023.
22. Guide SV, Gonzalez ME, Bagci IS, et al. Trial of beremagene geperpavec (B-VEC) for dystrophic epidermolysis bullosa. *N Engl J Med*. 2022;387(24):2211-2219.

Single Technology Appraisal

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

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.

Technical engagement response form

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

1 of 31

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 as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [NICE health technology evaluations: the manual](#) (section 5.4) for more information.

The deadline for comments is **5pm on Thursday 4 December 2025**. 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.

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)	Krystal Biotech
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: - the name of the company - the amount - the purpose of funding including whether it related to a product mentioned in the stakeholder list - whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	N/A

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
Limited data available on clinical effectiveness of B-VEC in patients with dominant DEB (section 2.3.1 of EAR)	No	We acknowledge that data specific to dominant dystrophic epidermolysis bullosa (DDEB) are limited, as demonstrated in the systematic literature reviews (SLR) presented in the company submission (CS), and also as noted by the evidence assessment group (EAG). This limitation is a consequence of the rarity of the condition and should be considered in the context of a substantial unmet need. Patients with DDEB experience significant disease burden and currently have no curative or disease-modifying treatment options available. Restricting access to beremagene geperpavec (B-VEC) based on limited data availability in DDEB risks denying a highly vulnerable patient population access to a therapy supported by a biologically plausible mechanism of action. The mechanism of action of B-VEC (topical delivery of <i>alpha chain of type VII collagen (COL7A1)</i> via HSV-1 vectors) is expected to be effective in both recessive dystrophic epidermolysis bullosa (RDEB) and DDEB, as the fundamental pathology in both involves loss of functional type VII collagen (COL7) and compromised dermal-epidermal adhesion. While patients with DDEB may retain one non-mutated allele of COL7A1, this does not obviate the pathophysiological potential for B-VEC to enhance wound healing. This is supported by anecdotal evidence from clinical use in the US, where patients with DDEB have demonstrated clinical responses to B-VEC.

Technical engagement response form

Key issue	Does this response contain new evidence, data or analyses?	Response
		Additionally, patients with DDEB make up more than a quarter (29%) of all B-VEC-treated patients in the US. Further, the Haute Autorité de Santé (HAS) early access authorization report noted that birch bark extract (BBE) provides only a modest benefit to patients in clinical practice, posing uncertainties regarding the durability of wound closure.¹ This aligned with the outcome of the Structured Expert Elicitation (SEE), where the clinical experts unanimously agreed that the effect of BBE on sustained wound closure was comparable to best supportive care (BSC). Briefly, the SEE was developed to identify model inputs based on relevant clinical experience. DEB is a complex and dynamic disease, making its management challenging; therefore, the experts included in the SEE were selected for their extensive experience in treating DEB and with both B-VEC and BBE. This experience included early clinical use of the two medications, participation in pivotal trials (EASE, GEM-3, and OLE), and having published multiple studies on DEB. Further details about the SEE, including the protocol and the full results, can be found in the attached appendix. Although BBE was recommended for both RDEB and DDEB, the pivotal trial did not show differences in the primary endpoint (proportion of patients with first complete closure of the EB target wound) between BBE and control gel in patients with DDEB (odds ratio [OR] 1.25, 95%CI 0.15, 10.7),² highlighting the need for therapeutic options for patients with DDEB. This result provides indirect comparative evidence suggesting that treatment effects are not meaningfully differentiated by DEB subtype.

Key issue	Does this response contain new evidence, data or analyses?	Response
		Clinical trial experience in the GEM trials demonstrates the clinical benefit of B-VEC in patients with DDEB. In GEM-3, one patient with DDEB (Subject 01-07) achieved complete closure of the B-VEC-treated wound by Month 6, meeting the primary endpoint for multiple consecutive assessments (Weeks 22, 24, and 26), while the placebo-treated wound did not heal. Open label extension (OLE) follow-up data of this patient show durable responses at treated wound sites. Similarly, a second patient with DDEB enrolled in the GEM-3 OLE (Subject 05-02) demonstrated repeated complete closures at multiple wound sites during follow-up. Although the sample size is small, these consistent individual patient results provide direct evidence of clinical benefit in the DDEB population. We are committed to gathering more data on the safety and efficacy of B-VEC in patients with DDEB through a post-authorization study; however, this should not delay access to B-VEC for patients with DDEB, a patient group that continues to experience a substantial disease burden. B-VEC has received marketing authorization by several regulatory bodies, including the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) with all three authorities approving B-VEC for the entire DEB indication (i.e., both RDEB and DDEB). HAS also granted B-VEC expedited approval in both RDEB and DDEB with a <i>COL7A1</i> mutation.¹ Additionally, the EMA specifically noted that B-VEC is expected “to treat wounds in patients of all ages with dystrophic epidermolysis bullosa, a serious, ultrarare genetic skin blistering disease caused by mutations in the collagen type VII alpha 1 chain (<i>COL7A1</i>) gene” and that the treatment is

Key issue	Does this response contain new evidence, data or analyses?	Response
		“expected to bring substantial therapeutic benefits and improve the quality of life for patients with this skin disorder.”³ Given the context of a rare and debilitating disease with no curative or disease-modifying treatments, the mechanistic rationale supporting B-VEC use in DDEB, together with supportive anecdotal experience, direct individual patient evidence from GEM-3 and OLE, and the inclusion of DDEB in global regulatory decisions, retaining DDEB within the modelled licensed population is supported.
An ITC between B-VEC and BBE based on a comparison of trial outcomes from the GEM-3 and EASE studies has not been provided (sections 3.9 and 3.10 of EAR)	Yes	In the model included in the CS, a BBE arm was included, with effectiveness inputs derived directly from the transition probabilities reported in HST28. However, the EAG did not agree with this approach, and instead conducted an indirect treatment comparison (ITC) for complete wound closure using data from GEM-3 and EASE. The results of this ITC were then applied to the BBE transition probabilities to estimate the transition probabilities for B-VEC. The Company has several concerns about the approach adopted by the EAG, relating to the ITC itself (as detailed in the Company’s Factual Accuracy Check), and to the way in which the ITC was implemented within the cost-effectiveness model: 1. In EASE, the average body surface area (BSA) treated was 735 cm², implying that not all open wound area was treated. According to Table 10 of HST28, the mean baseline body surface area percentage (BSAP) in EASE was 12%. Assuming a mean total BSA of approximately 12,000 cm² for a 16-year-old RDEB patient, this

Technical engagement response form

Key issue	Does this response contain new evidence, data or analyses?	Response
		corresponds to an average open wound area of approximately 1,450 cm²—almost double the 735 cm² reported as treated. 2. The consumption reported in the HST28 (i.e., 29.67 tubes per month; 4.66 dressing changes per week), implies than an average of 1.46 tubes were used per dressing change. Since one tube treats up to 250 cm² according to the Summary of Product Characteristics (SmPC), this corresponds to an average treated area of 366 cm², which is substantially less than the 735 cm² reported. Basing the transitions for B-VEC on the transitions for BBE from EASE implies that B-VEC does not treat all open wounds, which would underestimate its efficacy. In contrast, the vial consumption used by the EAG was sourced from the patient-level simulation ([PLS]; 6 health states), which considered that all wounds were treated. This results in a misalignment in the model between B-VEC consumption and treatment efficacy. 3. The transition probabilities in the model relied on the ‘company approximation method’, based on data from EASE. However, both the Committee and the EAG who assessed HST28 considered the updated transition probabilities to be more appropriate. Since these updated probabilities were confidential, they could not be applied in in the replicated HST28 model. As a result, the transition matrices used in the EAG’s preferred approach are inconsistent with those used for decision making for HST28, undermining the reliability of the model. 4. There is a structural issue with the transition probabilities reported in HST28. In both the BBE and BSC arms, nearly all patients leave

Technical engagement response form

Key issue	Does this response contain new evidence, data or analyses?	Response
		their respective health state (HS) 5 and HS 6 in the first month. As a result, no patients remain in HS 6 after one month; yet, in the subsequent month, the probability of transitioning from HS 6 to HS 5 is greater than 0%. This approach (i.e., the EAG's application of the ITC to HST28 transition probabilities) prevents any incremental benefit provided by B-VEC in patients starting in HS5 or HS6 to be captured. Under this approach, all patients in these severe health states move to a less severe state in the first cycle across all treatment arms and never return. This is a model artefact of the transition set from HST28, not a reflection of real-world outcomes, and it artificially eliminates potential treatment differences in the most severe patients. 5. During the SEE, the experts had difficulty answering questions around the durability of closure and duration of closure of chronic wounds when treated BBE. This unanimous point made by all three experts highlights a key feature of BBE: due to its mechanism of action, BBE can accelerate the natural healing process that would occur with BSC, but it does not affect the skin's structure or quality as it does not address the underlying disease mechanism. Consequently, any impact on durability cannot be assessed. This is an important limitation as to why comparing the two products through an ITC would not represent a clinically realistic scenario. It is also reflected in the very different endpoints used in the respective trials. Given the limitations of the ITC and that its full incorporation would not be representative of clinically realistic scenarios, the Company has taken a

Key issue	Does this response contain new evidence, data or analyses?	Response
		compromise approach. The Company assumed that recurrent and chronic wounds have different rates of wound closure. Given that wounds in the EASE and GEM trials were relatively small, these trials may be more representative of recurrent wounds than chronic wounds. Consequently, the weekly proportion of recurrent wounds closed (16.27%) was derived from the EAG's ITC (calculation provided in Table 8 of the appendix), while other related parameters were informed by the SEE conducted by the Company. The Company is committed to collaborating with the EAG and has aligned the modelling approach of the three treatment arms to address the EAG's concerns. BBE effectiveness and tube consumption was modelled within the PLS in the same way as it was done for B-VEC and BSC. Details on the new inputs to model the BBE arm are summarised in Table 8 of the provided Appendix.
Utility values are based on a vignette study despite there being EQ-5D estimates available (section 4.3.3.2 of EAR)	Yes	In line with the EAG's preference, the updated Company model now adopts a Generalised Linear Model (GLM) based on EuroQol 5-Dimension (EQ-5D) estimates from the EASE trial for the base case analysis. The EAG also identified an issue with the age-adjustment of carer utility, which has now been corrected in the updated model.
Validity of the company's patient level simulation as a source of effectiveness estimates (section 4.3.3.5 of EAR)	Yes	The Company acknowledges the concerns that the EAG raised about the suitability of the PLS as a source of effectiveness estimates, namely that chronic and recurrent wounds treated with B-VEC should not have the same rate of closure, and that the 'near-cure' phase is implausible and occurs too soon. To address the EAG's concerns, the Company has reviewed the relevant literature and consulted with clinical experts through

Technical engagement response form

Key issue	Does this response contain new evidence, data or analyses?	Response
		the preferred SEE approach, ensuring that the model reflects the most relevant clinical scenario. Based on the mechanism of action of B-VEC, and vial usage rates observed in the OLE and real-world practice, there are two phases of chronic wound closure: • Induction phase, which covers the first few months of treatment, during which the patient has more open wounds and there is a relatively high consumption of B-VEC vials. As treatment progresses, more wounds are closed and remain closed; and • Maintenance phase begins once the patient no longer has any existing open wounds and only wounds that (re)open need to be treated. During this phase, stabilisation of consumption occurs, at a lower level than during the induction phase. Reaching the most desirable HS in the model (i.e., Very Mild in the four-health state model, or HS 1 in the updated model) does not imply that there are no open wounds. Instead, the utilities and costs associated with this health state reflect that patients still have some open wounds. It is expected that, over time, maintenance phase is reached (i.e., all wounds have closed) and treatment is required only for reopened wounds. At this stage, reopened wounds are expected to be small, such that the BSA that is open would be minimal. However, the patient would not be 'cured' and would continue to require treatment with B-VEC to close reopened wounds.

Key issue	Does this response contain new evidence, data or analyses?	Response
		To further address the EAG's concerns, a lower rate of chronic wound closure derived from clinical expert opinion in the SEE conducted by the Company has been explored, which delays the point at which patients transition to the maintenance phase. BSC arm A recently published study by Fulchand et al, followed a cohort of patients with DEB for up to 6 months and tracked the rate of spontaneous wound closure.⁴ Notably, this study was not available when the original CS was made or during the drafting of responses to the EAG's questions. The study reported that in multivariate analyses, adjusting for participant age, wound location and baseline wound size, the recurrent wounds had 29-fold higher odds of spontaneous closure compared with the chronic wounds ($p=0.0045$). As informed by published literature, an odds ratio (OR) of 29 was applied to the 14.17% closing of wounds in GEM-1, which were mostly recurrent, resulting in a weekly closure rate of 0.57% for chronic wounds treated with BSC. B-VEC arm Given the mechanism of action of B-VEC (i.e., it addresses the underlying cause of disease by restoring COL7 production), the findings from Fulchand et al. cannot be applied to chronic wounds treated with B-VEC, and SEE conducted by the Company was used to inform the model on the healing rate of the wounds treated with B-VEC. The methods and results of SEE are reported in the SEE report that accompanies this submission. Inputs for the PLS were derived based on the responses from clinical experts to

Key issue	Does this response contain new evidence, data or analyses?	Response
		questions 2 and 3 of the SEE. The PLS engine was calibrated to identify the weekly chronic wound closure rate that provides the number of weeks to full closure of the respective wound areas consistent with expert opinion. Outcomes of the SEE are provided in the accompanying SEE report. Based on SEE, it was assumed that ■■■ of chronic wounds treated with B-VEC showed some improvement, and that the weekly rate of closure for wounds that responded to treatment was 36.7%. BBE arm The experts participating in the SEE highlighted that, due to its mechanism of action, BBE can accelerate the natural healing process that would occur with BSC, but does not affect the skin's structure or quality as it does not address the underlying disease mechanism in DEB. Experts agreed that chronic wounds treated with BBE rarely close fully, and consequently they were unable to answer similar questions for BBE as they did for B-VEC. Therefore, a recently published study was used to estimate the proportion of chronic wounds responding to treatment with BBE, and their rate of closure.⁵ • The study by Davidovic et al. reported on a total of 11 chronic wounds in patients with DEB who were treated with BBE: two wounds fully closed, three showed no improvement, and six were partially closed • Therefore, wounds with any improvement (wounds that responding) mad up 73% of the chronic wounds (8/11 = 73%)

Technical engagement response form

Key issue	Does this response contain new evidence, data or analyses?	Response
		- No details were provided regarding the extent of closure for the partially closed wounds; therefore, it was assumed that they closed by 50% - At Week 0, the area open was 100%, and at 7 months (30.4 weeks), the average area open was 38% ($[2 \times 0\% + 6 \times 50\%]/8 = 38\%$) - An exponential curve was then fitted to the data, resulting in a weekly proportion of the open area closing of 3.17% Notably, outcomes related to BBE reported by the clinical experts consulted during the SEE may differ from HST28 due to differences between trial settings and real-world clinical practice, where patient profiles and wound characteristics impact wound closure. For example, clinicians often treat large and chronic wounds whereas in the EASE trial, wounds may have been smaller in size, making real-world observations more relevant. Further, the experts noted that in clinical practice a large proportion of patients treated with BBE discontinue treatment shortly after starting it. Therefore, the new Company base case includes that 37.5% of BBE patients discontinue treatment after 3 months. Further, the PLS has been adapted and is now available for the six and seven health states model structures, respectively.
Estimation of vial usage from the patient level simulation (section 4.3.3.5 of EAR)	No	The Company acknowledges the EAG's concern regarding the estimation of vial usage in the PLS. As the PLS tracks the vials consumed over time in patients whose wounds are opening and closing, the vial usage measured in this tool reflects the

Technical engagement response form

Key issue	Does this response contain new evidence, data or analyses?	Response
		induction and maintenance phase associated with B-VEC treatment discussed above. Therefore, it is a good reflection of the vial consumption in practice. In the B-VEC trials, there were no patients receiving B-VEC for all of their open wounds; therefore, vial usage data from those trials would not reflect clinical practice. It is possible that a small number of residual or recurrent wounds would remain, yet collectively account for <1% of BSA as BSAP measures the total wound area, not the number of wounds. These wounds, however, would have minimal impact on the BSA affected. Data from GEM-3 and the OLE support the durability of wound closure with B-VEC, showing sustained closure of a median of ■ days. In the Company's PLS, reopened wounds are rapidly retreated and managed, resulting in sustained low BSAP.⁶ This represents effective maintenance therapy, and aligns with how B-VEC would be used in real-world clinical practice.
The company's preferred four-state model structure is dependent on a mapping algorithm which the EAG considers lacks face validity (section 4.3.3.6 of EAR)	Yes	The Company initially submitted a model with four health states: Very Mild, Mild, Moderate, and Severe. These states were selected to align with disease severity categories reported in the literature (mild, moderate, and severe), with the additional "Very Mild" state included to represent the improved health status that patients treated with B-VEC may achieve when most or all wounds have closed. Health state definitions, based on the proportion of BSAP affected by wounds, were informed by elicitation with UK clinical experts. To improve consistency with HST28, the EAG preferred aligning the health states in the current model to the six health states used for the BBE model. In addition to ensuring consistency with the prior appraisal, the EAG

Technical engagement response form

Key issue	Does this response contain new evidence, data or analyses?	Response
		considered that a six-health-state structure provided greater granularity in disease severity, resulting in a more accurate representation of the patient trajectory. The updated base case adopts health state definitions aligned with the model used for HST28, however, the Company notes that there are limitations to this approach and has provided a scenario analysis to address some of these limitations. Specifically, although this increased granularity in the six-health-state model structure versus the four-health-state model structure is indeed the case in the ‘moderate’ disease range, the health state definitions from the HST28 model provide <i>less</i> granularity in the milder disease range. This notable because the six-state HST28 model was designed to reflect a treatment that does not alter the underlying disease process. Specifically, BBE is a symptomatic topical treatment with modest efficacy, has no disease-modifying effect, and a mechanism of action that is unknown. In contrast, B-VEC is the first topical, redosable gene therapy targeting the root cause of DEB by delivering COL7A1, restoring full-length COL7 expression, normalising anchoring fibrils, and enabling durable wound closure. A key objective of B-VEC is to transition patients to a maintenance state, where there are no open wounds and treatment is only required for reopening wounds. Therefore, the granularity in the milder health states, where there is a smaller affected BSAP, is important for capturing the value of B-VEC. Consequently, the Company also presents a scenario analysis where a seventh health state is added, to represent the changes in BSAP affected

Key issue	Does this response contain new evidence, data or analyses?	Response
		by wounds at lower BSAP. The PLS has been adapted and has been provided for the six- and seven-health state model structures. With the use of the same health state definitions as used in the HST28 model, it is no longer necessary to map inputs from HST28 to the health states used in the current model. In the original Company model with four health states, inputs were aligned by health states reported in literature (i.e., by Mild, Moderate and Severe disease). To transition to the new six health state model structure, these inputs were mapped to six health states. The definitions used to map these inputs, based on BSAP affected with wounds have been used, are presented in Table 2 of the appendix. To conclude, the Company has aligned with the EAG's expectation of using the same health states as in HST28, removing the need to map health states. The Company asks that the EAG also consider the scenario of the seven-health state model, provided in the appendix, as it captures the full value of B-VEC in the milder health states.
The plausibility of reduced clinical manifestations and mortality in patients with reduced wound burden (section 4.3.3.8 of EAR)	Yes	The literature has reported an association between increasing disease severity, defined by larger areas of open wounds, and a higher prevalence of clinical manifestations.⁷ While B-VEC does not directly treat extracutaneous manifestations of DEB, it maintains patients in less severe health states, which are associated with a lower prevalence of clinical manifestations. On this basis, and following validation by clinical experts, clinical manifestations and mortality were modelled by health state. Extracutaneous clinical manifestations that were included in the model can be indirectly affected by B-VEC through a reduction of cutaneous wounds.

Technical engagement response form

Key issue	Does this response contain new evidence, data or analyses?	Response
		To simplify the inclusion of clinical manifestations in the model and to address the EAG's concerns regarding the complexity of the calculations, the Company has adjusted the formulae estimating the prevalence of irreversible manifestations to be more transparent. The formulae no longer track the prevalence of irreversible manifestations per health state, but rather for the cohort as a whole. In addition, the Company has included a scenario analysis that excluded concomitant medication and clinical manifestations to further ensure the robustness of the model and that the EAG's concerns are addressed.
Patients discontinuing treatment are assumed to stay in the state they occupy when discontinuing (section 4.3.3.12 of EAR)	Yes	The original CS assumed that patients who discontinue treatment with B-VEC or BBE remain in the same health state achieved while on treatment. This assumption was based on the mechanism of action of B-VEC, which restores COL7 and promotes reepithelialisation, such that some degree of residual structural repair is expected to exist after discontinuation. This durability of effect was supported by clinical trial evidence, including a time to reopening of wounds of █ days, and OLE data showing that many patients maintained clinical response over time, even when treatment intervals were extended or varied. Nonetheless, the Company accepts that this assumption may be overly optimistic. Accordingly, the model has been updated to adopt a more conservative approach, whereby patients discontinuing treatment with B-VEC or BBE are redistributed across health states in line with the health state distribution observed in the BSC arm.

Key issue	Does this response contain new evidence, data or analyses?	Response
Uncertainty regarding the feasibility of vial sharing (section 4.3.3.10 of EAR)	Yes	The Company has updated the model to include a base case of 80% vial optimisation, and scenario analyses of 0%, 50%, and 70% to address the EAG's concern about the feasibility of vial sharing. The Company acknowledges the lack of real-world published data supporting vial sharing of B-VEC. However, based on healthcare provider feedback and published literature considering medications other than B-VEC, it is appropriate to consider vial sharing in the model. Local UK clinicians and pharmacists have agreed to both the importance and feasibility of vial sharing, and there is agreement among stakeholders that vial optimisation is in the best interest of the NHSE as the service matures. Additionally, vial optimisation is a widely recognised strategy to reduce wastage and improve healthcare resource use and is commonly practiced in hospitals worldwide. In fact, Suzuki et al. reported that vial optimisation is practiced in approximately 83% of countries.⁸ Despite this, it is underused in HTA submissions. This concept helps to reduce wastage and results in cost savings, as shown in a study from the UK, where vial sharing strategies resulted in cost savings in 74% of cases.⁹ Furthermore, there are other examples supporting vial sharing from countries other than the UK. In the US, vial sharing is not permitted; however, the maximum weekly treatable wound area is smaller (160 cm²) than in Europe (200 cm²). As a result, European practice allows a single vial to treat a larger wound area, which is expected to support faster healing and reduce overall vial consumption over time. In addition, evidence from a French centre (n = 22) showed that vial optimisation reduced vial consumption by 35%. French clinical experts anticipate that efficiency will

Technical engagement response form

Key issue	Does this response contain new evidence, data or analyses?	Response
		continue to improve as the service becomes more established, supported by better coordination across centres and improvements in patients' health states over time, enabling multiple patients to be treated from a single vial. Taken together, these support the feasibility of vial sharing in clinical practice and associated benefits, such as reduced drug wastage and cost savings. Therefore, the application of vial sharing in the model is appropriate.

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: The EAG raised concerns regarding the modelling of mortality, specifically which survival curves from Petrof et al. (RDEB severe versus RDEB non-severe) should be applied to each health state, and the choice of parametric model used in the analysis.	Section 4.3.3.9	No	In accordance with EAG preference, the updated Company model now uses the Gompertz curve for both severe and non-severe RDEB. Additionally, the curve for severe RDEB is only used for the worst health state (HS 6 in the six health state structure), and all other health states have survival according to the curve for non-severe RDEB from Petrof et al. ¹⁰ Mortality assumptions for the proportion of the cohort with DDEB have remained unchanged.

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 2: The EAG requested that the Company provide an additional arm in the model, where B-VEC and BBE are administered concurrently.	NA; this request was made via email.	No	The Company acknowledges the EAG's request to introduce an arm including concurrent use of B-VEC and BBE. B-VEC is expected to facilitate durable wound closure and consequently reduce long-term treatment requirements, resulting in a lower consumption of medication over time. Given the limited time available, it was not feasible to integrate an additional arm into the model. Doing so would have required substantial revisions to the model structure, including updates to clinical, economic, and utility inputs, transition probabilities, as well as changes to the PLS and sensitivity analyses. These changes could not be completed within the available timeframe without compromising the methodological rigor of the model. Additionally, although the Company understand the request, but given the lack of data on the combination use of B-VEC and BBE, and the supporting clinical expert opinion the EAG has noted, incorporation of this arm into the model would introduce substantial additional uncertainty into the model. In addition, the Company has not seen B-VEC and BBE use in combination in the markets where they are commercially available.

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 3: The EAG identified an issue in the model, where the 33 patients representing themselves in reporting DEB subtype were double counted.	Section 4.2.1	Yes	This error has now been corrected. The values presented in Table 3 of the appendix are derived from published literature. ⁷ Based on these values, the updated model now assumes that 37% of patients treated with B-VEC have DDEB, and that 63% have RDEB.
Additional issue 4: The time horizon of the PLS was originally set at 3 years, after which the last set of transition probabilities were repeated in the Markov model. However, as by 3 years patients did not transition to new health states in both the B-VEC and BSC arm, this assumption implies that patients neither continued to improve nor deteriorate.	NA	Yes	Given the reduced rate of closure of chronic wounds in the B-VEC arm and the modelling of BBE within the PLS, it may take longer than initially modelled to reach a phase where patients are no longer moving between health states. Therefore, to ensure further transitions in health states are captured beyond 3 years, the time horizon of the PLS has been extended to 10 years.

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 (PAS discount not applied)

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	Incremental impact on the company's base-case incremental cost-effectiveness ratio (ICER)	
			Vs BSC	Vs BBE
	Previous company base case		ICER: [REDACTED] NMB*: [REDACTED]	ICER: [REDACTED] NMB*: [REDACTED]
Health state after treatment discontinuation	Patients that discontinue treatment with B- VEC or BBE remain in the same health state as they were in while on treatment.	Patients who discontinue treatment with B-VEC or BBE are now redistributed over the health states according to the distribution in the BSC arm.	ICER: [REDACTED] NMB*: [REDACTED] Incremental change vs previous base case: [REDACTED]	N/A
Clinical manifestations	A complex formula was used to calculate the prevalence of	The modelling of irreversible clinical manifestations has been simplified and is no longer reported per health state, but rather for the entire cohort.	ICER: [REDACTED] NMB*: [REDACTED] Incremental change vs	N/A

Technical engagement response form

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	Incremental impact on the company's base-case incremental cost-effectiveness ratio (ICER)	
			Vs BSC	Vs BBE
	irreversible manifestations.		previous base case: [REDACTED]	
Mortality	An exponential curve was used to model mortality.	Mortality is now modelled using the Gompertz curve for severe and non-severe RDEB, and the curve for severe RDEB is only used for the worst health state (HS 6 in the six health state structure), whereas all other health states incorporate the survival curve reported in Petrof et al. ¹⁰ for RDEB non-severe.	ICER: [REDACTED] NMB*: [REDACTED] Incremental change vs previous base case: [REDACTED]	N/A
Utility values caregivers	Patient utilities were derived from a vignette study.	A GLM based on EASE data is now used in the base case analysis.	ICER: [REDACTED] NMB*: [REDACTED] Incremental change vs previous base case: [REDACTED]	N/A
Four health state model structure	The model had four health states: Very Mild, Mild, Moderate and Severe. Inputs from HST28 were mapped onto the	The updated base case now uses a six-health state structure, aligned to the model used in HST28. A scenario analysis incorporating a seventh health state is presented to accurately reflect the effect of B-VEC in patients with a lower BSAP affected by wounds.	ICER: [REDACTED] NMB*: [REDACTED] Incremental change vs	N/A

Technical engagement response form

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	Incremental impact on the company's base-case incremental cost-effectiveness ratio (ICER)	
			Vs BSC	Vs BBE
	four health state structure.	The number of weekly reopened wounds was derived from published literature, where the average number of recurrent and chronic wounds per patient was 11 (SD: 10; range 0, 45) and 3 (SD: 2; range 0, 9), respectively. A normal distribution was assumed and the 16.7 th , 33.3 th , 50 th , 66.7 th and 83.3 th percentiles were used to provide the lower-bound of the health states 2, 3, 4, 5 and 6 respectively (Table 4 of the appendix). Baseline distribution over health states, clinical manifestations, and concomitant medication use was mapped onto the six health state structure (Tables 5-7 in the appendix).	previous base case: [REDACTED]	
PLS as a source of cost- effectiveness estimates	Chronic and recurrent wounds treated with B- VEC had the same rate of closure.	For the BSC arm, an odds ratio of 29 was applied to the 14.17% closing of wounds (which were mostly recurrent) in GEM-1 based on a newly published study. A weekly proportion of 0.57% wounds closing is now applied for chronic wounds treated with BSC. In the B-VEC arm, [REDACTED] of chronic wounds treated with B-VEC show some improvement. Wounds that response to treatment have a weekly closing rate of 36.7%. Finally, in the BBE arm, the weekly proportion of the open area closing was 3.17%, as described above.	ICER: [REDACTED] NMB*: [REDACTED] Incremental change vs previous base case: [REDACTED]	N/A

Technical engagement response form

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	Incremental impact on the company's base-case incremental cost-effectiveness ratio (ICER)	
			Vs BSC	Vs BBE
	The standard error (■■■■) was used to calculate the size of a reopened wound.	The Company implemented the use of standard deviation (4.41) as correctly suggested by the EAG approach in the model; however, it resulted in numerous instances where the predicted size of reopened wounds was negative, which is not clinically plausible. To address this issue, a lognormal distribution with the same mean and standard deviation was used in place of a normal distribution. As shown in Figure 1 of the appendix, the lognormal distribution provides a good fit to the data while ensuring that wound sizes are not negative values.	ICER: ■■■■ NMB*: ■■■■ Incremental change vs previous base case: ■■■■	NA
ITC	The model included a BBE arm, for which effectiveness inputs were informed directly by the transition probabilities reported in the Company	The updated model aligns the modelling of all treatment arms. BBE effectiveness and tube consumption are now modelled within the PLS using the same approach applied to B-VEC and BSC. Inputs used for BBE in the PLS are summarised in Table 8 of the appendix.	ICER: ■■■■ NMB*: ■■■■ Incremental change vs previous base case: ■■■■	ICER: ■■■■ NMB*: ■■■■ Incremental change vs previous base case: ■■■■

Technical engagement response form

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	Incremental impact on the company's base-case incremental cost-effectiveness ratio (ICER)	
			Vs BSC	Vs BBE
	Submission for HST28.			
Discontinuation BBE	8.3% after 90 days, in line with HST28	37.5% in line with clinical expert feedback	ICER: [REDACTED] NMB*: [REDACTED] Incremental change vs previous base case: [REDACTED]	ICER: [REDACTED] NMB*: [REDACTED] Incremental change vs previous base case: [REDACTED]
Utility values patient	There was an error in the implementation of age-adjustment of the utility of carers.	The error noted by the EAG has been corrected.	ICER: [REDACTED] NMB*: [REDACTED] Incremental change vs previous base case: [REDACTED]	ICER: [REDACTED] NMB*: [REDACTED] Incremental change vs previous base case: [REDACTED]
PAS discount New company base case	No discount	[REDACTED] PAS discount	ICER: [REDACTED] NMB*: [REDACTED] Incremental change vs previous base case: [REDACTED]	ICER: [REDACTED] NMB*: [REDACTED] Incremental change vs previous base case: [REDACTED]

*NMB calculated considering a threshold of £36,000 (£30,000 * 1.2 multiplier)

Technical engagement response form

Sensitivity analyses around revised base case

Table 1: Scenario analyses around revised base case

Scenario	ICER	
	vs BSC	vs BBE (at list price)
Company base case		
7 health state model structure		
Vial optimization proportion: 70%		
Vial optimization proportion: 50%		
Vial optimization proportion: 0%		
Duration of wound closure B-VEC:		
Baseline distribution over health states based on EASE trial		
Clinical manifestations and concomitant medications excluded		
BBE discontinuation at 90 days: 25%		
BBE discontinuation at 90 days: 50%		

BBE, birch bark extract; B-VEC, beremagene geperpavec; ICER, incremental cost-effectiveness ratio

Results validation

Figure 1 presents the distribution of patients over health states over time, where patients in the BBE arm show greater improvements versus baseline than patients in the BSC arm, but less than patients in the B-VEC arm. Validity of model outcomes can also be observed from the average BSAP over time in the BBE arm, calculated from the current model (in the scenario analysis where baseline distribution over the health states is in line with EASE trial), compared to the observed change from baseline in the EASE trial, showing good alignment.

Figure 1: Distribution of patients over health states

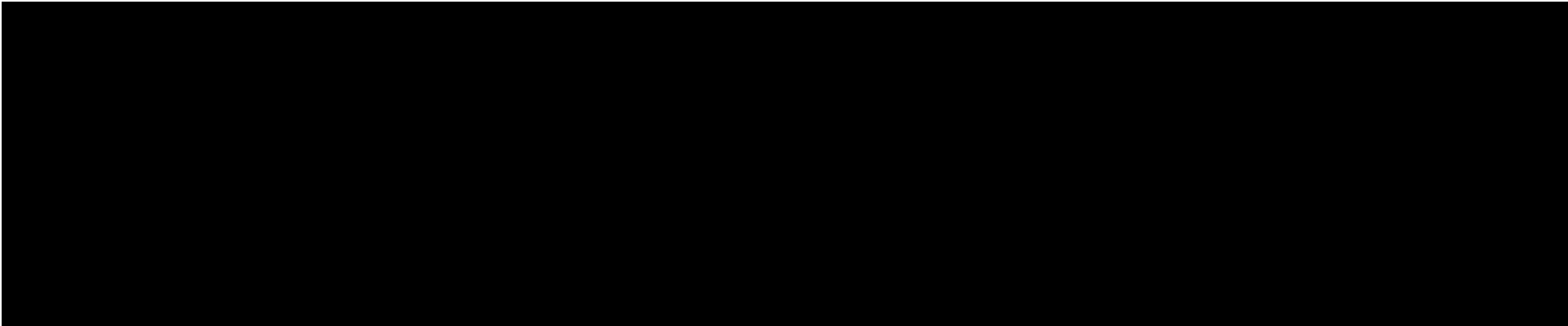


Table 2: Change in BSAP over time in BBE arm of current model (with EASE baseline distribution) compared to EASE trial

	Current model						Average BSAP	BSAP change from baseline	EASE BSAP change from baseline ¹¹
	HS1	HS2	HS3	HS4	HS5	HS6			
Average BSA within health state									
Time (months)	Distribution over health states								
0									
3									-4.2%
12									-5.9%
24									-3.7%

BSA, body surface area; BSAP, body surface area percentage; HS, health state

References

1. Haute Autorité de Santé. Décision n° 2025.0224/DC/SEM du 2 octobre 2025 du collège de la Haute Autorité de santé portant autorisation d'accès précoce de la spécialité VYJUVEK (bérémagène géperpavec). 2024.
2. Kern JS, Sprecher E, Fernandez MF, et al. Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: results from the phase III randomized double-blind phase of the EASE study. *Br J Dermatol*. 2022;188(1):12-21.
3. European Medicines Agency (EMA). Human medicines in 2025. 2026; <https://www.ema.europa.eu/en/news/human-medicines-2025>.
4. Fulchand S, Nazaroff J, Harris N, et al. Natural history study of recessive dystrophic epidermolysis bullosa wounds and patient reported outcomes using mobile application home photography. *Sci Rep*. 2025;15(1):28767.
5. Davidovic M, Gewert S, Has C. Real-World Experience With Oleogel-S10 for Wounds in Epidermolysis Bullosa. *JEADV Clinical Practice*.n/a(n/a).
6. Krystal Biotech Inc. GEM-1 Clinical Study Report: A Phase 1/2 Study of B-VEC, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB). 24 May 2022.
7. Eng VA, Solis DC, Gorell ES, et al. Patient-reported outcomes and quality of life in recessive dystrophic epidermolysis bullosa: A global cross-sectional survey. *J Am Acad Dermatol*. 2021;85(5):1161-1167.
8. Suzuki S, Gilbar P, Yu B, et al. Current status of drug vial optimization use to prevent waste associated with injectable anticancer agents. *J Oncol Pharm Pract*. 2019;25(1):244-246.
9. Gilbar PJ, Chambers CR, Musicco F. Preventing drug vial wastage and reducing expenditure associated with injectable cancer drugs: International oncology pharmacy survey. *J Oncol Pharm Pract*. 2022;28(6):1332-1339.
10. Petrof G, Papanikolaou M, Martinez AE, et al. The epidemiology of epidermolysis bullosa in England and Wales: data from the national epidermolysis bullosa database. *Br J Dermatol*. 2022;186(5):843-848.
11. Direktoratet medisinske produkter. Filsuvez methodological assessment report 2025.

ID3959 TECHNICAL ENGAGEMENT APPENDIX

To ensure the robustness of the cost-effectiveness model, the new scenario analyses listed in Table 1 have been included.

Table 1: Updated scenario analyses

Scenario analysis	Description
1	Duration of closure of [REDACTED] days for the B-VEC arm
2	Exclusion of concomitant medications and clinical manifestations from the model, to address the concerns by the EAG (Key Issue 7)
3	Baseline distribution over health states in line with the EASE trial
4	0%, 50%, and 70% vial optimisation to address uncertainty about feasibility of vial optimisation
5	Model structure with seven health states to capture the efficacy of B-VEC in patients with lower BSA affected by wounds
6	26% and 50% discontinuation in the BBE arm

BBE, birch bark extract; BSA, body surface area; B-VEC, beremagene geperpavec; EAG, External Assessment Group.

Table 2: Comparison of health state definitions between the initial company model, HST28, and the presented scenario analysis

Initial Company model (4 health states)	New company base case (6 health states; based on HST28)	Scenario analysis (7 health states)
Very Mild (BSAP ≤2.1%)	HS1 (BSAP <5%)	HS1 (BSAP ≤2.1%)
Mild (BSAP 2.1-5%)		HS2 (BSAP 2.1 - <5%)
Moderate (BSAP 5-25%)	HS2 (BSAP 5 - <8%)	HS3 (BSAP 5 - <8%)
	HS3 (BSAP 8 - <11%)	HS4 (BSAP 8 - <11%)
	HS4 (BSAP 11 - <19%)	HS5 (BSAP 11 - <19%)
	HS5 (BSAP 19 - <25%)	HS6 (BSAP 19 - <25%)
Severe (BSAP >25%)	HS6 (BSAP ≥25%)	HS7 (BSAP ≥25%)

BSAP, body surface area percentage; HSX, health state X.

Table 3: Distribution of patients according to disease subtype

Subtype	Self-reported, n	Caregiver reported, n	Total, n (%)
DDEB	14	17	31 (37%)
RDEB	19	34	53 (63%)
Total	33	51	84 (100%)

DDEB, dominant dystrophic epidermolysis bullosa; RDEB, recessive dystrophic epidermolysis bullosa.

Table 4: Number of wounds per health state at risk of reopening

Health state		Number of chronic wounds Range (average)	Number of recurrent wounds Range (average)
6 health states	7 health states		
HS1	HS1 and HS2	0-1 (0.5)	0-1 (0.5)
HS2	HS3	2-2 (2)	2-6 (4)
HS3	HS4	3-3 (3)	7-10 (8.5)
HS4	HS5	3-3 (3)	11-15 (13)
HS5	HS6	4-4 (4)	16-20 (18)
HS6	HS7	>5 (7)	>20 (33)

HSX, health state X.

Table 5: Baseline distribution over health states in six health state model structure

Health state	RDEB	DDEB	Note
HS1	0%	0%	Assumption
HS2	11%	38%	Mild in Bruckner et al ¹
HS3	10%	10%	Moderate in Bruckner et al, divided by three ¹
HS4	10%	10%	
HS5	10%	10%	
HS6	60%	33%	Severe in Bruckner et al ¹

DDEB, dominant dystrophic epidermolysis bullosa; HSX, health state X; RDEB, recessive dystrophic epidermolysis bullosa.

Table 6: Probabilities and rates of clinical manifestations in six health state model structure

Health state	Reversible (probabilities)			Irreversible (rates)			Category Eng et al ²
	Infections	Anaemia	Osteoporosis	SCC	Mitten deformity of foot	Mitten deformity of hand	
HS1	36.4%	22.7%	4.6%	0%	0.72%	0.06%	Mild
HS2	72.5%	55%	7.5%	0.06%	0.77%	0.16%	Moderate
HS3	72.5%	55%	7.5%	0.06%	0.77%	0.16%	
HS4	72.5%	55%	7.5%	0.06%	0.77%	0.16%	
HS5	72.5%	55%	7.5%	0.06%	0.77%	0.16%	
HS6	76.2%	76.2%	28.6%	0.25%	1.97%	0.32%	Severe

HSX, health state X; SCC, squamous cell carcinoma.

Table 7: Concomitant medication use by health state in the six-health state model structure

	Psychiatric medications		Routine analgesics			Anti-itch medication			Laxatives	Topical anti-biotics	Medi-honey	Analgesics (dressing changes)			Category Eng et al ²
	SSRI/TCA	Benzodiazepines	Ibuprofen	Gabapentin	Opiates	First gen anti-histamines	Second gen anti-histamines	Topical corticosteroids				Ibuprofen	Gabapentin	Opiates	
HS1	14%	0%	50%	0%	14%	23%	14%	5%	50%	77%	0%	23%	0%	9%	Mild
HS2	5%	5%	63%	15%	23%	18%	10%	13%	38%	65%	20%	40%	15%	18%	Moderate
HS3	5%	5%	63%	15%	23%	18%	10%	13%	38%	65%	20%	40%	15%	18%	
HS4	5%	5%	63%	15%	23%	18%	10%	13%	38%	65%	20%	40%	15%	18%	
HS5	5%	5%	63%	15%	23%	18%	10%	13%	38%	65%	20%	40%	15%	18%	Severe
HS6	14%	14%	57%	29%	52%	43%	29%	10%	48%	48%	29%	38%	19%	43%	

HSX, health state X; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants

Figure 1: Distribution of wound size at the time of reopening

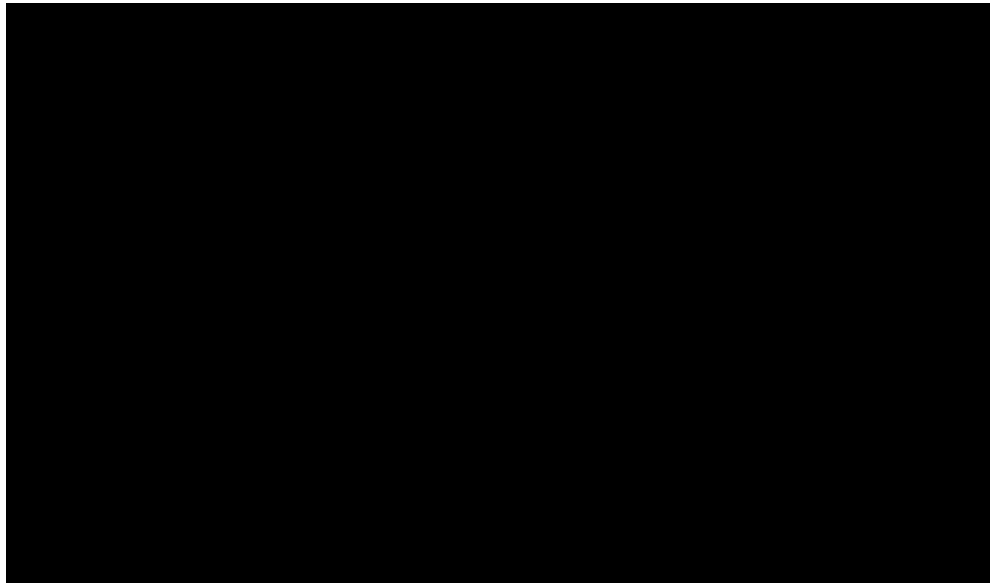


Table 8: PLS inputs for BBE

Parameter	Value	Source
Weekly closing proportion of recurrent wounds	16.27%	Based on EAG's ITC: $1 - e^{\frac{\ln(1-B-VEC \text{ proportion})}{3.12}}$
Proportion of chronic wounds that improve	73%	Davidovic et al. 2025 ³
Weekly closing proportion of chronic wounds that improve	3.17%	Davidovic et al. 2025 ³
Median time to wound reopening	14.7 days	SEE
Area treated per tube	250 cm ²	BBE SmPC
Average dressing changes per week	3	Davidovic et al. 2025 ³

BBE, birch bark extract; B-VEC, beremagene geperpavec; EAG, External Assessment Group; ITC, indirect treatment comparison; PLS, patient-level simulation; SEE, structured expert elicitation; SmPC, summary of product characteristics.

References

1. Bruckner AL, Losow M, Wisk J, et al. The challenges of living with and managing epidermolysis bullosa: insights from patients and caregivers. *Orphanet J Rare Dis.* 2020;15(1):1.
2. Eng VA, Solis DC, Gorell ES, et al. Patient-reported outcomes and quality of life in recessive dystrophic epidermolysis bullosa: A global cross-sectional survey. *J Am Acad Dermatol.* 2021;85(5):1161-1167.
3. Davidovic M, Gewert S, Has C. Real-World Experience With Oleogel-S10 for Wounds in Epidermolysis Bullosa. *JEADV Clinical Practice*.n/a(n/a).

Structured Expert Elicitation to Inform Key Parameters included in the Cost-Effectiveness Analysis of B-VEC in DEB

Report

29 January 2026
Version 1.0

Table of Contents

Table of Contents	2
Abbreviations.....	5
1. Introduction	6
1.1. Background	6
1.2. The methodological approach.....	7
1.3. Objectives	8
2. Identification and selection of experts.....	8
2.1.1. Remuneration	8
2.1.2. Conflicts of interest	8
3. Structured expert elicitation (SEE).....	9
3.1. Quantities	9
3.2. Evidence Dossier	10
3.3. Training and preparation.....	10
3.3.1. Training materials and managing bias	10
3.3.2. Pilot phase and material refinement	11
3.4. Individual elicitation	11
3.4.1. Encoding judgements	12
3.5. Elicitation workshop	13
3.5.1. Encoding judgements	13
3.5.2. Personnel roles.....	14
3.5.3. Fitting distributions and aggregation	15
3.5.4. Feedback	16
3.6. Data protection and anonymity	17
4. Results	18
4.1. SEE	18
4.1.1. Clinician selection	18
4.1.2. The quantities.....	19
4.1.3. Individual elicitations.....	19
4.1.4. Group elicitation.....	21
4.1.5. Feedback	26
4.2. Validation of assumptions for the health economic model.....	27
4.2.1. Question 1	27
4.2.2. Question 2	28
4.2.3. Question 3	28
4.3. Conclusions	29
5. References.....	32
6. Appendix A: Evidence Dossier.....	36

List of tables

Table 1 Roles allocated to project personnel	14
Table 2 Description of clinicians who participated in the SEE.....	18
Table 3 Quantiles elicited from each expert during the individual elicitations of Quantity 2	20
Table 4 Quantiles elicited from each expert during the individual elicitation of Quantity 1	21
Table 5 Quantiles elicited after the group discussion of Quantity 1	22
Table 6 Quantiles elicited from each expert during the individual elicitation of Quantity 3	23
Table 7 Quantiles elicited after the group discussion of Quantity 3.....	23
Table 8 Quantiles elicited from each expert during the individual elicitation of Quantity 4	24
Table 9 Quantiles elicited after the group discussion of Quantity 4.....	26
Table 10 Feedback from experts about the elicitation.....	27

List of Figures

Figure 1 Example probability distribution plot.....	16
Figure 2 Probability distributions of each individual elicitation for Quantity 2 and final distribution after pooling.	20
Figure 3 Final probability distribution for Quantity 1	22
Figure 4 Final probability distribution for Quantity 3	24
Figure 5 Final probability distribution for Quantity 4	26

Abbreviations

Acronym	Definition
BBE	Birch bark extract
B-VEC	Beremagene geperpavec
CEM	Cost-effectiveness model
COL7	Type VII collagen
COL7A1	Collagen type VII alpha 1 chain
DEB	Dystrophic epidermolysis bullosa
DSU	Decision Support Unit
EAG	Evidence Assessment Group
EU	European Union
FIM	Fixed interval method
HRQoL	Health-related quality of life
HSV-1	Herpes simplex virus type 1
ID	Identification
L	Lower bound
M	Median
MRC	Medical Research Council
NICE	National Institute for Health and Care Excellence
p25	25 th percentile
p50	50 th percentile
p75	75 th percentile
Q	Quantity
SEE	Structured expert elicitation
SHELF	Sheffield elicitation framework
SLR	Systematic Literature Review
U	Upper bound
UK	United Kingdom
VIM	Variable-interval method

1. Introduction

1.1. Background

Dystrophic epidermolysis bullosa (DEB) is a rare, inherited, and debilitating skin fragility disorder caused by mutations in the collagen type VII alpha 1 chain (COL7A1) gene encoding type VII collagen. [1, 2] It typically presents at birth or within the first year of life and is characterized by painful blistering and scarring of the skin following minimal trauma, leading to persistent wounds, impaired healing, and cumulative morbidities over time. [1, 3-5] People with DEB experience extracutaneous manifestations, progressive complications, and premature mortality, often due to aggressive squamous cell carcinoma in severe cases. [4, 6-9] The disease has a profound impact on daily functioning and results in substantial decrements in health-related quality of life (HRQoL), necessitating lifelong management. [5, 10, 11]

The current standard of care for DEB is limited to symptom management and secondary complication control, which inadequately addresses the disease. [11, 12] Wound care is time-consuming, painful, and distressing, often requiring hours of daily attention, multiple dressing changes, and assistance from caregivers, with the burden increasing alongside disease severity. [5, 11, 13] There are no approved curative or NICE-recommended disease-modifying therapies; while birch bark extract (BBE) is approved in the United Kingdom (UK) and Europe and has been positively evaluated by National Institute for Health and Care Excellence (NICE), its mechanism remains incompletely defined, its benefits – though meaningful in wound healing – are not curative, and it does not modify the underlying disease course. [14-18]

Beremagene geperpavec (B-VEC) is a replication-defective herpes simplex virus type 1 (HSV-1) – based gene therapy vector that has been engineered to deliver the COL7A1 gene encoding type VII collagen (COL7). [19, 20] The HSV-1 platform has a large payload capacity suitable for the full COL7A1 gene, natural tropism for skin cells, and the ability to evade host immune responses, enabling repeat topical dosing without integration into host DNA. Following cutaneous application, B-VEC transduces keratinocytes and fibroblasts, depositing its genome in the nucleus to initiate transcription of full-length human COL7A1. The resulting COL7 protein is secreted and assembles into anchoring fibrils, which are critical for dermal–epidermal adhesion and skin integrity. [19, 20]

Clinical development of B-VEC has demonstrated its ability to deliver functional COL7A1, restore ultrastructural features of the skin, and normalize anchoring fibril formation. In the pivotal phase 3 trial, 71% of B-VEC–treated wounds achieved complete closure at 3 months (vs 20% placebo), and 67% remained closed at 6 months (vs 22% placebo). Durability of response, defined as 100% closure at both 3 and 6 months, was observed in 50% of B-VEC – treated wounds compared with 7% in the placebo group. These findings establish B-VEC as the first gene therapy to demonstrate clinically meaningful and durable wound healing in patients with DEB.

A cost-effectiveness model (CEM) for B-VEC in the treatment of DEB has been developed and submitted as part of the reimbursement application to the NICE in England. During its review, the Evidence Assessment Group (EAG) identified an important uncertainty regarding the rate of closure of chronic, large wounds treated with B-VEC. In the natural history of DEB, recurrent wounds typically heal but are prone to re-blistering, whereas chronic wounds remain open for eight weeks or longer and present greater challenges to healing. However, data from the GEM trials do not provide sufficient evidence to distinguish between closure rates of chronic *versus* recurrent wounds, meaning the differential impact of B-VEC across these wound types cannot be directly quantified. As a result, the submitted version of the CEM assumed identical closure rates for both recurrent and chronic wounds, an approach the EAG considered implausible.

Additionally, from the review of the EAG it became clear that there was also an evidence gap for the rate of closing of chronic wounds treated with BBE, one of the comparator treatments in the CEM, as well as for how long (any) wounds that were closed through treatment with BBE remain closed.

To address these evidence gaps, a structured expert elicitation (SEE) is warranted. NICE guidance indicates that in the absence of robust empirical data—whether from randomized controlled trials, non-randomized studies, or patient registries—expert elicitation can provide credible evidence to inform model assumptions, with structured approaches explicitly preferred [7]. Conducting a SEE therefore enabled incorporation of expert judgment on the likely differential effect of B-VEC in chronic versus recurrent wounds, strengthening the evidence base and ensuring that the CEM more accurately reflects real-world clinical practice.

1.2. The methodological approach

Model parameters in economic evaluations are often uncertain due to a limited or poorly documented evidence base. This uncertainty must be characterised, as analyses using uncertain evidence may mislead decision-makers and are likely to be challenged by the NICE committee. Expert input is therefore essential to validate the model structure and parameters.

In this context, the current project consists of a SEE process aimed to quantify expert judgments on the wound closure in chronic wounds treated with B-VEC, and the duration of closure of wounds treated with BBE. The SEE process followed a three-step approach: the review of the evidence dossier and following the SEE training, an individual elicitation process, and a workshop where the elicitation was performed again in a moderated group session.

1.3. Objectives

The SEE aims to generate quantitative estimates for key inputs in the CEM, targeting specific values and their variability, ensuring that the inputs are accurately quantified for robust model calibration.

2. Identification and selection of experts

For the SEE process six experts were recruited, as outlined in the Sheffield elicitation framework (SHELF) guidance.[21]. Additionally, a member of the Krystal Biotech medical team participates in the pilot exercises (see Section and 3.3.2).

The clinicians who participated to the SEE process have a minimum of one year of clinical experience with B-VEC and BBE, in addition to specialist expertise in DEB diagnosis, management, and wound care.

The panel therefore included dermatologists with clinical experience with B-VEC and BBE, ensuring that judgments are informed by both disease knowledge and real-world therapeutic use. Given the rarity of the condition and the specific aim of eliciting information on the closure of chronic *versus* recurrent wounds, no geographical restrictions were imposed on expert selection, as differences in clinical practice are not expected to impact the efficacy of B-VEC.

The participants had substantive expertise, that is possess skills and knowledge about the domain of interest, regarding the assessment, treatment, and management of DEB.

Normative expertise (the participant's ability to accurately assess and communicate their beliefs in probabilistic form) was not a necessary criterion and, therefore, was not assessed. Training surrounding encoding judgements and biases was provided during the first SEE workshop to improve normative skills.

2.1.1. Remuneration

Contingent on the completion of the workshops and the feedback on the workshop minutes, participants received financial remuneration based on fair market value.

2.1.2. Conflicts of interest

Participants were asked to disclose relevant personal or financial conflicts of interest. It was not possible to involve only clinicians who had no previous involvement with the sponsor company due to the condition's rarity. Those with the most experience in the field are also most likely to report potential conflicts of interest [22]. Thus, the project team from the sponsoring company should use its discretion when selecting experts, ensuring a diverse sample is ultimately included to 'balance out' the effect of motivational biases. It is important to note that all participating experts had consultancy

roles with both the manufacturer of B-VEC (Krystal Biotech) and the manufacturer of BBE (Chiesi Farmaceutici).

Below the declarations of interests of the three experts who participated in the SEE process:

- [REDACTED]: “I am advisor for Chiesi and Krystal, I have also given talks for both companies, as well as for Novartis and Regeneron.”
- [REDACTED]: “I served as consultant for Krystal biotech and Chiesi Farmaceutici.”
- [REDACTED]: “I performed various meeting, and advisory board in the last two years with Krystal, Chiesi, Sunpharma.”

3. Structured expert elicitation (SEE)

SEE refers to a process of quantifying, typically in probabilistic form, expert judgements about uncertain quantities [21-24].

While there are no standardised guidelines for conducting SEE, NICE provides generic guidance stating that, in the absence of empirical data from randomised control trials, non-randomised studies or registries, expert elicitation can be used to provide evidence and specifies structured approaches as preferred [25, 26].

As such, the project aligns to the SHELF, developed by Professor Oakley and Professor O’Hagan of the Sheffield University [21]; this framework was largely mentioned and recommended in the last NICE Decision Support Unit (DSU) [22]. SHELF is very flexible, allowing multiple methodological approaches for different scenarios.

The goal of the SEE is to maximise the robustness of the estimation of the uncertain quantity of interest, i.e. key quantitative input used in the CEM, and to manage the associated uncertainty.

As previously mentioned, the SEE process was structured around three main phases: the training and preparation, the individual elicitation process, and a final workshop for group discussion with final elicitations and mathematical aggregation. Each step is presented in detail in Sections 3.3, 3.4, and 3.5 below.

3.1. Quantities

The quantities elicited are the relative closure of chronic wounds treated with B-VEC, and the duration of closure of wounds treated with BBE.

These quantities were selected because:

- data from the GEM trials do not provide sufficient evidence to distinguish between closure rates of chronic wounds, meaning the differential impact of B-VEC across these wound types cannot be directly quantified.
- the duration of wounds closure under treatment with BBE, one of the comparator treatments in the CEM is not available in EASE trial or published real-world experience.

Initially, the SEE included quantities relating to closure of chronic wounds under BBE. However, experts indicated that they were unable to provide informed estimates for these quantities due to insufficient follow-up and limited experience with comparable cases. On this basis, the planned BBE chronic-wound quantities were removed from the elicitation via a formal protocol amendment (SEE_B-VEC in DEB_Protocol Amendment_5 January 2026).

3.2. Evidence Dossier

To mitigate availability bias, an evidence dossier contextualising the questions presented, and summarising evidence related to the quantities of interest was developed. The evidence dossier was informed based on the Systematic Literature Review (SLR) that has been conducted for inclusion in the dossier for the National Institute for Health and Care Excellence and any additional unpublished evidence on B-VEC treatment efficacy provided by the manufacturer.

Aligning with the methods outlined in SHELF protocol, the dossiers included a short description of the objectives of the SEE, of the quantities to elicit, of trials of interest, in addition to the existing estimates of the quantities of interest, where available, or relevant data to reduce bias during the elicitation. The dossier included relevant details of the methods and results reported in the identified articles. Moreover, the sociodemographic and clinical characteristics and baseline outcomes were outlined for the identified studies to provide context for the sample's outcomes.

The evidence dossier was shared with the experts one week prior to the individual elicitation (See **Appendix A: Evidence Dossier**).

3.3. Training and preparation

3.3.1. Training materials and managing bias

A training slide-deck was produced and shared with the experts with the evidence dossier at one week prior to the individual elicitation. The training slide-deck was developed using resources available from the SHELF website. In addition, the experts were requested to follow the online SHELF training. As such, the experts were trained on the concept of subjective probabilities and the elicitation process, with a specific focus on the explanation of the upper and lower plausible limits and quartile method, that is the provision of the 25th (p25), 50th (median), and 75th (p75) percentiles for the quantity of interest (see Section 3.5.1). The training ensured that experts understood how to express their uncertainty and beliefs in probabilistic terms prior to the elicitation.

Importantly, to ensure the participating experts can sufficiently understand and describe their beliefs in probabilistic terms, training was provided to facilitate normative skills, including a description of the impact of bias and heuristics (outlined below).

- **Cognitive Biases** arise when decision-makers do not process the full range of available information, resulting from limitations in cognitive capacity, time pressure, or a lack of motivation to expend cognitive effort on a task. Said biases may also arise when the individual does not possess sufficient normative skills and cannot make appropriate probabilistic judgements, hence the necessity of training. Influential types of cognitive bias include anchoring (i.e. where the expert fixates on an initially presented value) and availability (i.e. where the expert relies on salient examples of an outcome, neglecting those that less easily come to mind) bias [22].
- **Motivational Biases** (also referred to as ‘self-serving’ biases) result from the participant being invested in a specific outcome (for instance, the efficacy of a particular treatment). Acknowledging relevant conflicts of interest may mitigate motivational bias; however, experts are conversely susceptible to availability bias from doing so as information is made salient, hence the cited eligibility criteria and presentation of an evidence dossier. Influential types of motivational bias include confirmation (i.e. where the experts provide estimates that align with their existing beliefs and preferences) and desirability (i.e. where the expert overestimates the likelihood of positive events) bias [22].
- **Overconfidence Bias** refers to the uncertainty surrounding future outcomes being underestimated and may result from the cited cognitive and motivation biases. Overconfidence bias can result in the elicited probability distributions being too narrow and may indicate insufficient substantive expertise or result from a fear of being judged by the other experts for their uncertainty [22].

The evidence dossier was sent at least one week before individual elicitation meeting.

3.3.2. Pilot phase and material refinement

A pilot exercise was conducted with one clinician member of Krystal Biotech team, employing the methods outlined in the current report. The pilot exercise followed the same procedure and have the same goals described in Section 3.4. The pilot participant was also asked to identify and provide additional relevant articles (if any are available that were not included in the dossier). The results determined whether the training materials, evidence dossier, judgement encoding material and post-task feedback require alterations. Based on the elicited feedback, the project team updated the materials (e.g. phrasing, language, question order) as necessary.

3.4. Individual elicitation

Individual-level elicitation, whereby an expert provides judgements independently without interacting with other experts or the facilitator, is cited as the most effective

way of eliciting beliefs as it mitigates the risk of bias due to experts influencing each other and promotes accountability to the decision-maker [22, 27-29]. Moreover, it is the preferred level of elicitation specified in the SHELF protocol, in SHELF and in the DSU [21, 22, 26].

The individual elicitation meeting consisted of two parts:

- First part: A brief recap of the SHELF online training to ensure that all clinical experts are aligned with the elicitation methodology. During this part an example quantity was shown "what proportion of DEB patients are recessive DEB?". This example helped experts to understand the thinking process behind forming judgments for each of the parameters in the elicitation.
- Second part: Completion of the individual elicitation. This was carried out independently by each expert, although participants were able to ask questions or request clarification regarding the task as needed.

The individual elicitation interviews were conducted online via Microsoft Teams on 29 December 2025, 8 January 2026, and 19 January 2026, respectively (one session per expert).

3.4.1. Encoding judgements

A variable-interval method (VIM), specifically the quartile approach, was used to encode experts' judgements as probability distributions. There is no conclusive evidence supporting the variable versus the fixed interval method (FIM), but the latest DSU pointed out the hidden complexity linked to the selection of the appropriate granularity of the bins for the "bins and chips" method, that is one of the most commonly used FIM. We aligned with this indication and opted for the VIM approach.

Experts first defined plausible limits (i.e. the value such that the expert believes there is a 0.01 probability that the quantity of interest fall below or above the limit, with a 0.98 probability that the 'true' value falls between each limit). They were trained to test their range by gauging their reaction to an imagined scenario where someone provides an estimate that falls above or below the cited limits; if they responded that the person has misunderstood or misremembered, it was assumed they are confident in their judgement. [30] After the plausible limits' elicitation, that minimise the risk of cognitive bias, the experts were asked to elicit the median (50th percentiles), then the 25th and 75th percentiles for all quantities (quartile method). [21]

We selected the appropriate probability distribution based on the dependence structure of the quantities being elicited. In the simplest case, when the probabilities are considered independent (e.g., single proportions such as the probability of an event occurring in a population), we used Beta distributions, elicited via the 25th, 50th, and 75th percentiles. These were fitted using an excel elicitation file. When the probabilities correspond to mutually exclusive and collectively exhaustive categories

without a natural hierarchy (e.g., probabilities of choosing between three different treatments), we used a Dirichlet distribution. The experts were asked to provide the 25th, 50th, and 75th percentiles for each category, and these were used to fit the Dirichlet distribution by estimating the α parameters via the quartile method.

The experts were provided with an overview and instructions for the encoding task and given an example to ensure they possess the necessary normative skills.

An excel elicitation file was built to enter the elicited summaries and fit suitable distributions, selected according to the dependence structure of each quantity:

- Independent proportions (e.g. probability of a single event) were modelled with Beta distributions derived from the quartiles; the plausible limits were used to fine-tune the shape parameters.
- Positive continuous quantities (e.g. time to event or treatment duration) were represented by Gamma distributions.

3.5. Elicitation workshop

As explained in Section 3.4 above, individual-level elicitation is considered the most appropriate way to elicit beliefs [21, 22, 26-29]. However, a limitation of relying solely on individual-level elicitation concerns whether experts feel confident expressing uncertainty without engaging in group discussion. The elicitation workshop mitigates this limitation, whereby experts engaged in group discussion, and their beliefs were elicited again. The workshop was held online and delivered via the teleconferencing application Microsoft Teams.

The SHELF [21] recommends that experts, following the provision of judgements individually, engages in a facilitated group discussion until they reach a consensus. The approach taken for the current study implemented this approach.

Only the quantities for which the estimated distributions differed substantially among experts were discussed at the workshop.

When expert estimates were aligned, with no substantial differences, their distributions were mathematically aggregated (pooled) offline.

3.5.1. Encoding judgements

For each quantity, the experts provided estimates independently using the same method used for the individual elicitations (see Section 3.4).

Subsequently, the distribution of their responses was presented, and the experts discussed differences in their judgements, share their expertise and opinion, and consider their rationale for their beliefs. This group discussion should facilitate the understanding of the rationale behind the individual elicitation and any potential disagreement in the distributions among the experts. Consensus is not forced, but

understanding the differences and their rationale is essential. To facilitate the exercise, the facilitator introduced the perspective of the RIO (Rational Impartial Observer), a hypothetical individual who is fully informed by the evidence and the discussion, but free from personal biases or interests. Experts were asked to step into the RIO's perspective for the second elicitation and provide a revised judgment that reflected what such an impartial observer might believe, considering all the information shared during the discussion. This step helped to reduce anchoring and overconfidence and encouraged convergence toward a well-informed distribution.

The facilitator and coordinator actively engaged with experts during the workshops to confirm comprehension and address questions.

After discussion of each quantity, the group with the support of the analyst and the facilitator provided upper and lower plausible limits along with quantiles for each quantity. The probability distribution was shown to the experts and final adjustments of the quantities were made if needed. Once the discrepant quantities were finalised, the validation of the main assumptions of the economic model was planned. If no time was left for the validation, then they were included in the minutes circulated after the workshop.

Minutes were drafted describing the group discussion, the evidence, the justifications of the values for the quantities of interest. The minutes were shared with participants to ensure they accurately reflected the discussion, and the final distributions. Means and standard deviations of the final distributions as well as 95% confidence intervals were shared with the experts in the minutes. Feedback about the process was also collected in the minutes.

3.5.2. Personnel roles

Group discussions are subject to influential group members dominating discussions [31-33]. Experts may also be reluctant to discuss or provide opposing beliefs due to fear of adverse social judgement or evaluations from other group members (referred to as 'evaluation apprehension') [34, 35]. Thus, the roles allocated to project personnel, including that of a facilitator, were clearly defined (summarised in Table 1), as recommended in the SHELF methods.

Table 1 Roles allocated to project personnel

Role	Definition	Personnel
Client	The person or organisation requiring the elicitation. The client provides input for the wider context.	Raul Arocho
Coordinator	The person (or people) responsible for coordinating	Maria De Francesco

	the elicitation activity, including the pre-elicitation tasks and training.	
Facilitator	The person responsible for managing the elicitation workshops, engaging the entire group and protecting the process from becoming dominated by a subset of the experts. The facilitator works with the experts to obtain accurate judgements and emboldens them to avoid the suppression of opposing beliefs to reach a (false) consensus.	Maria De Francesco
Analyst	The person responsible for running the distribution fitting software during the second workshop.	Joana Canilho
Adviser	An individual with knowledge of the field that is capable of assisting the team to avoid miscommunication or misinterpretation between the facilitator and experts.	Marjolijn van Keep

3.5.3. Fitting distributions and aggregation

For quantities that were similar among the experts after the individual elicitation, mathematical aggregation, specifically linear pooling, was employed to generate an aggregated distribution representing an average of the distributions elicited from each expert. Linear pooling is the most common aggregation approach used in healthcare decision-making and acknowledges diversity of expertise, allowing between-expert variability to be reflected in an overall distribution [22, 36]. Following each elicitation exercise, a suitable parametric distribution was fitted to the experts' elicited values, and the single distributions were mathematically aggregated using equal weights. The analyses were performed using an Excel elicitation file based on the R-based functions provided by SHELF [21].

Plots comparing fitted distributions with experts' quantiles (i.e., to assess goodness of fit) and the experts' individual and aggregate probability distributions were produced.

Figure 1 displays an example of a plot comparing individual and pooled distributions.

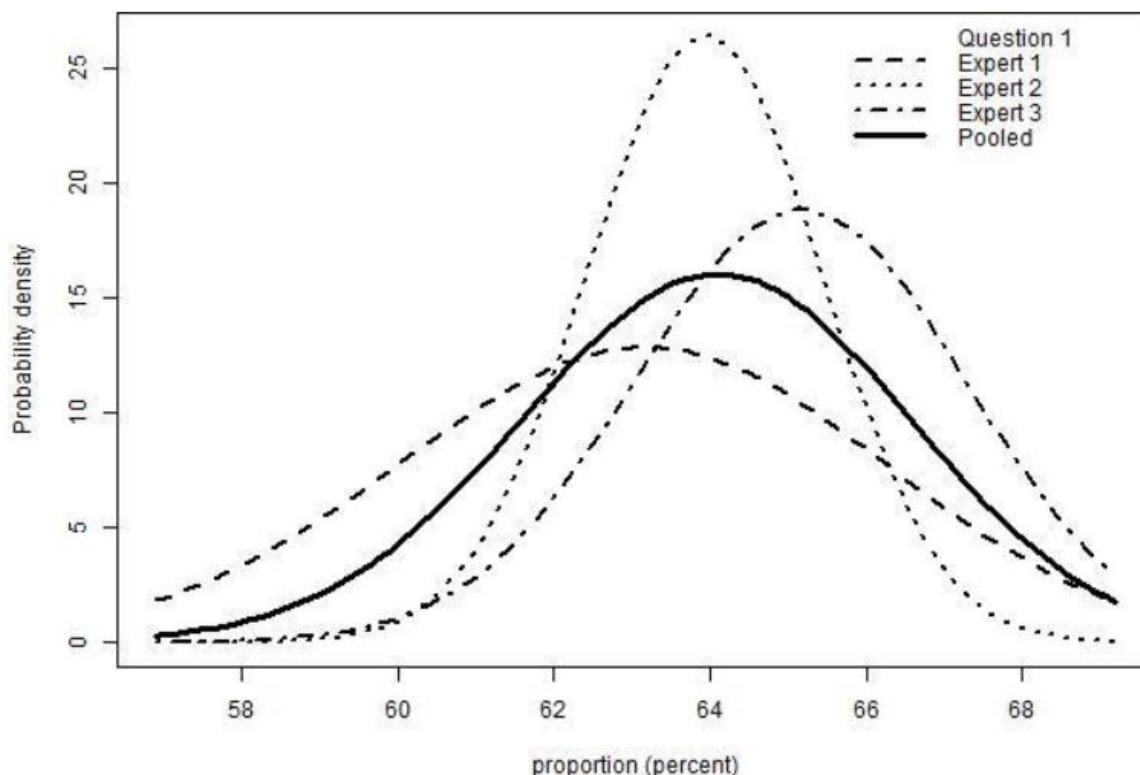


Figure 1 Example probability distribution plot

* The data displayed are an example and not representative of the quantities of interest or anticipated results [37].

The generated distribution plot was displayed to the experts to inform the group discussion before commencing a second elicitation exercise. The mean (expected value) of the pooled distributions was calculated, representing the point estimate for each parameter.

The final distributions were presented to the experts. Experts had the opportunity to review and provide comments on these final distributions. Any feedback received during this stage was documented.

3.5.4. Feedback

3.5.4.1. Rationale statements

During the elicitation workshop, experts provided a rationale for their answers, including how and why they made their judgements, checking the internal consistency of the expert's response, recording assumptions and limiting bias [22, 38]. Namely, collecting feedback enables experts to explore their knowledge (knowledge that is not frequently expressed precisely), maintain self-consistency and, therefore, avoid cognitive biases [38]. Healthcare professionals from different specialisations possess differing levels of normative and substantive skills as the context in which they work may expose them to different clinical experiences. Consequently, the reasoning

underpinning their judgements may explain between-expert variation in responses [22].

The facilitator encouraged the experts to refer to and explicitly explore the rationales provided during the individual-level elicitation exercises, and the justification behind subsequent revisions was noted in the follow-up rationale statements.

3.5.4.2. Qualitative feedback

In the minutes, experts were presented with a short post-exercise questionnaire to obtain qualitative feedback on the procedure [22].

The questionnaire enable the project team to assess the understanding of the process of the experts, with a focus on:

- How easy or difficult the experts found the completion of the judgement encoding exercises (five-point Likert scale).
- Whether or not the training provided was sufficient.
- Whether the group discussions influenced the expert's responses and, if so, in what ways (discrete choice).

The feedback questions can also be useful for understanding potential outliers; if the exercise, for example, was not clear to one of the experts, their judgement might be incorrect, more biased, or more uncertain than others.

3.6. Data protection and anonymity

Participants completed the individual elicitation exercise during the first workshop. Subsequently, the dataset was saved and will be stored on a password-protected network drive for ten years following project completion. Responses did not contain personally identifiable data, and participants were identified only using their response ID letter. The project team was able to identify individual responses via the experts' allocated ID letter; however, anonymity was maintained within the workshops (unless individuals choose to disclose their answers) and reporting (e.g. publications).

4. Results

4.1. SEE

4.1.1. Clinician selection

Clinicians were identified based on their expertise in the diagnosis and management of DEB and their experience with B-VEC and BBE. All six clinicians approached were dermatologists, of whom three agreed to participate in the SEE. Table 2 presents the identities and key characteristics of the three participating clinicians.

Table 2 Description of clinicians who participated in the SEE

Name	Affiliation	City	Specialisation
██████████	██████████	██████	Dermatologist
██████████	██████████	██████	Dermatologist
██████████	██████████	██████	Dermatologist

██████████, dermatologist, leads one of the largest B-VEC treatment centres outside the European Union (EU) and was among the first sites to treat a patient with B-VEC (December 2023). She also participated in the BBE clinical trial and has authored multiple publications in DEB, including on BBE. “I am trained as a dermatologist and have more than 30 years of working experience. For about 15 years, my activities were focused on genetics and dermatologic research: genetic testing for EB and other genodermatoses, genetic basis of skin fragility, molecular mechanisms of EB and genotype-phenotype correlations. In the last 8 years I am the senior dermatologist taking care of patients with EB and since 2024 I am the lead of the EB centre in Freiburg, the main EB centre in Germany. Currently my research is focused on translational readthrough drugs for EB and on modelling the systemic complications of EB.”

██████████, dermatologist, was among the early EU centres to initiate B-VEC treatment (from May 2024). She also participated in the BBE clinical trial and has authored several publications in DEB, including on B-VEC. “I started dealing with genetic skin diseases, such as Epidermolysis bullosa, since 2010 during my fifth year in med school and continued through dermatology residency program. I currently work as a first-level medical consultant in paediatric dermatology and I’m in charge of the genodermatoses outpatient clinic at Ospedale Maggiore Policlinico in Milan.”

██████████ dermatologist, was the only EU clinician involved in the GEM-3 and OLE studies. Two Italian patients in the B-VEC programme were enrolled from her hospital, and she was a visiting physician with Prof. Marinkovich to follow patients during both GEM-3 and OLE. She has co-authored multiple DEB publications, including with Prof. Marinkovich. “During my specialization I was with a Grant , Debra International , at San Thomas Hospital ,London, England for learn how to manage patients with EB,

during the years 1995-1999. Since 2014 I work in a University hospital at Policlinico of Bari, Italy, and I have in charge adults patients with EB. In 2022 I was in United States, in California, at Stanford University for a period, to follow two patients with EB from my country who were participating to a trial with BVEC.”

4.1.2. The quantities

Four quantities were included for the elicitation.

One quantity was a proportion (fit with the beta distribution):

Q1 Among chronic wounds (open >8 weeks) treated with B-VEC, what proportion show any measurable improvement (i.e., any reduction in wound area from baseline) over time?

Three quantities were time duration (fit with the gamma distribution):

Q2 Consider a wound area that has been open for more than 8 weeks, located on the back, with baseline area 1,200 cm² (≈50% of an RDEB adult back) that has shown any measurable improvement after starting treatment with B-VEC. Assuming B-VEC can be applied to a maximum of 200 cm² per week, how many weeks from the first B-VEC application does it typically take for the wound area to reach complete closure?

Q3 Consider a wound area that has been open for more than 8 weeks located on the elbow, with baseline area 50 cm² (≈8% of an RDEB adult arm) that has shown any measurable improvement after starting treatment with B-VEC. Assuming B-VEC can be applied to a maximum of 200 cm² per week, how many weeks from the first B-VEC application does it typically take for the wound area to reach complete closure?

Q4 Once a recurrent or chronic wound treated with BBE has fully closed (100% epithelialization with no drainage), for how many days does it typically remain closed?

4.1.3. Individual elicitations

Individual elicitations were organised between the expert and the facilitator. They lasted around 1 hour and 15 minutes each.

An initial analysis was conducted for all quantities. Only one quantity (Q2) showed close alignment across experts' fitted distributions; therefore, mathematical aggregation (pooling) was applied for this quantity. The results of this analysis are reported in the following paragraph, and all experts confirmed that they were satisfied with the resulting probability distributions.

Quantity 2

“Consider a wound area that has been open for more than 8 weeks, located on the back, with baseline area 1,200 cm² (≈50% of an RDEB adult back) that has shown any

measurable improvement after starting treatment with B-VEC. Assuming B-VEC can be applied to a maximum of 200 cm² per week, how many weeks from the first B-VEC application does it typically take for the wound area to reach complete closure?”

The quantiles in Table 3 were elicited during the individual elicitation.

Table 3 Quantiles elicited from each expert during the individual elicitations of Quantity 2

	ExpA	ExpB	ExpC
L	20.0	10.0	24
p25	30.0	25.0	26
p50	32.0	30.0	30
p75	35.0	36.0	35
U	45.0	45.0	50

Abbreviations: Exp: Expert; L: Lower bound; p25: 25th percentile; p50: Median (50th percentile); p75: 75th percentile; U: Upper bound.

Group elicitation was not performed during the final workshop since the individual elicitation outputs were highly aligned across experts (very similar lower/upper limits, medians, and quartiles), with the three distributions strongly overlapping. Then, the quantiles elicited were mathematically aggregated. The plots of the individual probability distributions and of the pooled distribution are reported in Figure 2.

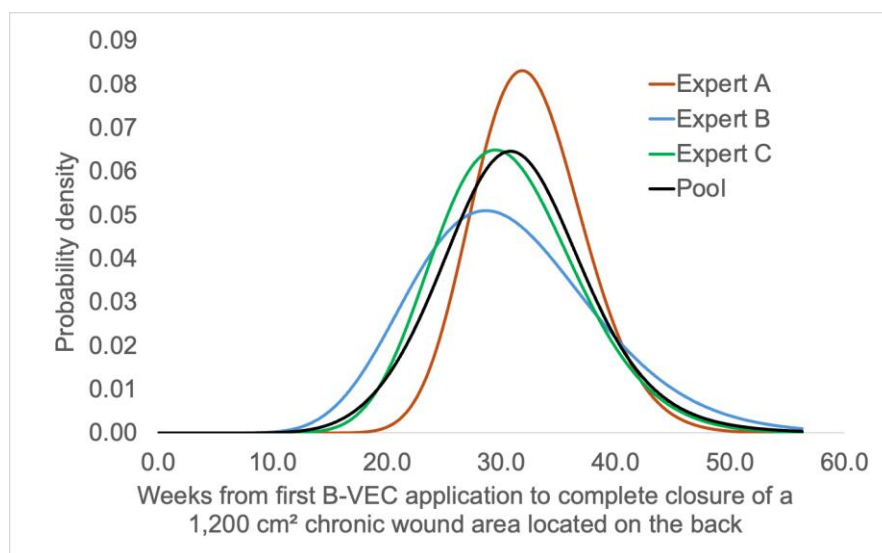


Figure 2 Probability distributions of each individual elicitation for Quantity 2 and final distribution after pooling.

The mean and standard deviation of the pooled distribution are 31.30 and 6.49 weeks, respectively. The 2.5-, 50.0-, and 97.5-quantiles are 19.04, 31.07, and 45.12, respectively. The median was closely aligned to the mean and the interquartile range was reported as consistent

During the final workshop, the facilitator presented the pooled distribution to the experts. Experts were comfortable with the result and raised no concerns during the review of Quantity 2, reflecting it as a strong-consensus input.

4.1.4. Group elicitation

The quantities included in this paragraph are the ones selected for discussion during the final workshop because judged significantly different among experts. Quantity 2 was not selected for discussion since the responses from the three experts on the individual elicitation were quite aligned.

The final workshop was held on January 27th 2026 and lasted approximately 1 hour and 30 minutes.

Quantity 1

“Among chronic wounds (open >8 weeks) treated with B-VEC, what proportion show any measurable improvement (i.e., any reduction in wound area from baseline) over time?”

The individual elicitations presented in Table 4 were showed during the group discussion.

Table 4 Quantiles elicited from each expert during the individual elicitation of Quantity 1

	ExpA	ExpB	ExpC
L	■	■	■
p25	■	■	■
p50	■	■	■
p75	■	■	■
U	■	■	■

Abbreviations: Exp: Expert; L: Lower bound; p25: 25th percentile; p50: Median (50th percentile); p75: 75th percentile; U: Upper bound.

The facilitator presented the experts with the fitted distributions from the individual elicitations and noted that, while the responses were not completely misaligned, there were clear differences in the shape and spread of the distributions. In particular, it was highlighted that Expert B had set a much lower lower-plausible limit (and therefore a wider spread), whereas Expert C’s distribution was more skewed toward higher response rates, and Expert A was broadly aligned with Expert C but allowed slightly more uncertainty.

Expert A explained that most chronic wounds show measurable change, with only a small number of very chronic wounds showing little response; however, Expert A acknowledged that confounding factors (e.g., patient-level variability such as nutritional status and other factors) can influence response, and stated that if revising scores, they would likely increase their lower values. A indicated they could agree with

L = 5 and preferred to keep U = , shifting more probability mass toward the upper end of the distribution.

Expert B agreed with the points raised by Expert A and with the proposed L and U. The facilitator reiterated that “any improvement” does not mean complete closure, but any reduction in wound burden, either in size or depth, to ensure consistent interpretation across experts.

Expert A took the initiative to propose the U and L values as and , respectively. Expert C and Expert B agreed. Expert C recognized that proposed in the individual elicitation, but can agree that some wounds can be non-responders, then the was considered reasonable for all the experts.

The quantiles presented in Table 5 were elicited and all experts agreed with the distribution in Figure 3.

Table 5 Quantiles elicited after the group discussion of Quantity 1

L	
p25 (Q1)	
p50 (M)	
p75 (Q3)	
U	

Abbreviations: L: Lower bound; p25: 25th percentile; p50: Median (50th percentile); p75: 75th percentile; Q: Quantile; U: Upper bound.

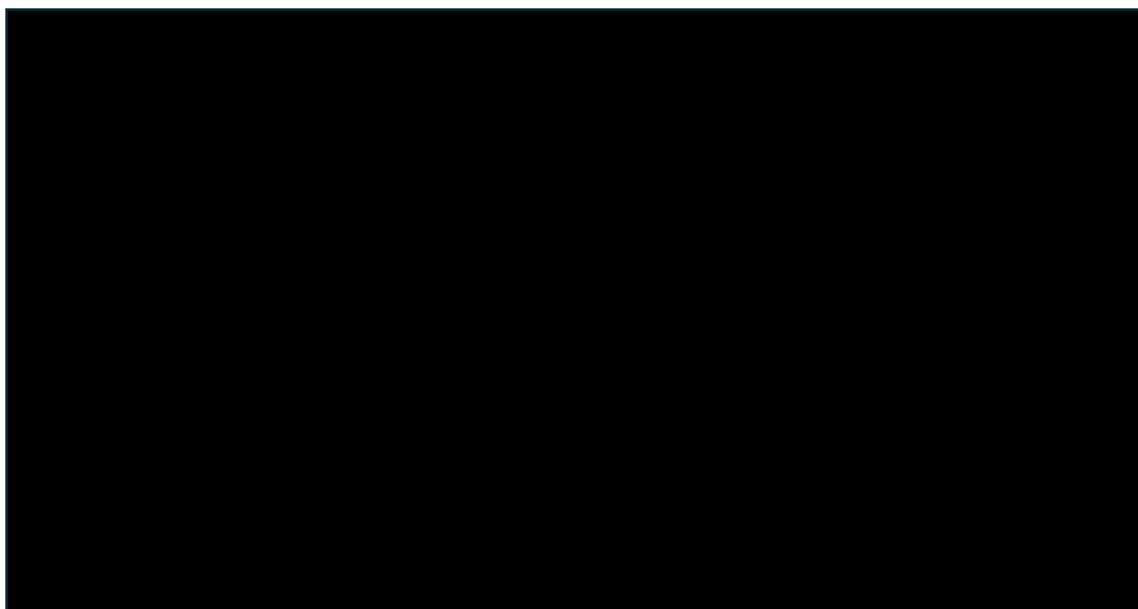


Figure 3 Final probability distribution for Quantity 1

The mean and standard deviation of the fitted distribution were and , respectively; the 2.5-, 50.0-, and 97.5-quantiles are , and , respectively.

Quantity 3

“Consider a wound area that has been open for more than 8 weeks located on the elbow, with baseline area 50 cm² (~8% of an RDEB adult arm) that has shown any measurable improvement after starting treatment with B-VEC. Assuming B-VEC can be applied to a maximum of 200 cm² per week, how many weeks from the first B-VEC application does it typically take for the wound area to reach complete closure?”

The individual elicitations presented in Table 6 were shown to the experts and briefly discussed.

Table 6 Quantiles elicited from each expert during the individual elicitation of Quantity 3

	ExpA	ExpB	ExpC
L	2.0	2.0	4.0
p25	5.0	4.0	8.0
p50	7.0	7.0	12.0
p75	7.5	8.0	18.0
U	8.0	10.0	30.0

Abbreviations: Exp: Expert; L: Lower bound; p25: 25th percentile; p50: Median (50th percentile); p75: 75th percentile; U: Upper bound.

The facilitator noted that Expert A's plausible limits had a relatively narrow spread (2–8 weeks), Expert C's were much wider (4–30 weeks), and Expert C proposed a longer time to closure (higher central estimate) than A and B.

Expert C explained that the longer duration reflected the elbow being a high-friction/trauma-prone site, which can be harder to heal in daily life; however, when reconsidering the small wound size (50 cm²), she indicated closure could be closer to the lower end (e.g., ~5 weeks) and proposed revising his upper plausible limit down to 12 weeks (L=2, U=12).

Expert A thinks even considering an elbow, his experience is that it can heal fast, then she prefers to keep his response close by what she said in the individual elicitation.

Expert B supported keeping the median at 7 weeks, noting the wound is still chronic and located in a high-friction area.

Expert C said that median should be close to L, for example 5. B prefers to assume median as 7. Expert A agreed with Expert B but Expert C really prefer 4-5 weeks. Expert B justified why she prefers 7 as median, saying that since it is an area with high friction and the wound is chronic, it probably took more time than 5 weeks and would prefer to assume 7. Expert C was convinced with this argument, then they all agree to follow with an M of 7.

Expert B suggested 5 for the p25 and they all agreed.

Expert C suggested 9 for the p75 and they all agreed.

The quantiles presented in Table 7 were elicited and all experts agreed with the distribution in Figure 4.

Table 7 Quantiles elicited after the group discussion of Quantity 3

L	2.0

p25 (Q1)	5.0
p50 (M)	7.0
p75 (Q3)	9.0
U	12.0

Abbreviations: L: Lower bound; p25: 25th percentile; p50: Median (50th percentile); p75: 75th percentile; Q: Quantile; U: Upper bound.

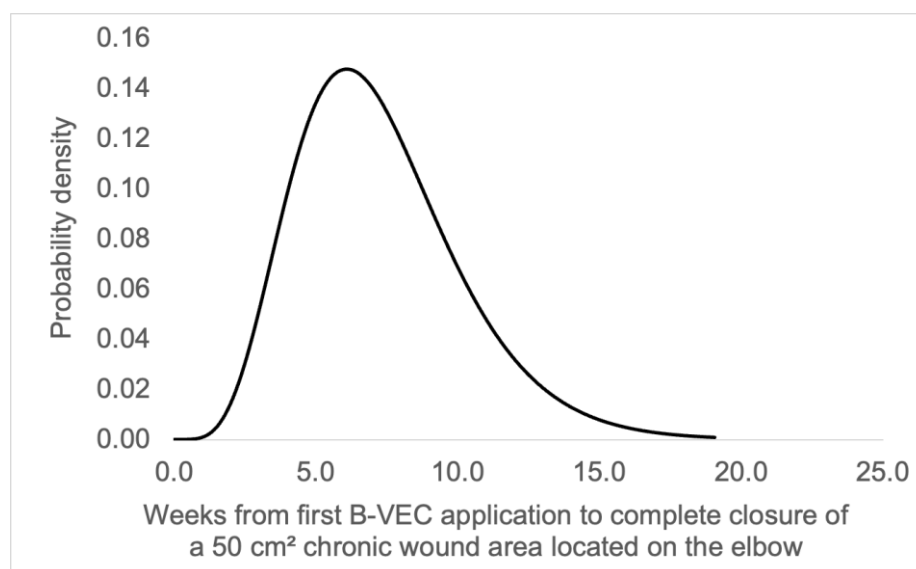


Figure 4 Final probability distribution for Quantity 3

The mean and standard deviation of the fitted distribution were 7.23 and 2.87, respectively; the 2.5-, 50.0-, and 97.5-quantiles are 2.69, 6.86, and 13.91, respectively.

Quantity 4

“Once a recurrent or chronic wound treated with BBE has fully closed (100% epithelialization with no drainage), for how many days does it typically remain closed?”

The individual elicitations presented in Table 8 were showed during the group discussion.

Table 8 Quantiles elicited from each expert during the individual elicitation of Quantity 4

	ExpA	ExpB	ExpC
L	■	■	■
p25	■	■	■
p50	■	■	■
p75	■	■	■
U	■	■	■

Abbreviations: Exp: Expert; L: Lower bound; p25: 25th percentile; p50: Median (50th percentile); p75: 75th percentile; U: Upper bound.

The facilitator noted that there was greater divergence for p75 than for earlier quantities, driven mainly by differences in the upper plausible limit (including one expert giving a very long duration, up to ~■■■ days), while the other experts expected faster reopening and shorter plausible ranges.

Expert A shared that is very hard to respond to this question and she emphasised that durability with BBE is highly variable and difficult to quantify.

Expert B also said that they have no control of the duration of wound closure because we are not at home with the patient. So, effectively, it depends also on where is the located lesion. If it is a higher friction area, the duration of closure could be less (two or three days). If it is an area where we do not have such a friction, it could stay closer some days longer, but we are still talking about days. So she assumed she can revise his data on a lower, based on the mechanism of action of BBE, but also on the kind of lesions and the fact that they are not controlling the therapy (they do not know how they do apply and how is the lesion).

Expert A shared it is difficult to respond to that question precisely because sometimes the wound close and they receive nice pictures, but a week later she could have the opposite and this was extremely random. So she could go with some of the values of Expert B, but she thinks 30 days is already too much to say that the wounds will stay closed. So she proposed to go until two weeks. she thinks the range goes from a few days to a few weeks, if the region is not mechanically stressed. she proposed also to keep the lower at two or three days.

Expert C agreed with Expert A and Expert B and mentioned that the values she gave in the individual elicitation should be lower. Expert C clarified that during the individual elicitation she misunderstood the question, thus explaining why the values provided in the individual elicitation are not correct. Expert C supported the view that BBE's main contribution is speed of closure, not structural skin change/durability, noting no clear modification of skin fragility (hence reopening may be similar to BSC).

The facilitator asked if they expect to see any difference in duration of closure with BBE and BSC. Expert C doesn't see a real change or a modification using BBE in skin the of this type of patients compared with BSC. Expert C explained that BBE's main contribution is speed of closure, not structural skin change/durability, noting no clear modification of skin fragility, hence reopening may be similar to BSC.

Expert A thinks that checking the wound status in different time points in the clinical trials is not an informative way to see the efficacy of the product because they are ignoring what is happening in between. Expert A said that wounds are very dynamic, they are constantly changing. What she sees checking the results of those clinical trials is not what happen in the real life. Expert A tend to agree with values proposed by Expert B in his individual elicitation.

The facilitator reminded the experts that the median duration of closure in the GEM-1 BSC arm was 16.5 days, and asked whether it would be consistent for the BBE estimates to be lower (i.e., shorter durability) than BSC as they are suggesting. Expert A proposed using 15 days as a reasonable central estimate and noted that, in their view, this is BBE equivalent to best supportive care in terms of durability of closure; Expert B agreed. Expert A also cautioned that BSC may include protective dressings,

which could itself prolong apparent closure compared with not using it: “if best supportive care is something like polymem, and where you put a thick layer of foam that protects, then it’s more protected than without.”.

Expert A also highlighted that any comparison is confounded by the type of EB and mechanical trauma: severe RDEB skin can reopen with minimal trauma, while less severe subtypes may remain closed longer, making it hard to “put everything in the same pot.”

The quantiles elicited are presented in Table 9 and all experts agreed with the distribution in Figure 3.

Table 9 Quantiles elicited after the group discussion of Quantity 4

L	■
p25 (Q1)	■
p50 (M)	■
p75 (Q3)	■
U	■

Abbreviations: L: Lower bound; p25: 25th percentile; p50: Median (50th percentile); p75: 75th percentile; Q: Quantile; U: Upper bound.

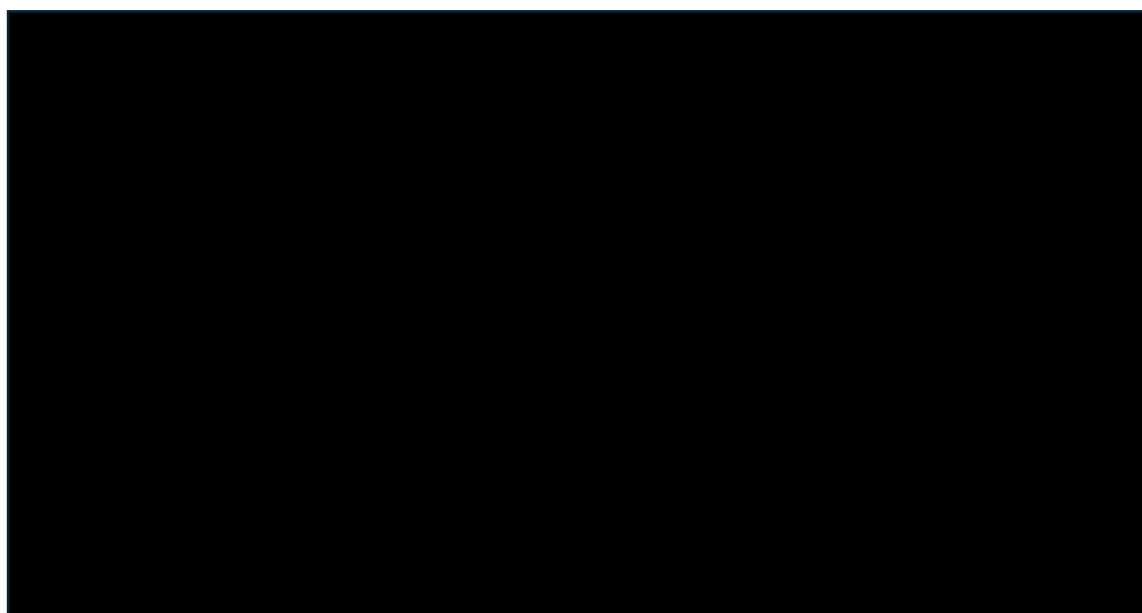


Figure 5 Final probability distribution for Quantity 4

The mean and standard deviation of the fitted distribution were ■ and ■, respectively; the 2.5-, 50.0-, and 97.5-quantiles are ■, and ■, respectively.

4.1.5. Feedback

Experts provided their feedback about the SEE exercise (Table 10). In addition, Expert B added an asterisk to her response regarding the clarity of the quantity wording and noted: “My initial response to Q4 was based on a misunderstanding of the question;

and that after better understanding I subsequently revised my estimates during the workshop's group elicitation".

Table 10 Feedback from experts about the elicitation.

Question	ExpA	ExpB	ExpC
I found the elicitation exercise easy to complete	3	3	3
The wording of the quantities was clear	4	1	4
The training provided was sufficient for making my quantile judgements	5	5	4
The facilitation was neutral and helpful during individual & group phases	5	5	5
Group discussion improved my second-round answers	5	5	5
I had adequate time for each task	5	5	4
I felt free to state my own beliefs without pressure to conform	5	5	5
The elicited values and justifications accurately reflect my views	5	5	5

Scores: 1 = Strongly disagree; 2 = Disagree; 3 = Neither agree nor disagree; 4 = Agree; 5 = Strongly agree.

Abbreviations: Exp: Expert; NA: Not answered.

4.2. Validation of assumptions for the health economic model

We planned to discuss three main model assumptions if there was time left at the end.

4.2.1. Question 1

After a wound closes under BBE, would you expect the reopening dynamics to be broadly similar to BSC in terms of the speed and size of reopening?

Expert B said it is hard to generalise because BBE does not change the underlying skin defect, and reopening depends on why the wound reopens and on lesion location; she noted that reopening could be the same size as under BSC, depending on the site: "it's difficult to say because you don't change the defect in the skin. It could be the same size or maybe it could be smaller. Depends on the site of the lesion."

The facilitator then clarified the intent of the question: rather than asking for an exact magnitude of reopening, it was meant to check whether a wound closed under BBE would be expected to follow broadly similar reopening dynamics (speed/size trajectory) to a wound closed under BSC, or whether experts would expect a difference.

Expert A reinforced that wounds are highly dynamic and influenced by multiple factors previously discussed. Comparing BBE vs BSC in terms of reopening dynamics Expert A mentioned: “For me it’s equal. I cannot decide on this.”

Expert B and Expert C agreed with Expert A that any consistent difference between BBE and BSC reopening dynamics is difficult to assert.

4.2.2. Question 2

Thinking of discontinuation as a patient-level decision to stop BBE entirely (i.e., revert to BSC), what proportion of patients do you consider most likely to discontinue, and what is the main reason? In routine practice, is 50% discontinuation plausible?

Expert B suggested that around half of patients may stop. The main driver is tolerability/acceptability, particularly itching. Expert B noted clinicians cannot observe real-world use, so the amount applied may vary, potentially worsening symptoms. Expert B also highlighted seasonality and formulation issues: in summer the ointment can become more liquid/runny and feel sticky/greasy, which patients dislike and may lead them to stop. Adherence was described as easier in preschool children because caregivers apply treatment, but more difficult in adolescents/adults, especially when itching is worse or the product feels greasy.

Expert A was mentioned it is not possible to say whether 50% discontinuation is a generalizable figure, emphasizing that outcomes and wound trajectories are highly variable and were not formally quantified; impressions are often based on patient reports and photos, making precise estimation difficult.

Expert C reported a lower rate of complete discontinuation (~█████%) in his experience. Expert C observed that patients may start enthusiastic but over time often reduce intensity of use (less quantity, fewer wounds, less frequent application) rather than stopping completely; Expert C recalled two patients who stopped, with others continuing at reduced frequency.

Final response (synthesis): ~█████% complete discontinuation (stop entirely/revert to BSC), with discontinuation primarily driven by itching/tolerability, product acceptability (greasy/sticky/runny, especially in hot weather), and adherence challenges (particularly in adolescents/adults vs caregiver-managed younger children).

4.2.3. Question 3

Inputs calculated from Davidovic et al., JEADV Clinical Practice (2025): responder rate and weekly area-closure in chronic wounds treated with BBE.

- *Total of 11 wounds in DEB patients (the remainder were in JEB): 2 fully closed; 3 with no improvement; 6 partially closed*
- *Any improvement (responders wounds): 8/11 = 73%.*
- *Assumption of 50% closure in partially closed wounds, since no detail is provided.*

- *Average open area among responders: 100% at Week 0 → 38% open at 7 months (30.4 weeks), calculated as = (2 fully closed x 0% + 6 partially closed x 50%)/8 wounds.*
- *Fitting an exponential curve, then results in a weekly proportion of the open area closing of 3.17%.*

Is this estimation reasonable to model closure of chronic wounds under BBE treatment in the cost-effectiveness model?

The facilitator explained that, because eliciting chronic-wound closure under BBE proved challenging, an alternative approach is to use data from Davidovic et al. (2025) to parameterise chronic-wound dynamics under BBE. The facilitator walked through the estimation of 73% chronic wounds response and weekly chronic area-closure rate of 3.17% with BBE, based on the published data. The facilitator noted that this calculation required assuming 50% closure for partially closed wounds because the publication did not quantify the extent of partial closure.

Expert A noted that wound trajectories are highly variable over time: even when wound outlines were traced and overlaid across visits, the same wound's shape and extent changed markedly from one time point to the next. As a result, Expert A cautioned against relying too heavily on these data as a precise representation of real-world wound dynamics.

The group agreed the approach can be treated as a pragmatic modelling workaround with some caveats ("not truly exponential"; partial-closure assumption needed likely favouring BBE).

4.3. Conclusions

A structured expert elicitation was undertaken to address key evidence gaps informing the cost-effectiveness model submitted to NICE in England, specifically the closure of chronic wounds under B-VEC treatment and the reopening dynamics of wounds closed under BBE treatment.

The SEE is a structured process to obtain probability distributions from experts on quantities of interest. The SEE process incorporated multiple elements intended to support robust judgements and minimise biases and heuristics, including development and circulation of an evidence dossier, briefing on the elicitation task and probabilistic reasoning, live consistency checks (including the SHELF thought experiment), and a facilitated group discussion with feedback on fitted distributions.

This methodology, and the SHELF framework in particular, is recommended by NICE [39] and is recognised as a robust approach for quantifying uncertain parameters.

The SEE was conducted in three phases: preparatory training (SHELF e-learning and review of the evidence dossier), individual elicitation interviews, and a final workshop

to elicit group judgements. The same facilitator led all phases, ensuring continuity and consistency in communication and support.

Overall, the approach performed well for quantities that clinicians could reasonably observe in practice and for which comparatively stable judgements could be formed. Eliciting plausible limits and quartiles (rather than single point estimates) enabled experts to express the variability they observe in clinical care. The thought-experiment checks supported internal coherence of elicited distributions and facilitated convergence towards group judgements without forcing consensus. For Q2, the close agreement between individual distributions increased confidence in the pooled estimate. For other quantities where initial responses differed, the workshop discussion clarified the rationale underpinning each judgement and supported agreement on group distributions acceptable to all experts.

Some challenges were observed for quantities relating to wound dynamics under BBE, which experts reported are difficult to observe and quantify in routine practice and for which limited evidence is available. A protocol amendment was implemented to remove planned quantities on closure of chronic wounds under BBE, as experts did not feel able to provide estimates. The durability-of-closure quantity (applicable to recurrent or chronic wounds) was retained. Experts reported that this question was difficult to answer due to substantial variability in wound behaviour and the expectation that BBE does not induce a structural improvement in skin fragility. Experts noted that, because underlying fragility is unchanged, heterogeneity similar to that observed under best supportive care is likely to persist under BBE, with outcomes influenced by lesion location (mechanical stress), EB subtype/severity, wound characteristics, and patient-level factors. Despite these challenges, the facilitated group discussion enabled participants to share experience and judgments and ultimately to agree a distribution for this quantity of interest, recognising that it should capture the variability observed in clinical practice rather than rely on a single point estimate.

Some fatigue was observed towards the end of sessions; however, all participants remained engaged and actively contributed to the group discussion throughout the workshop. The individual interviews served to reinforce key elicitation concepts, helped anticipate areas of difficulty, and informed planning for the group workshop. The period between individual interviews and the workshop also allowed experts time to consolidate the methodology and reflect on their initial responses.

In conclusion, while SEE is cognitively demanding, particularly for clinical experts, the process, supported by training, facilitation, and structured consistency checks, enabled experts to provide distributions that reflected their beliefs and appropriately characterised uncertainty for model parameterisation. Feedback questionnaire responses acknowledged the challenges but indicated that the facilitation and training were helpful and that the elicited quantities were representative of their expert judgement.

5. References

1. Has, C., et al., *Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility*. Br J Dermatol, 2020. **183**(4): p. 614–627.
2. Petrof, G., et al., *The epidemiology of epidermolysis bullosa in England and Wales: data from the national epidermolysis bullosa database*. British Journal of Dermatology, 2022. **186**(5): p. 843–848.
3. Denyer, J., E. Pillay, and J. Clapham, *Best practice guidelines for skin and wound care in epidermolysis bullosa. An International Consensus*. 2017.
4. Fine, J.D., *Inherited epidermolysis bullosa*. Orphanet J Rare Dis, 2010. **5**: p. 12.
5. Tang, J.Y., et al., *A systematic literature review of the disease burden in patients with recessive dystrophic epidermolysis bullosa*. Orphanet J Rare Dis, 2021. **16**(1): p. 175.
6. Cianfarani, F., et al., *Pathomechanisms of altered wound healing in recessive dystrophic epidermolysis bullosa*. Am J Pathol, 2017. **187**(7): p. 1445–1453.
7. Mellerio, J.E., *Infection and colonization in epidermolysis bullosa*. Dermatol Clin, 2010. **28**(2): p. 267–9.
8. Mellerio, J.E., et al., *Management of cutaneous squamous cell carcinoma in patients with epidermolysis bullosa: best clinical practice guidelines*. Br J Dermatol, 2016. **174**(1): p. 56–67.
9. Nystrom, A., L. Bruckner-Tuderman, and D. Kiritsi, *Dystrophic epidermolysis bullosa: secondary disease mechanisms and disease modifiers*. Front Genet, 2021. **12**: p. 737272.
10. Angelis, A., et al., *Social/economic costs and health-related quality of life in patients with epidermolysis bullosa in Europe*. Eur J Health Econ, 2016. **17**(Suppl 1): p. 31–42.
11. Bruckner, A.L., et al., *The challenges of living with and managing epidermolysis bullosa: insights from patients and caregivers*. Orphanet J Rare Dis, 2020. **15**(1): p. 1.
12. Fulchand, S., et al., *Patient-reported outcomes and quality of life in dominant dystrophic epidermolysis bullosa: A global cross-sectional survey*. Pediatr Dermatol, 2021. **38**(5): p. 1198–1201.
13. Eng, V.A., et al., *Patient-reported outcomes and quality of life in recessive dystrophic epidermolysis bullosa: A global cross-sectional survey*. J Am Acad Dermatol, 2021. **85**(5): p. 1161–1167.
14. National Institute for Health and Care Excellence (NICE), *Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]. Committee papers*. 2023.
15. European Medicines Agency (EMA). *Filsuvez (Oleogel-S10) 0.5g–1.0 g birch bark gel. Summary of Product Characteristics*. 2022 4 July [cited 2022 29 November].
16. European Medicines Agency (EMA). *EPAR Medicine Overview: Filsuvez (birch bark extract)*. 2022 4 July [cited 2022 29 November]; Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/filsuvez>.

17. European Medicines Agency (EMA). *Committee for Medicinal Products for Human Use (CHMP) assessment report: Filsuvez*. 2022 4 April [cited 2022 4 December]; Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/filsuvez>.
18. Medicines and Healthcare products Regulatory Agency (MHRA). *Filsuvez Gel Summary of Product Characteristics*. 2022 18 August [cited 2023 3 April]; Available from: <https://www.medicines.org.uk/emc/product/13971/smpc/print>.
19. Guide, S.V., et al., *Trial of Beremagene Geperpavec (B-VEC) for Dystrophic Epidermolysis Bullosa*. N Engl J Med, 2022. **387**(24): p. 2211–2219.
20. Gurevich, I., et al., *In vivo topical gene therapy for recessive dystrophic epidermolysis bullosa: a phase 1 and 2 trial*. Nat Med, 2022. **28**(4): p. 780–788.
21. Oakley, J.E. and O.H. Tony. *The Sheffield Elicitation Framework (SHELF)*. 2025 [cited 2025 10 June]; Available from: <https://shelf.sites.sheffield.ac.uk>.
22. Bojke, L., et al., *Developing a reference protocol for structured expert elicitation in health-care decision-making: a mixed-methods study*. Health Technology Assessment (Winchester, England), 2021. **25**(37): p. 1.
23. Soares, M.O., et al., *Experiences of structured elicitation for model-based cost-effectiveness analyses*. Value in health, 2018. **21**(6): p. 715–723.
24. Soares, M., et al., *Recommendations on the Use of Structured Expert Elicitation Protocols for Healthcare Decision Making: A Good Practices Report of an ISPOR Task Force*. Value in Health, 2024. **27**(11): p. 1469–1478.
25. National Institute for Health and Care Excellence, *NICE health technology evaluations: the manual*. . Published January 31, 2022.
26. University of Sheffield. *Technical support document 26: Expert elicitation for long-term survival outcomes*. 2025 [cited 2025 18 June]; Available from: <https://www.sheffield.ac.uk/nice-dsu/tsds/expert-elicitation-tsd>.
27. O'Hagan, A., et al., *Uncertain judgements: eliciting experts' probabilities*. 2006.
28. Philips, Z., et al., *Review of guidelines for good practice in decision-analytic modelling in health technology assessment*. Health technology assessment (Winchester, England), 2004. **8**(36): p. iii–iv, ix.
29. Meads, C., et al., *Positron emission tomography/computerised tomography imaging in detecting and managing recurrent cervical cancer: systematic review of evidence, elicitation of subjective probabilities and economic modelling*. Health technology assessment (Winchester, England), 2013. **17**(12): p. 1.
30. Zapata-Vázquez, R.E., O.H. Anthony, and L. and Soares Bastos, *Eliciting expert judgements about a set of proportions*. Journal of Applied Statistics, 2014. **41**(9): p. 1919–1933.
31. Gosling, J.P., *SHELF: the Sheffield elicitation framework*. Elicitation: The science and art of structuring judgement, 2018: p. 61–93.
32. van Gelder, T., R. Vodicka, and N. Armstrong, *Augmenting expert elicitation with structured visual deliberation*. Asia & the Pacific Policy Studies, 2016. **3**(3): p. 378–388.
33. Sunstein, C.R. and R. Hastie, *Wiser: Getting beyond groupthink to make groups smarter*. 2015: Harvard Business Press.
34. Kerr, N.L. and R.S. Tindale, *Group performance and decision making*. Annu. Rev. Psychol., 2004. **55**: p. 623–655.
35. Montibeller, G. and D. Von Winterfeldt, *Cognitive and motivational biases in decision and risk analysis*. Risk analysis, 2015. **35**(7): p. 1230–1251.

36. Cadham, C.J., et al., *The Use of Expert Elicitation among Computational Modeling Studies in Health Research: A Systematic Review*. Medical Decision Making, 2022. **42**(5): p. 684–703.
37. Jankovic D, S.M., Bojke L, Horscroft J, Lee D. *R code for building bespoke Shiny apps for conducting SEE*. 2022; Available from: <https://www.york.ac.uk/che/economic-evaluation/steer/>.
38. Choy, S.L., R. O'Leary, and K. Mengersen, *Elicitation by design in ecology: using expert opinion to inform priors for Bayesian statistical models*. Ecology, 2009. **90**(1): p. 265–277.
39. National Institute for Health and Care Excellence *TSD26: Expert elicitation for long-term survival outcomes*. 2025.

6. Appendix A: Evidence Dossier

Evidence Dossier 4.0

Expert elicitation exercise for Beremagene geperpavec (B-VEC) in Dystrophic Epidermolysis Bullosa (DEB)

Notes for experts		
<i>This dossier has been compiled to support the upcoming elicitation workshop you have kindly agreed to participate in. This document should contain all relevant and supplementary information that may help you and other workshop participants to formulate their judgements on the quantities of interest (defined in full in Section Error! Reference source not found.). We ask you to review this document, as subject experts, in order to ensure we have included all relevant information that may influence participants when making their judgements. The provision of this dossier aims to minimise potential availability bias within the exercise by ensuring all participants have the same evidence base to support their judgement making.</i> <i>To help guide you when reviewing the dossier, we ask you to consider the key review points below.</i>		
Are the elements in Section 1 clear? <i>Please consider the description of the disease background, population of interest, overview of the pivotal trial and rationale of the workshop.</i>	☐	
Are the quantities of interest clearly defined?	☐	
Is the evidence base, presented in Sections 4 and 5, a) clearly presented and easy to understand; b) complete (i.e., are any key studies missing); c) or missing any key information points?	☐	
Would any modification to the format, make the dossier more accessible to you?	☐	
Please provide any additional comments or clarification points you would like addressed prior to the elicitation workshop.	☐	

Contents

Abbreviations.....	39
1 Overview	40
1.1 Background	40
1.2 Target population	41
1.3 Intervention(s) overview	43
1.3.1 Current treatment options and clinical pathway of care	43
1.3.2 B-VEC	43
1.4 Pivotal trials	44
1.4.1 B-VEC: Summary of study design and methodology	44
1.4.2 BBE: Summary of study design and methodology	45
1.5 Rationale for the elicitation workshop	46
2 Quantities of interest.....	46
3 Evidence summary.....	46
3.1 GEM-1/2 trial.....	49
3.1.1 Complete wound closure at 3 months.....	49
3.1.2 Durability of response	51
3.2 GEM-3 trial	51
3.2.1 Complete wound closure at 6 months.....	51
3.2.2 Complete wound closure at 3 months.....	52
3.2.3 Durable wound closure	52
3.3 GEM-3 OLE trial.....	53
3.4 EASE trial	54
3.4.1 Proportion of patients with first complete closure of EB target wound by Day 45	54
3.4.2 Time to complete target wound closure.....	55
4 Supporting evidence	55
4.1 Trial evidence for the intervention(s)	55
4.2 External evidence	58
Appendix A: Clinical trials supplementary information.....	71
4.3 GEM-1/2	71
4.3.1 Eligibility criteria	71
4.3.2 Exclusion criteria	71
4.3.3 Method of randomisation	72
4.3.4 Permitted and disallowed concomitant medication	73
4.3.5 Duration of follow-up, lost to follow-up information	73
4.3.6 Primary outcomes (including scoring methods and timings of assessments)	73
4.3.7 Other outcomes used in the economic model/specified in the scope	73
4.3.8 Pre-planned subgroups	73
4.4 GEM-3	74
4.4.1 Eligibility criteria	74
4.4.2 Exclusion criteria	74
4.4.3 Method of randomisation	74
4.4.4 Intervention and comparators	74
4.4.5 Duration of follow-up, lost to follow-up information	75

4.4.6	Permitted and disallowed concomitant medication	75
4.4.7	Primary outcomes (including scoring methods and timings of assessments)	75
4.4.8	Other outcomes used in the economic model/specified in the scope	76
4.4.9	Preplanned subgroups	76
4.5	EASE	76
4.5.1	Eligibility criteria	76
4.5.2	Exclusion criteria	77
4.5.3	Method of randomisation	77
4.5.4	Intervention and comparators	77
4.5.5	Duration of follow-up, lost to follow-up information	78
4.5.6	Permitted and disallowed concomitant medication	78
4.5.7	Primary outcomes (including scoring methods and timings of assessments)	79
4.5.8	Other outcomes	79
Appendix B: General background and mechanism of action of B-VEC		81
Reference list.....		81

Abbreviations

BSA	Body surface area
BSC	Best supportive care
B-VEC	Beremagene geperpavec
CEM	Cost-effectiveness model
COL7	Type VII collagen
DDEB	Dominant dystrophic epidermolysis bullosa
DEB	Dystrophic epidermolysis bullosa
DNA	Deoxyribonucleic acid
EAG	Evidence Assessment Group
EB	Epidermolysis bullosa
HRQoL	Health-related quality of life
HSV-1	Herpes simplex virus type 1
KEB	Kindler epidermolysis bullosa
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Care Excellence
OLE	Open-label extension
PTW	Partial thickness wounds
RCT	Randomised control trial
RDEB	Recessive dystrophic epidermolysis bullosa
SEE	Structured expert elicitation
SoC	Standard of care
UK	United Kingdom

7. Overview

7.1. Background

- Dystrophic epidermolysis bullosa (DEB) is a rare, inherited, and debilitating skin fragility disorder caused by mutations in the COL7A1 gene encoding type VII collagen. [1, 2] It typically presents at birth or within the first year of life and is characterized by painful blistering and scarring of the skin following minimal trauma, leading to persistent wounds, impaired healing, and cumulative morbidities over time. [1, 3-5] People with DEB experience extracutaneous manifestations, progressive complications, and premature mortality, often due to aggressive squamous cell carcinoma in severe cases. [4, 6-9] The disease has a profound impact on daily functioning and results in substantial decrements in health-related quality of life (HRQoL), necessitating lifelong management. [5, 10, 11]
- The current standard of care for DEB is limited to symptom management and secondary complication control, which inadequately addresses the disease. [11, 12] Wound care is time-consuming, painful, and distressing, often requiring hours of daily attention, multiple dressing changes, and assistance from caregivers, with the burden increasing alongside disease severity. [5, 11, 13] There are no approved curative or NICE-recommended disease-modifying therapies; while birch bark extract (Filsuvez) is approved in the UK and Europe and has been positively evaluated by NICE, its mechanism remains incompletely defined, its benefits—though meaningful in wound healing—are not curative, and it does not modify the underlying disease course. [14-18]
- Beremagene geperpavec (B-VEC) is a replication-defective herpes simplex virus type 1 (HSV-1)–based gene therapy vector that has been engineered to deliver the COL7A1 gene encoding type VII collagen (COL7). [19, 20] The HSV-1 platform has a large payload capacity suitable for the full COL7A1 gene, natural tropism for skin cells, and the ability to evade host immune responses, enabling repeat topical dosing without integration into host deoxyribonucleic acid (DNA). Following cutaneous application, B-VEC transduces keratinocytes and fibroblasts, depositing its genome in the nucleus to initiate transcription of full-length human COL7A1. The resulting COL7 protein is secreted and assembles into anchoring fibrils, which are critical for dermal–epidermal adhesion and skin integrity. [19, 20]
- Clinical development of B-VEC has demonstrated its ability to deliver functional COL7A1, restore ultrastructural features of the skin, and normalize anchoring fibril formation. In the pivotal phase 3 trial, 71% of B-VEC–treated wounds achieved complete closure at 3 months (vs 20% placebo), and 67% remained closed at 6 months (vs 22% placebo). Durability of response, defined as 100% closure at both 3 and 6 months, was observed in 50% of B-VEC–treated wounds compared with 7% in the placebo group. These findings establish B-VEC as the first gene therapy to demonstrate clinically meaningful and durable wound healing in patients with DEB.

- A cost-effectiveness model (CEM) for B-VEC in the treatment of DEB has been developed and submitted as part of the reimbursement application to the National Institute for Health and Care Excellence (NICE) in England. During its review, the Evidence Assessment Group (EAG) identified an important uncertainty regarding the rate of closure of chronic, large wounds treated with B-VEC. In the natural history of DEB, recurrent wounds typically heal but are prone to re-blistering, whereas chronic wounds remain open for eight weeks or longer and present greater challenges to healing. However, data from the GEM trials do not provide sufficient evidence to distinguish between closure rates of chronic versus recurrent wounds, meaning the differential impact of B-VEC across these wound types cannot be directly quantified. As a result, the submitted version of the CEM assumed identical closure rates for both recurrent and chronic wounds, an approach the EAG considered implausible.
- Additionally, from the review of the EAG it became clear that there was also an evidence gap for the rate of closing of chronic wounds treated with birch bark extract (BBE), one of the comparator treatments in the CEM, as well as for how long (any) wounds that were closed through treatment with BBE remain closed.
- To address these evidence gaps, a structured expert elicitation (SEE) is warranted. NICE guidance indicates that in the absence of robust empirical data—whether from randomized controlled trials, non-randomized studies, or patient registries—expert elicitation can provide credible evidence to inform model assumptions, with structured approaches explicitly preferred.[21] Conducting a SEE will therefore enable incorporation of expert judgment on the likely differential effect of B-VEC in chronic versus recurrent wounds, strengthening the evidence base and ensuring that the CEM more accurately reflects real-world clinical practice.
- During the individual elicitation, it became clear that the experts were unable to provide estimates for chronic wound area closure under BBE treatment, citing limited experience and insufficient follow-up to support informed judgments. A protocol amendment was therefore implemented to remove the planned BBE chronic-wound quantities (Quantities 4–6 in the previous evidence dossier version 3.0), while retaining elicitation on B-VEC closure rates and the duration of closure under BBE.

7.2. Target population

- The target population for the CEM comprised people with DEB who are: paediatric patients <6 years old; paediatric patients between 6-17 years old; or adult patients (≥18 years old). These age subgroups were created because the differences between them were considered relevant, especially in terms of total body surface area (BSA), which determines the absolute area with open wounds to be treated. These patient groups align with the populations in the pivotal B-VEC clinical trials, GEM-3 and GEM-1, and with the Summary of Product Characteristics (SmPC) for B-VEC, which states “Vyjuvek is indicated for the treatment of wounds in patients

with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene, from birth.” [22]

- The phase 3 trial, GEM-3 (NCT04491604), enrolled 31 patients 6 months or older with genetically confirmed DEB. The phase 1/2 trial, GEM-1 (NCT03536143), enrolled 9 patients with RDEB.
- Table 7.1 presents the baseline distribution of patients according to the age subgroups and DEB subtype based on GEM-3 data (Krystal Biotech, data on file), average age and the average BSA for each age subgroup.

Table 7.1: Baseline distribution and characteristics of patients in GEM-3 according to age subgroups

Age subgroups	Proportion of patients*	Average age, years*	RDEB			DDEB		
			Average weight (kg) †	Average height (cm) †	Average BSA (cm ²), calculated‡	Average weight (kg) †	Average height (cm) §	Average BSA (cm ²), calculated‡
0 to <6 years	12.90%	2.25	11.06	88.07	5,129	12.95	90.74	5,607
6 to <18 years	48.39%	12.62	25.41	137.71	10,097	41.98	151.71	13,408
≥18 years	38.71%	27.99	38.81	164.68	13,764	63.63	172.21	17,541

BSA=body surface area; DDEB=dominant dystrophic epidermolysis bullosa; RDEB=recessive epidermolysis bullosa
 * based on GEM-3 data[23]
 † based on Reimer *et al.* (2020)[24] in the respective age and weighted by gender in GEM-3 data for each age group
 ‡ based on the Du Bois equation[25]
 § based on WHO growth tables for the general population[26]

- In addition to age groups, the model also considered the proportion of patients with RDEB and DDEB, respectively. This is because, according to UK clinical expert elicitation and published data,[24] patients with RDEB are smaller and have a shorter life expectancy compared to the general population, while patients with DDEB have height, weight and life expectancy similar to those of the general population. Based on Bruckner *et al.*, it was considered that 57.6% (19 of the 33 included patients) have RDEB, and the remaining 42.4% (14 of the 33 included patients) have DDEB.[11]
- The proportion of patients in each age group and average age are based on GEM-3 data.[23] Reimer *et al.* (2020) reported data on the weight and height of 200 German children with EB (157 with RDEB and 43 with JEB).[24] The height and weight of RDEB patients was derived using the 50th percentile of RDEB data from this study, considering the mean age in each subgroup. The height and weight of DDEB patients was derived using the 50th percentile of general population growth curves in the UK considering the mean age in each subgroup. This approach was taken because clinical experts consulted by Krystal Biotech noted that the height and weight of DDEB patients is aligned with that of the general population. The weight and height data reported for the oldest age groups of Reimer *et al.* (22-27 years) and the general population statistics (18 years), for RDEB and DDEB respectively, were used for the adult cohort of the analysis.[24]

BSA was calculated based on the Du Bois equation[25] (Equation 1 below).

$$BSA[m^2] = Weight [kg]^{0.425} \times Height [cm]^{0.725} \times 0.007184 \quad (\text{Equation 1})$$

- In terms of gender distribution, there is no evidence indicating a different predisposition to DEB between males and females. However, in line with the observed data from GEM-3, it was considered that 64.5% of patients (independent of age subgroup) are males.[23]

7.3. Intervention(s) overview

7.3.1. Current treatment options and clinical pathway of care

- Current standard of care (SoC), which is limited to the management of symptoms and secondary complications, inadequately addresses DEB.[11, 12]
- Wound care for individuals with DEB is time-consuming, often requiring several hours a day and assistance from one or two carers.[5] The burden intensifies with the severity of the disease, as wounds become increasingly painful, prone to infection, and require constant attention, including multiple dressing changes daily. [5, 11, 13] This painful routine, which causes significant emotional distress, is compounded by the need to carefully handle dressings to avoid further skin damage, making it a distressing experience for patients and carers.[3, 11, 27]
- Birch bark extract [BBE] gel for cutaneous application is the first epidermolysis bullosa-specific treatment to receive marketing approval in the UK and Europe and received a positive recommendation from NICE, via Highly Specialised Technology (HST) evaluation, in September 2023 (HST28)[14]; however, the precise mechanism of action is unclear, it has limited efficacy and is not disease-modifying.[15-18]
 - BBE is a topical gel containing a dry extract from birch bark, which includes substances known as triterpenes, for the treatment of partial thickness wounds (PTW) associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.[18]
 - BBE should be administered topically at least every 4 days, at a thickness of 1 mm to the surface of the wound and covered by a sterile non-adhesive wound dressing.[18]
 - Currently, BBE gel is the only treatment option available to patients with DEB, however, this therapy is not disease-modifying or curative and has shown limited clinical efficacy.[17]

7.3.2. B-VEC

- B-VEC is a replication-defective, herpes simplex virus 1 (HSV-1)–based, topical, redosable gene therapy designed to restore the structural stability of the skin for directly treated wounds. [19, 20]
- The recommended dose of B-VEC is based on age:

- Patients above 3 years: maximum weekly dose of 4×10^9 PFU, with the total administration volume of 2 mL. It should cover no more than 200 cm² of wound area.
- Patients from birth to 3 years: maximum weekly dose of 2×10^9 PFU, with the total administration volume of 1 mL. It should cover no more than 200 cm² of wound area.
- B-VEC addresses the root cause of DEB via delivery of the COL7A1 gene and functional correction of COL7 expression.[19]
- Repeated topical application of B-VEC results in full-length COL7 protein expression, normalised anchoring fibril formation, and durable and consistent wound closure.[19, 20]
- Treatment with B-VEC leads to significant improvement in the number of wounds with complete and durable closure.
- B-VEC is anticipated to be the first topical and redosable gene therapy with marketing authorisation for the treatment of patients with DEB supported by data from two placebo-controlled trials.[19, 20]
- B-VEC is expected to be approved by Medicines and Healthcare products Regulatory Agency (MHRA) in the UK in May 2026.

7.4. Pivotal trials

7.4.1. B-VEC: Summary of study design and methodology

The clinical development programme for B-VEC included:

- One phase 3 randomised control trial (RCT) (GEM-3) in patients aged ≥ 6 months with genetically confirmed DEB and two cutaneous wounds similar in size, appearance, and anatomical region
- One phase 1/2 RCT (GEM-1) in patients aged ≥ 6 years with molecularly confirmed RDEB and at least two skin areas with at least one wound in each area

GEM-3

- Phase 3, double-blind, inpatient randomized, placebo-controlled trial involving patients 6 months of age or older with genetically confirmed dystrophic epidermolysis bullosa.
- For each patient, a primary wound pair was selected, with the wounds matched according to size, region, and appearance. The wounds within each pair were randomly assigned in a 1:1 ratio to receive weekly application of either B-VEC or placebo for 26 weeks.
- The primary end point was complete wound healing of treated as compared with untreated wounds at 6 months.
- Secondary end points included complete wound healing at 3 months and the change from baseline to weeks 22, 24, and 26 in pain severity during changes in wound dressing, assessed with the use of a visual analogue scale (scores range from 0 to 10, with higher scores indicating greater pain).

GEM-1/2

- Randomized, placebo-controlled, phase 1 and 2 clinical trial evaluated matched wounds from nine RDEB patients receiving topical B-VEC or placebo repeatedly over 12 weeks.
- No grade 2 or above B-VEC-related adverse events or vector shedding or tissue-bound skin immunoreactants were noted.
- HSV-1 and C7 antibodies sometimes presented at baseline or increased after B-VEC treatment without an apparent impact on safety or efficacy.
- Primary and secondary objectives of C7 expression, anchoring fibril assembly, wound surface area reduction, duration of wound closure, and time to wound closure following B-VEC treatment were met.
- A patient-reported pain–severity secondary outcome was not assessed given the small proportion of wounds treated. A global assessment secondary endpoint was not pursued due to redundancy with regard to other endpoints.
- These studies show that B-VEC is an easily administered, safely tolerated, topical molecular corrective therapy promoting wound healing in patients with RDEB.

7.4.2. BBE: Summary of study design and methodology

The clinical development programme for BBE included:

- One phase 3 RCT (EASE) in patients with DEB, JEB, or Kindler epidermolysis bullosa (KEB) and a target partial-thickness wound lasting ≥ 21 days and < 9 months that was 10–50 cm². [28]

EASE

- Double-blind, randomised, controlled, phase III, 90-day efficacy and safety study with a 24-month open-label, single-arm follow-up phase. [29]
- Subjects were randomised 1:1 to receive either BBE gel or control gel. Randomisation was conducted according to blinded patient number, and the randomisation key was held solely by an independent statistician. [29]
- The primary end point was the proportion of patients with first complete target wound closure within 45 days based on investigator assessment. [29]
 - Secondary end points included time to first complete closure of the EB target wound and proportion of patients with first target wound closure within day 90 ± 7 days; incidence and maximum severity of target wound infection between baseline and day 90 ± 7 days; total body wound burden using the skin activity component of the EB Disease Activity and Scarring Index (EBDASI); pain and itch (with scales chosen according to patient age); and body surface area percentage (BSAP) affected by EB PTWs. Additional patient-reported outcomes included background pain, Wound-QoL, sleep, work days/school days missed and Treatment Satisfaction Questionnaire for Medication. [29]

7.5. Rationale for the elicitation workshop

- The primary objective of the SEE process is to generate point estimates of key clinical parameters, along with information on their variability and distribution, for use in the health economic model of B-VEC in DEB currently under evaluation by NICE in England.
- The quantities to be elicited are related to the closure of chronic wounds under B-VEC treatment and duration of closure of a wound (chronic or recurrent) after closure with BBE treatment.

8. Quantities of interest

QoI 1	Among chronic wounds (open >8 weeks) treated with B-VEC, what proportion show any measurable improvement (i.e., any reduction in wound area from baseline) over time?
QoI 2	Consider a wound area that has been open for more than 8 weeks, located on the back, with baseline area 1,200 cm ² (≈50% of an RDEB adult back) that has shown any measurable improvement after starting treatment with B-VEC. Assuming B-VEC can be applied to a maximum of 200 cm ² per week, how many weeks from the first B-VEC application does it typically take for the wound area to reach complete closure?
QoI 3	Consider a wound area that has been open for more than 8 weeks located on the elbow, with baseline area 50 cm ² (≈8% of an RDEB adult arm) that has shown any measurable improvement after starting treatment with B-VEC. Assuming B-VEC can be applied to a maximum of 200 cm ² per week, how many weeks from the first B-VEC application does it typically take for the wound area to reach complete closure?
QoI 4	Once a recurrent or chronic wound treated with BBE has fully closed (100% epithelialization with no drainage), for how many days does it typically remain closed?

9. Key facts

9.1. Proportion of patients with complete wound closure

Table 9.1: Proportion of patients with complete wound closure on B-VEC trials

Time point	B-VEC arm	Placebo as proxy to BSC	Source
GEM-1/2 trial			
At week 8	92.86%	0.00%	Gurevich et al (2022) [20]
At week 10	78.57%	33.33%	
At week 12	83.33%	14.29%	
At week 8 & 10	78.57%	0.00%	
At week 10 & 12	75.00%	0.00%	
At week 8 & 10 or at week 10 & 12	78.57%	0.00%	
GEM-3 trial			
At month 3	71.00%	20.00%	Guide et al. (2022) [19]
At month 6	67.00%	22.00%	

Both at months 3 and 6	49.70%	7.10%	GEM-3, data on file [30]
At weeks 8, 10 and 12	47.70%	16.50%	
At weeks 22, 24 and 26	43.20%	6.50%	
GEM-3 OLE trial			
At week 1	89.47%	NA	GEM-3 OLE, data on file [31]
At month 3	84.21%	NA	
At month 6	61.11%	NA	
At month 9	82.35%	NA	
At month 12	62.50%	NA	

BSC, best supportive care; NA, not available

Table 9.2: Proportion of patients with complete wound closure on BEE trials

Time point	BEE arm	Placebo as proxy to BSC	Source
At day 14	14.70%	13.20%	Kern et al. (2023) [28]
At day 30	31.20%	21.90%	
At day 45	41.30%	28.90%	
At day 60	46.80%	36.80%	
At day 90	50.50%	43.90%	

BSC, best supportive care

9.2. Proportion of patients with complete wound closure by type of wound

Table 9.3: Proportion of patients with complete wound closure by type of wound on B-VEC trials

Time point	B-VEC arm	Placebo as proxy to BSC	Source
Recurrent wounds			
Within 12 weeks	94.12%	81.82%	GEM-1/2, data on file [32]
Chronic wounds			
Within 12 weeks	66.67%	NA	GEM-1/2, data on file [32]
Within 203 days	50.00%	NA	Agence Nationale de Sécurité du Médicament [33]

BSC, best supportive care; NA, not available

Table 9.4: Proportion of patients with complete wound closure by type of wound on BBE trials

Time point	BBE arm	Placebo as proxy to BSC	Source
Chronic wounds			
Within 7 months	18.18%	NA	Davidovic et al. (2025) [34]

BSC, best supportive care; NA, not available

Table 9.5: Proportion of patients with complete wound closure by type of wound on

BSC

Time point	RWE as proxy to BSC	Source
Chronic wounds		
Within 6 months	16.67%	Fulchand et al. (2025) [35]

BSC, best supportive care; NA, not available; RWE, real world evidence

9.3. Median time to complete wound closure (days)

Table 9.6: Median time to complete wound closure (days) in B-VEC usage

Time point	B-VEC arm	Placebo as proxy to BSC	Source
All wounds	13.5	22.5	GEM-1/2, data on file [32]
Chronic wounds	182 (26 weeks)	NA	Karakioulaki et al. (2025) [36]

BSC, best supportive care; NA, not available

Table 9.7: Median time to complete wound closure (days) on BSC

Time point	RWE as proxy to BSC	Source
Recurrent wounds	5.7	Fulchand et al. (2025) [35]
Chronic wounds	25.7	

BSC, best supportive care

9.4. Duration of wound closure (days)

Table 9.8: Median time to complete wound closure (days) in B-VEC trials

Time point	B-VEC arm	Placebo as proxy to BSC	Source
All wounds	103	16.5	GEM-1/2, data on file [32]
All wounds	180	NA	GEM-3, data on file [30]
All wounds	360	NA	GEM-3 + GEM-3 OLE, data on file [37]

BSC, best supportive care

10. Evidence summary

10.1. GEM-1/2 trial

10.1.1. Complete wound closure at 3 months

In the phase 1/2 GEM-1 study, all except one wound treated with B-VEC had closed by 3 months (Figure 10.1). The exception was a chronic (5 year) dorsal foot wound that partially closed at 1 month, was not closed at 3 months, but completely closed upon retreatment, and remained healed throughout monitoring (8 months), highlighting the effectiveness of repeated application of B-VEC.[20]

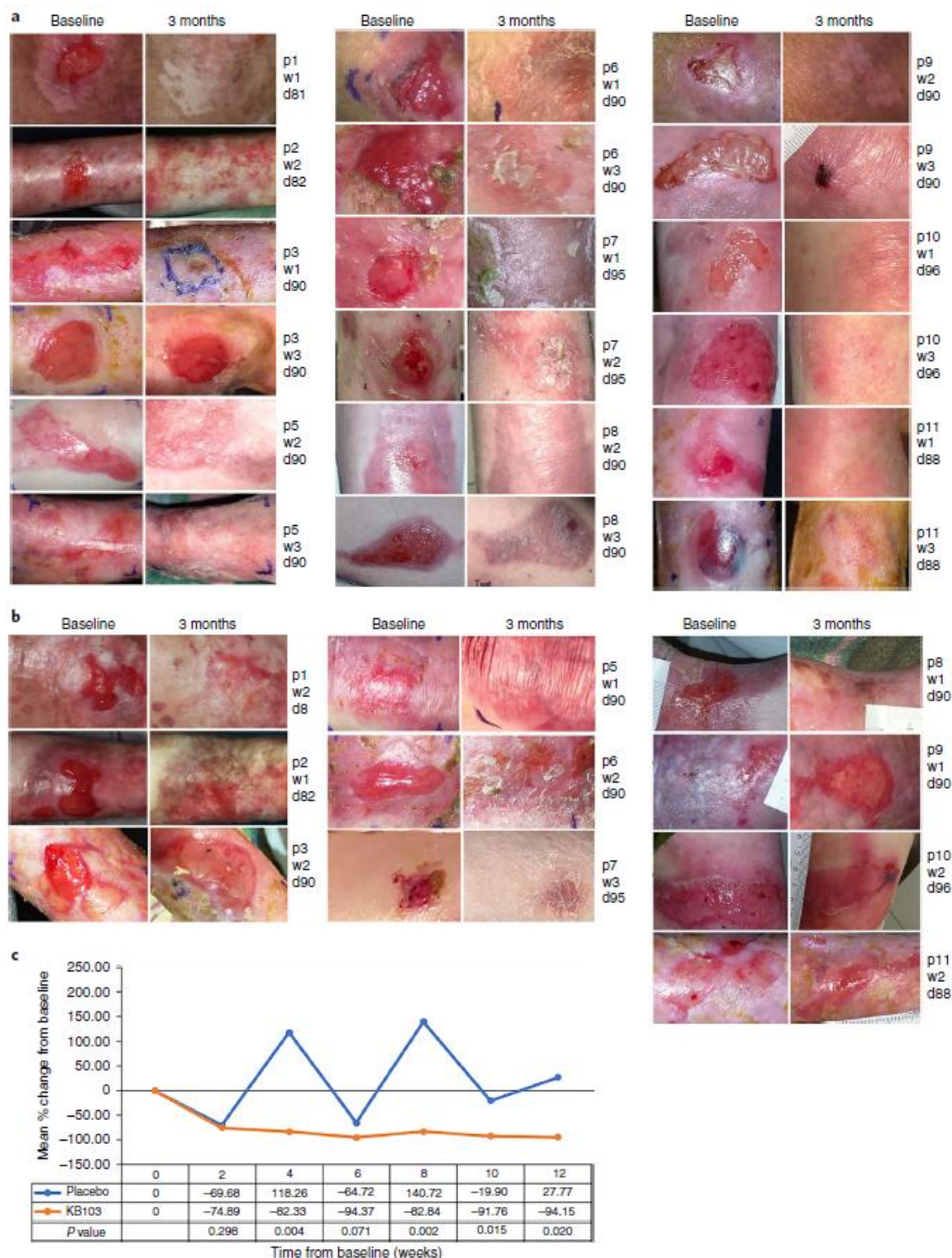


Figure 10.1: Wound closure in patients with RDEB following topical B-VEC or placebo

^{a,b}Photos of B-VEC–treated (a) or placebo–treated (b) wounds (w#) on the indicated patients (p#) at baseline, and approximately 3 months after treatment.

^cMean percent change from baseline in the area of all target wounds in patients 1–11.

KB103 (B-VEC)=beremagene geperpavec

Source : Gurevich *et al.* (2022).[20]

B-VEC–treated wounds were statistically significantly different from placebo wounds ($p=0.0026$) based on complete wound closure responder analysis, which is indicative of

improved wound closure with B-VEC (Table 10.1). Furthermore, the treatment effect on reduction in wound area was statistically significant ($p < 0.025$) at Weeks 8, 10, and 12 (Table 10.1).[20]

Table 10.1: GEM-1: Primary endpoint analysis for wound closure (observed data)

Endpoint	B-VEC	Placebo*	Difference, %
Complete wound closure, n (%) [†]			
Week 8 (n=21)	13/14 (93)	0/7 (0)	93
Week 10 (N=20)	11/14 (79)	2/6 (33)	46
Week 12 (n=19)	10/12 (83)	1/7 (14)	69
Complete wound closure, n (%) [†]			
Weeks 8+10 (N=21)	11/14 (79)	0/7 (0)	79
Weeks 10+12 (N=19)	9/12 (75)	0/7 (0)	75
Responder analysis: complete wound closure [†] at Weeks 8+10 or Weeks 10+12 (3 months); (n=21)	11/14 (79)	0/7 (0)	79 p=0.0026 [‡]
Results and analysis reported are based upon observed data without imputed values for missing data. *One patient was not imaged and was excluded from the responder analysis. [†] Complete closure defined as $\geq 90\%$ reduction in wound surface area from baseline. [‡] Significant at $p < 0.025$. The phase 1 protocol collected wound closure data at weeks 6 and 12 (no Week 8 or Week 10 datapoints), therefore the phase 1 patients (patients 1 and 2) were excluded from the responder analysis. Patient 4 withdrew after initial dosing due to inability to travel. Included in the analysis are data from Week 8 for patients 3–10, Week 10 for patients 3–10 (missing datapoint for patient 10, placebo), and Week 12 for patients 3–10 (missing datapoints for patient 7, B-VEC). B-VEC=beremagene geperpavec Source : Gurevich <i>et al.</i> (2022)[20]			

10.1.2. Durability of response

In the phase 1/2 GEM-1 study, median duration of wound closure was longer with B-VEC than placebo (103.0 vs. 16.5 days), as shown in Table 10.2.

Table 10.2: GEM-1: Primary endpoint analysis for time to and durability of wound closure (observed data)

Endpoint	B-VEC	Placebo	p value*
Time to complete closure, 95% CI, days ^{†,‡}	13.5 (8–21)	22.5 (8–64)	0.0216
Duration of closure, median (95% CI), days [†]	103.0 (94–118)	16.5 (0–66)	0.0009
*p value based on log-rank test. [†] Complete closure defined as $\geq 95\%$ reduction in wound surface area from baseline. [‡] Time to wound closure was defined as the time from the first treatment to complete wound closure ($\geq 95\%$ reduction in wound surface area from baseline) observed for 2 consecutive weeks. Results and analysis reported are based upon observed data without imputed values for missing data. B-VEC=beremagene geperpavec; CI, confidence interval Source: Gurevich <i>et al.</i> (2022)[20]; Krystal Biotech Data on File (GEM-1 [KB103-001] CSR) [38]			

10.2. GEM-3 trial

10.2.1. Complete wound closure at 6 months

In the phase 3 GEM-3 study, the primary endpoint of superiority of B-VEC over placebo in terms of the percentage of wounds with complete closure at 6 months was met. Of the 31 wound pairs in the ITT population, 67% of wounds treated with BVEC and 22% of

wounds- treated with placebo were completely healed at 6 months, a statistically significant difference of 46 points (95% CI 24, 68; $p=0.002$; Table 10.3).[19] The definition of complete wound closure used in GEM-3 required that wounds be completely healed (100% wound closure from the exact wound area selected at baseline, specified as skin reepithelialisation without drainage, as determined by the investigator) for at least two consecutive weeks, representing a high bar for patients who often have recurrent wounds that are prone to reopening quickly.[19, 39] Requiring closure at two time points distinguished the transient closure observed in wounds exposed to placebo from the more durable closure observed in wounds exposed to B-VEC.

Table 10.3: GEM-3: Primary and key secondary endpoint analyses (imputed data)

Endpoint	B-VEC (n=31)	Placebo (n=31)	Absolute difference, % (95% CI)	p value
Primary endpoint: complete wound closure at 6 months,* n (%)	20.9 (67)	6.7 (22)	46 (24–68)	0.002
Key secondary endpoint: complete wound closure at 3 months,† n (%)	21.9 (71)	6.1 (20)	51 (29–73)	<0.001
Complete wound closure was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin reepithelialisation without drainage, as determined by the investigator. The primary and key secondary endpoints were analysed in the ITT population. Multiple imputation methods were used to account for missing data. Fractional counts are due to the multiple imputation procedure (MAR) used for analysis. In the first stage of multiple imputation, imputations for missing data are generated based on statistical characteristics of the data and this procedure is repeated many times, resulting in data sets with replaced missing information. In the second stage, any analysis of the imputed data sets can be conducted within each of the imputed data sets as if there were no missing data. After the statistical analysis is run separately on each imputed data set, the estimates of interest from all the imputed datasets are combined into a single estimate using standard combining rules. Hypothesis testing was performed with the use of an exact McNemar test. *Primary wounds were assessed at Weeks 22+24 or Weeks 24+26. †Primary wounds were assessed at Weeks 8+10 or Weeks 10+12. B-VEC=beremagene geperpavec; CI=confidence interval; ITT=intent-to-treat; MAR=missing at random Source: Guide <i>et al.</i> (2022)[19]				

10.2.2. Complete wound closure at 3 months

Key secondary endpoint analysis found that B-VEC led to complete wound closure in significantly more wounds than placebo control at 3 months (71% vs. 20%; $p<0.001$); (Table 10.3).[19]

10.2.3. Durable wound closure

Supplementary analysis assessed complete wound closure at various time points (Table 10.4). A durable response was defined as meeting the responder definition for complete wound closure both at 3 months (Weeks 8 and 10 or Weeks 10 and 12) and at 6 months (Weeks 22 and 24 or Weeks 24 and 26).[19] Durability was also assessed by considering the proportion of wounds that met the definition of closure at both 3 months and 6 months (meeting both the primary and key secondary endpoints simultaneously). Using this rigorous definition, once-weekly treatment with B-VEC led to durable complete wound closure in 49.7% treated wounds compared with 7.1% placebo-treated wounds ($p=0.002$).[19]

Table 10.4: GEM-3: Supplementary analyses for durability of wound closure (imputed data)

Endpoint	B-VEC (n=31)	Placebo (n=31)	Absolute difference, % (95% CI)
Durability of response,* n (%)	15.4 (49.7)	2.2 (7.1)	42.6 (22.6–62.6)
Complete wound closure, n (%)			
Weeks 8, 10, and 12	14.8 (47.7)	5.1 (16.5)	31.3 (10.6–51.9)
Weeks 22, 24, and 26	13.4 (43.2)	2.0 (6.5)	36.8 (19.8–53.7)
Complete wound closure was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin reepithelialisation without drainage, as determined by the investigator. Percentages are based on the number of participants in the ITT population; CIs are based on McNemar test. Fractional counts are due to the multiple imputation procedure (MAR) used for analysis. In the first stage of multiple imputation, imputations for missing data are generated based on statistical characteristics of the data and this procedure is repeated many times, resulting in data sets with replaced missing information. In the second stage, any analysis of the imputed data sets can be conducted within each of the imputed data sets as if there were no missing data. After the statistical analysis is run separately on each imputed data set, the estimates of interest from all the imputed datasets are combined into a single estimate using standard combining rules. *Defined as meeting the responder definition for complete wound closure both at 3 months (Weeks 8+10 or Weeks 10+12) and at 6 months (Weeks 22+24 or Weeks 24+26). B-VEC=beremagene geperpavec; CI=confidence interval; ITT=intent-to-treat; MAR=missing at random Source: Guide <i>et al.</i> (2022)[19]			

10.3. GEM-3 OLE trial

- An open-label extension study was conducted with 47 subjects (24 rollover from GEM-3; 23 treatment naïve) receiving B-VEC weekly to target wound areas for up to 112 weeks (median 81 weeks).
- Thirty-five subjects (74.5%) reported one or more adverse events; most were mild or moderate in severity. Fourteen subjects experienced 17 serious adverse events and ten experienced 14 severe adverse events; none was considered treatment related. No adverse events led to treatment or study discontinuation.
- Patient-reported outcomes indicated high levels of treatment satisfaction, but were inconclusive with regard to quality of life.
- Among rollover subjects, wounds that received B-VEC during phase III maintained high closure rates during the open-label extension (range 61.1–89.5%, assessed baseline to month 12).
- A summary of the response for rollover subjects in the GEM-3 OLE study is provided in the Table 10.5. Out of the 24 rollover subjects, 19 were evaluated (five patients did not consistently attend follow-up visits). The responder rate ranged from 61.1% to 89.5% in the OLE study (up to Month 12) and was comparable to the rates observed at Months 3 and 6 in the Phase 3 study.

Table 10.5 Summary of Responders for Rollover Subjects

Visit	Responders/Subjects (%)
Month 3 (Phase 3)	13/19 (68.4)
Month 6 (Phase 3)	14/19 (73.7)
Week 1	17/19 (89.5)
3 Months	16/19 (84.2)
6 Months	11/18 (61.1)
9 Months	14/17 (82.4)
12 Months	10/16 (62.5)

Note: responders were subjects with complete wound closure for primary wounds previously treated with B-VEC during the phase 3 study (B-VEC-03).

Source: Krystal Biotech, Data on File (GEM-3 OLE CSR, Table 14.2).[40]

10.4.EASE trial

10.4.1. Proportion of patients with first complete closure of EB target wound by Day 45

In the overall population (i.e., patients with DEB and JEB), complete closure of target wounds, defined as skin reepithelization without drainage within 45±7 days of treatment, was achieved in 41.3% of wounds treated with BBE, compared to 28.9% of those treated with the control gel (RR 1.44, 95% CI 1.01–2.05; P=0.013) Figure 10.2. This represents a 44% higher likelihood of wound closure with BBE versus control gel. [28]

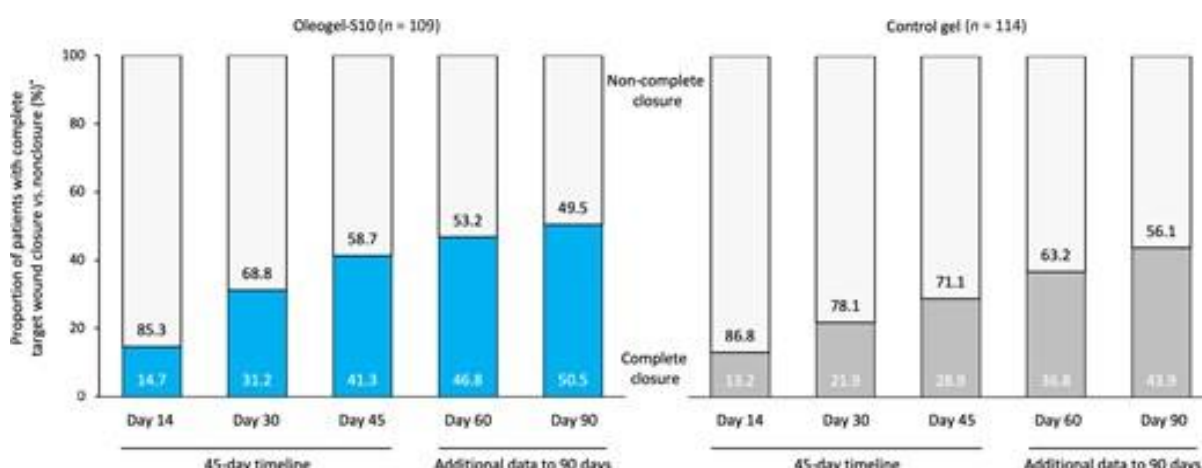


Figure 10.2: Proportion of patients with first complete closure of EB wound by visit

Note: In the BBE (Oleogel S10) group, 91 (83.5%) had RDEB, 6 (5.5%) had DDEB, and 11 (10.1%) had JEB. In the control group, 84 (73.7%) had RDEB, 14 (12.3%) had DDEB, and 15 (13.2%) had JEB. Two patients with EB simplex (EBS) were enrolled and were included in the analysis; a subsequent protocol amendment excluded EBS.

DDEB=dominant dystrophic epidermolysis bullosa; EB=epidermolysis bullosa; RDEB=recessive dystrophic epidermolysis bullosa

Source: Kern et al. (2022)[28]

Subgroup analysis by EB subtype showed that the likelihood of complete wound closure by Day 45 was significantly higher in the BBE group than in the control group in patients with RDEB (odds ratio [OR] 2.52, 95% CI 1.27, 4.98). However, there were no differences between BBE and control gel in patients with DDEB (OR 1.25, 95% CI 0.15, 10.7). [28]

10.4.2. Time to complete target wound closure

An analysis of time to first target wound closure up to day 90 was conducted over the key timepoints during the DBP; mean of 37.7 (SD 21.7, 95% CI 50.0, NE) days and 44.5 days (SD 26.2, 95% CI 89.0, NE) in the BBE arm and control gel arm, respectively.[28] In the overall population, the difference in the time to first target wound closure in the two arms was not statistically significant (log-rank test, $P=0.302$).[28] Notably, no statistical difference was observed in any of the EB subtypes, including RDEB or DEB.

11. Supporting evidence

11.1. Trial evidence for the intervention(s)

GEM-1/2 (study duration of 12 weeks)	
Resource	Description
Krystal Biotech, data on file	<i>In vivo topical gene therapy for recessive dystrophic epidermolysis bullosa: a phase 1 and 2 trial</i> • Data description: ○ From 9 patients for whom data is available, 27 wounds were selected (2 to be treated with B-VEC and the other with placebo), for additional 2 patients, 2 wounds were selected (1 to be treated with B-VEC and the other with placebo). ○ From the 20 wounds treated with B-VEC, 3 were chronic and 17 were recurrent. ○ All the placebo wounds were recurrent. • Results: ○ From the 3 chronic wounds (all of which were treated with B-VEC), one never closed, the others closed at Day 13 and 8 (average 10.5 days) respectively. The baseline size of those 3 wounds were 3.16, 6.00 and 9.70 cm². ○ From the 17 recurrent wounds treated with B-VEC, one never closed (baseline size of 12.5 cm²), the remaining 16 closed after a mean time of 23.88 days (SE: 19.29; range: 8-81 days). The mean baseline size of those 16 wounds was 7.02 cm² (SE: 5.22; range: 2.00-15.60 cm²). ○ From the 11 wounds treated with placebo (all recurrent), 2 never closed, the remaining closed after a mean time of 37 days (SE: 33.29; range: 12-95 days). ○ For the wounds that never closed (1 chronic in B-VEC, 1 recurrent in B-VEC and 2 recurrent on placebo) the baseline sizes of wounds were 6.00, 12.50, 3.10 and 6.61 cm². • Conclusions: ○ B-VEC accelerates the wound closure (mean time to wound closure in B-VEC and placebo of 19.29 and 37 days, respectively) ○ The baseline size of wounds seems to be not related to the B-VEC effectiveness since 4 wounds with more than 12.5 cm² can heal, while the biggest wound that never heal had 12.5 cm² at baseline. ○ The low number of chronic wounds brings limitations and uncertainty in data interpretation, however 2 out of the 3 chronic wounds treated with B-VEC showed a quick closure (after an average of 10.5 days), suggesting that B-VEC can be effective in chronic wounds.

Krystal Biotech, data on file	Based on the patient-level data we have estimated the weekly rate of closure of wound areas in the GEM-1 trial. When extrapolating this, and considering the maximum weekly area treated with B-VEC, we can extrapolate how long it would take on average to completely close a recurrent wound area: • of approximately 1,200 cm² (approximately 50% of the entire back of an adult with RDEB): 26 weeks • of approximately 500 cm² (approximately 40% of the front leg of an adult with RDEB): 10 weeks • of approximately 50 cm² (approximately 8% of the arm of an adult with RDEB): 7 weeks It may take longer for a similar size area to close if the wound is chronic. The below table specifies how long it would take for a wound area of various sizes to completely close if the rate of closing of chronic wound areas would be 75% or 50% of that of recurrent wound areas respectively <table><tr><th>Size of area</th><th>Same rate as recurrent wound area</th><th>75% of the rate of recurrent wound area</th><th>50% of the rate of recurrent wound area</th></tr><tr><td>1,200 cm²</td><td>26 weeks</td><td>29 weeks</td><td>45 weeks</td></tr><tr><td>500 cm²</td><td>10 weeks</td><td>18 weeks</td><td>28 weeks</td></tr><tr><td>50 cm²</td><td>7 weeks</td><td>10 weeks</td><td>15 weeks</td></tr></table>	Size of area	Same rate as recurrent wound area	75% of the rate of recurrent wound area	50% of the rate of recurrent wound area	1,200 cm ²	26 weeks	29 weeks	45 weeks	500 cm ²	10 weeks	18 weeks	28 weeks	50 cm ²	7 weeks	10 weeks	15 weeks													
Size of area	Same rate as recurrent wound area	75% of the rate of recurrent wound area	50% of the rate of recurrent wound area																											
1,200 cm ²	26 weeks	29 weeks	45 weeks																											
500 cm ²	10 weeks	18 weeks	28 weeks																											
50 cm ²	7 weeks	10 weeks	15 weeks																											
EASE (study duration of 90 days)																														
Kern et al. (2023)[41]	Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: results from the phase III randomized double-blind phase of the EASE study • Data description: ○ 223 patients with dystrophic EB, junctional EB or Kindler EB and a target PTW lasting ≥ 21 days and < 9 months that was 10–50 cm², were enrolled and randomized via computer-generated allocation tables 1:1 to BBE (N=109) or control gel (N=114) – both with standard-of-care dressings. ○ Study gel was applied to all wounds at least every 4 days. • Results: ○ BBE resulted in 50.5% of patients with first complete target wound closure within 90 days, compared with 43.9% in the control gel arm. This difference (50.5% vs. 43.9%) was not statistically significant (RR 1.16, 95% CI 0.88–1.52; P = 0.296).																													
EASE OLE (study duration of 24 months)																														
HST28 NICE committee papers [14]	Highly Specialised Technology Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505] Committee Papers • In the submission document of BBE to NICE in the UK, a table was presented with the baseline demographics and wounds characteristics (Table 11.1) Table 11.1: Baseline participant demographics and wound characteristics from <table><tr><th rowspan="2">Total body surface area percentage category</th><th colspan="2">EASE double blind phase</th><th colspan="2">EASE open label phase</th></tr><tr><th>BBE gel</th><th>Control gel</th><th>BBE gel</th><th>Control gel</th></tr><tr><td><10%</td><td>53.2%</td><td>62.3%</td><td>54.0%</td><td>61.9%</td></tr><tr><td>10-25%</td><td>34.9%</td><td>23.7%</td><td>35.0%</td><td>24.8%</td></tr><tr><td>>25%</td><td>11.9%</td><td>13.2%</td><td>11.0%</td><td>12.4%</td></tr><tr><td>Missing</td><td>0%</td><td>0.9%</td><td>0%</td><td>1.0%</td></tr></table> EASE double blind phase and open label phase	Total body surface area percentage category	EASE double blind phase		EASE open label phase		BBE gel	Control gel	BBE gel	Control gel	<10%	53.2%	62.3%	54.0%	61.9%	10-25%	34.9%	23.7%	35.0%	24.8%	>25%	11.9%	13.2%	11.0%	12.4%	Missing	0%	0.9%	0%	1.0%
Total body surface area percentage category	EASE double blind phase		EASE open label phase																											
	BBE gel	Control gel	BBE gel	Control gel																										
<10%	53.2%	62.3%	54.0%	61.9%																										
10-25%	34.9%	23.7%	35.0%	24.8%																										
>25%	11.9%	13.2%	11.0%	12.4%																										
Missing	0%	0.9%	0%	1.0%																										

	• The percentage of patients treated with BBE in each total body surface area percentage category are stable in the double blind and open label phases. Note that at baseline of the open label phase, part of the wounds were already treated with BBE in the double blind phase. This means that the benefit of BBE is not bringing patients to categories with less body surface area covered with wounds.																																																						
Murrel et al (2025) [42]	Long-term safety and efficacy of Oleogel-S10 (birch bark extract) in epidermolysis bullosa: 24-month results from the phase III EASE study • Data description: ○ The 205 patients who completed the EASE double blind phase were offered the opportunity to enter this single-arm phase, where everyone received BBE for long-term safety and efficacy follow-up. • Results: ○ Patients enrolled to BBE in the double-blind phase and that continued treatment in OLE achieved a -4.3% and -3.7% mean change in body surface area percentage from baseline to 3 month (6 months of Filsuvez usage, if we add the 3 months in DBP) and 24 months (N=59), respectively (Table 11.2 and Figure 11.1). ○ Patients enrolled to placebo in the double-blind phase and that started the treatment with BBE in OLE also achieved a -1.7% and -3.7% mean change in body surface area percentage from baseline to 3 month (6 months of Filsuvez usage, if we add the 3 months in DBP) and 24 months (N=69) (Table 11.2 and Figure 11.1). Table 11.2: Mean change in body surface area percentage from baseline in the double-blind phase of the EASE study <table><tr><th></th><th>DBP baseline</th><th>Day 90/ OLE baseline</th><th>OLE month 3</th><th>OLE month 12</th><th>OLE month 24</th></tr><tr><td colspan="6">BBE group</td></tr><tr><td>N</td><td>109</td><td>100</td><td>85</td><td>67</td><td>59</td></tr><tr><td>Mean (SD) change from baseline</td><td>-</td><td>-4.2 (6.9)</td><td>-4.3 (8.1)</td><td>-4.3 (8.1)</td><td>-3.7 (9.0)</td></tr><tr><td>P-value</td><td>-</td><td><0.001</td><td><0.001</td><td><0.001</td><td>0.003</td></tr><tr><td colspan="6">Former control gel group</td></tr><tr><td>N</td><td>113</td><td>96</td><td>86</td><td>72</td><td>69</td></tr><tr><td>Mean (SD) change from baseline</td><td>-</td><td>-2.6 (9.0)</td><td>-1.7 (9.8)</td><td>-3.7 (8.0)</td><td>-3.7 (7.2)</td></tr><tr><td>P-value</td><td>-</td><td>0.005</td><td>>0.05</td><td><0.001</td><td><0.001</td></tr></table>		DBP baseline	Day 90/ OLE baseline	OLE month 3	OLE month 12	OLE month 24	BBE group						N	109	100	85	67	59	Mean (SD) change from baseline	-	-4.2 (6.9)	-4.3 (8.1)	-4.3 (8.1)	-3.7 (9.0)	P-value	-	<0.001	<0.001	<0.001	0.003	Former control gel group						N	113	96	86	72	69	Mean (SD) change from baseline	-	-2.6 (9.0)	-1.7 (9.8)	-3.7 (8.0)	-3.7 (7.2)	P-value	-	0.005	>0.05	<0.001	<0.001
	DBP baseline	Day 90/ OLE baseline	OLE month 3	OLE month 12	OLE month 24																																																		
BBE group																																																							
N	109	100	85	67	59																																																		
Mean (SD) change from baseline	-	-4.2 (6.9)	-4.3 (8.1)	-4.3 (8.1)	-3.7 (9.0)																																																		
P-value	-	<0.001	<0.001	<0.001	0.003																																																		
Former control gel group																																																							
N	113	96	86	72	69																																																		
Mean (SD) change from baseline	-	-2.6 (9.0)	-1.7 (9.8)	-3.7 (8.0)	-3.7 (7.2)																																																		
P-value	-	0.005	>0.05	<0.001	<0.001																																																		

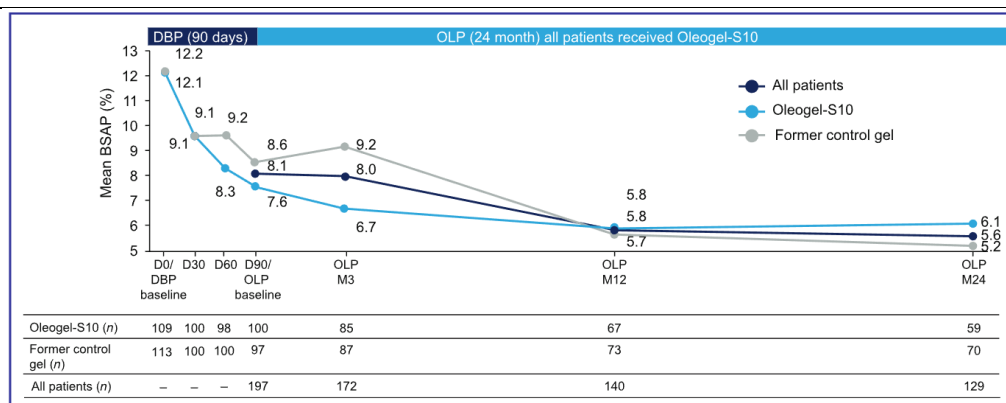


Figure 11.1: Mean body surface area percentage (BSAP) from baseline of the double-blind phase (DBP) to month 24 in the open-label phase (OLP). Data shown are the absolute mean BSAP values at each timepoint. Assessments recorded within OLP visit windows were lower than expected largely due to the COVID-19 pandemic. Therefore, a post hoc analysis was produced without visit windows in the OLP. Day 90/OLP baseline: the last assessment before the first open-label treatment and at day 90 (eight patients did not have a day-90 visit). D, day; M, month

- **Conclusions:**
 - The BBE benefit achieved in the double-blind phase was considered stable in the OLE
 - Patients in placebo in the double-blind phase achieved the BBE benefit in the OLE after 12 months of treatment

11.2.External evidence

Source of evidence	
Resource	Description
Brena, 2025[43]	Topical gene therapy for severe recessive dystrophic epidermolysis bullosa: clinical outcomes and multidisciplinary management in three patients treated with beremagene geperpavec (B-VEC) in Italy - Retrospective case series describing three patients with genetically confirmed RDEB: two children and one young adult-treated between 2024 and 2025 at two Italian tertiary centres. All patients had extensive chronic skin involvement and received weekly topical B-VEC. - Case 1 and 2 had 60% of body surface area affected with wounds (40% with chronic wounds) (Figure 11.2). Case 3 is documented as having 70% of body surface area covered with wounds (half of which were chronic wounds) (Figure 11.3). - Weekly administration of B-VEC reduced wound surface area by $\geq 70\%$ in Case 1, $\geq 50\%$ in Case 2, and $>60\%$ in Case 3, accompanied by improved wound depth and reduced bleeding. The high rate of wound surface area reduction shows the effectiveness of B-VEC in chronic wounds.

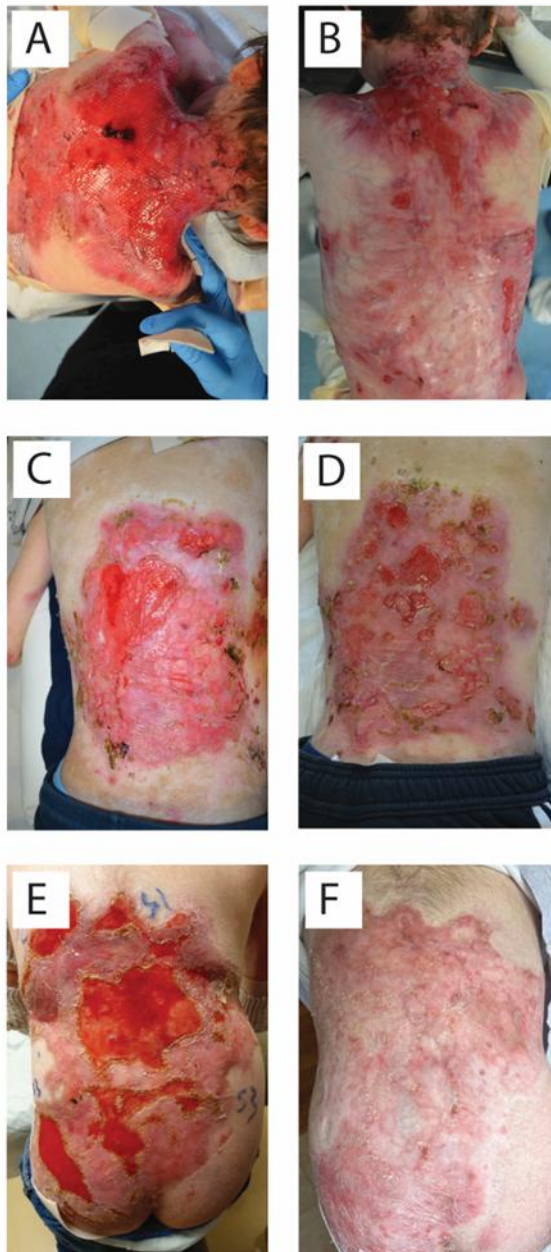


Figure 11.2: Clinical progression of wound healing in the back following B-VEC treatment in patients with RDEB. A and B: Case 1, dorsal target wound before (A) and after (B) 12 months of B-VEC therapy. C and D: Case 2, dorsal wound prior to treatment (C) and after 12 months of B-VEC application (D). E and F: Case 3, extensive chronic wounds of the lower back and gluteal region before (E) and after (F) 6 months of B-VEC therapy.

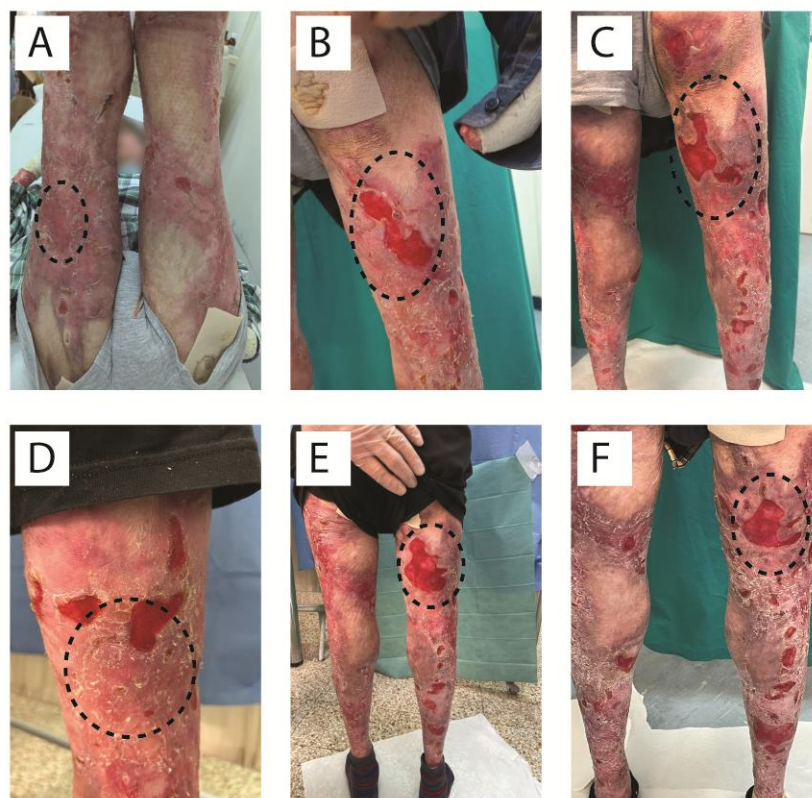


Figure 11.3: Case 3. October 2024: superficial and well-controlled wounds in the right posterior thigh (A); December 2024: reopening of a wound in the right posterior thigh (target wound) (B); January 2025: complete closure of the target wound and emergence of a new medial wound (C); March 7, 2025: reduction of both wounds (D); March 21, 2025: reopening of the target wound (E); April 2025: partial closure of the target wound with evidence of re-epithelization (F).

Autorisations d'accès compassionnel (AAC) report from France, 2024[33]

- Number of patients treated with B-VEC: 8
- Mean and median duration of follow-up: 138 and 161 days, respectively (range: 39-203 days)
- All the wounds treated where chronic with a mean size at baseline of 15.88 cm² (range 4 – 35 cm²)
- From 8 wounds:
 - 1 healed after 1, 3 and 6 months of B-VEC exposure.
 - 1 healed after 1 and 3 months of B-VEC exposure, being opened at 6 months (this patient had a treatment interruption due to vacations).
 - 1 healed after 1 month of B-VEC exposure, having no more registries after that (due to vacation period, some administrations were missed);
 - 2 did not close after 1 and 3 months, being missing the 6 months observation (due to vacation period, some administrations were missed);
 - 1 wound did not close at month 1 and did not have any additional registries after that due to a surgical procedure;
 - There is no observation for 2 patients (one of those moved to other country).

	<i>In this sample, 50% (3/6) of chronic wounds healed, even the duration of closure cannot be observed.</i>
Eng et al. (2021)[13]	<i>Chronic wounds remain open for 8 weeks or longer.</i>
Devries et al. (2004)[44]	<i>Relative extent of skin involvement in inherited epidermolysis bullosa (EB): Composite regional anatomic diagrams based on the findings of the National EB Registry, 1986 to 2002</i> <i>This study sought to generate accurate anatomic “density” diagrams depicting the relative extent and location of skin lesions within each major EB subtype.</i> <i>Diagrams were created for each major EB type, on the basis of medical history and physical examination findings obtained from 1986 to 2002 from 3280 consecutive enrollees in the National EB Registry.</i> <i>Figure 11.4 and Figure 11.5 show the of composite anatomic diagrams representing frequency of skin involvement (how often a site is affected across patients) in different anatomic sites in DDEB and RDEB, respectively, based on medical history data.</i> The figure displays two human figures, front and back views, illustrating the frequency of skin involvement in dominant dystrophic epidermolysis bullosa (DDEB). The figures are color-coded according to a legend on the right, which shows the percentage of patients affected in different anatomic sites. The legend categories are: < 1% (white), 1-5% (yellow), 5.1-10% (orange), 10.1-25% (green), 25.1-50% (blue), 50.1-75% (purple), and 75.1-100% (black). The front view shows high involvement (purple and black) on the arms and hands, and moderate involvement (green and blue) on the torso and legs. The back view shows high involvement (purple and black) on the arms and hands, and moderate involvement (green and blue) on the torso and legs. Figure 11.4 . Composite anatomic diagram representing frequency of skin involvement in different anatomic sites in dominant dystrophic epidermolysis bullosa (DDEB), based on medical history data.

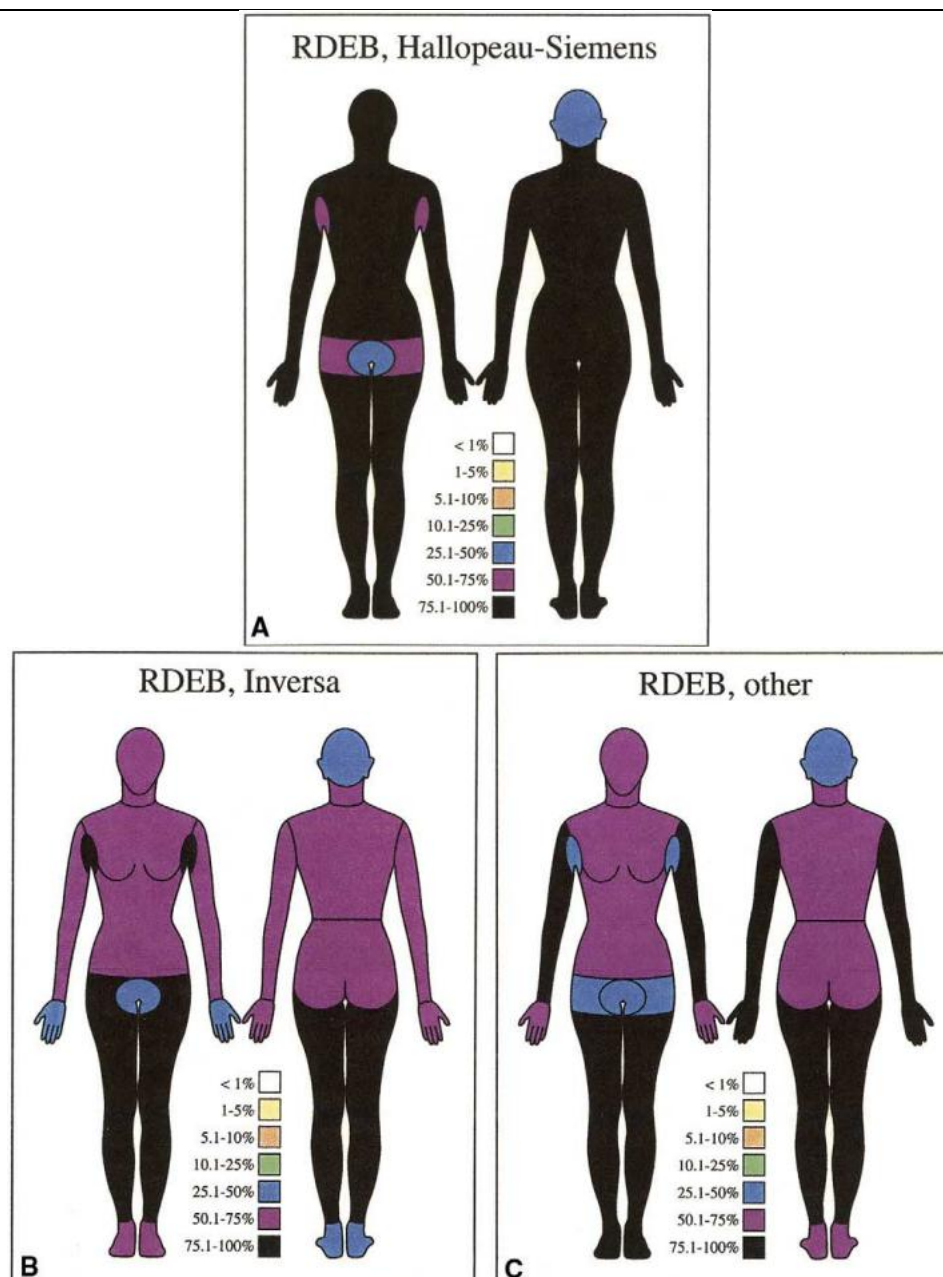


Figure 11.5 Composite anatomic diagram representing frequency of skin involvement in different anatomic sites in generalized RDEB Hallopeau Siemens (A), RDEB inversa (B), and all other subtypes of RDEB (C), based on medical history data

- Figure 11.6 and Figure 11.7 show the composite anatomic diagrams representing the relative percentage of surface area involvement (how much surface area a site contributes to the total affected area in one patient's examination) in different anatomic in DDEB and RDEB, respectively, based on medical history data.

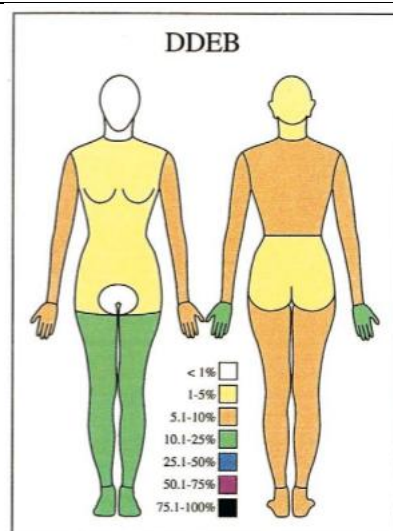


Figure 11.6 Composite anatomic diagram representing relative percentage of surface area involvement in different anatomic sites in DDEB, based on physical examination data

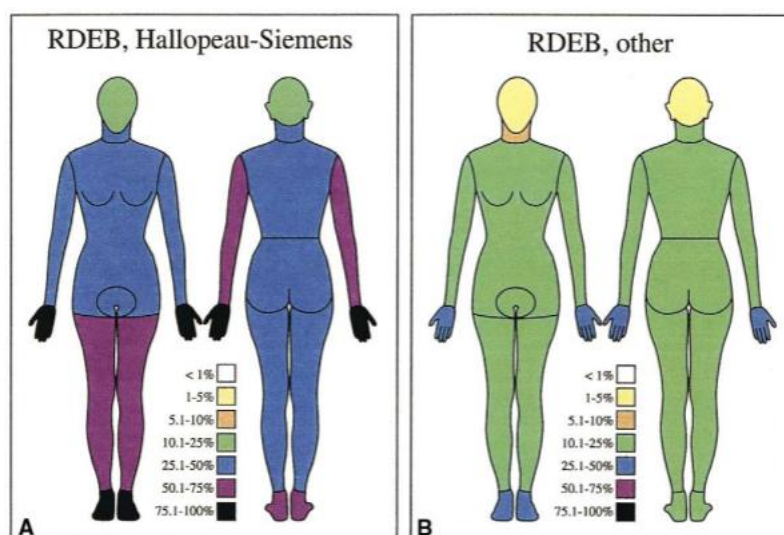


Figure 11.7 Composite anatomic diagram representing relative percentage of surface area involvement in different anatomic sites in generalized RDEB

Davidovic et al.
(2025) [34]

Real-World Experience With Oleogel-S10 for Wounds in Epidermolysis Bullosa

Data description:

- *This study aims to evaluate the use of BBE in 16 patients with different types of EB in a real-world setting.*
- *Chronic wounds were chosen for follow-up and assessment, and considered as target wounds. Patients used BBE as labelled.*
- *Wounds, pain, and itch were assessed, and patients were asked how they felt about the treatment at each follow-up visit.*
- *The wound area ranged from 1 cm² to more than 20 cm².*
- *The sample is compounded by:*
 - *3 JEB patients*
 - *2 RDEB intermediate*

- 8 RDEB severe
- 1 DDEB

Table 11.3: Patients' characteristics in the study

Pat. Nr.	Sex	Age (years)	EB type and subtype	Localisation of chronic target wounds
1	F	19	JEB int-LAMA3	Left hip, gluteal left
2	F	36	JEB int-COL17A1	Ears
3	M	47	JEB int-COL17A1	Gluteal
4	M	55	RDEB int	Lower leg right, head frontal right
5	M	12	RDEB severe	Right lower leg
6	M	16	RDEB severe	Lower back
7	F	17	RDEB severe	Right hand and heels on both sides
8	F	19	RDEB severe	Upper left leg dorsal, upper right leg ventral
9	F	24	RDEB severe	Upper legs
10	M	24	RDEB severe	Head, neck, face
11	F	19	DDEB	Ventral sides of lower legs
12	M	6	RDEB int	Lower leg
13	M	3	RDEB severe	Ventral left lower leg
14	F	12	RDEB severe	Upper arms, knees

Results:

- Two patients who did not use the medication were excluded from the analysis. Data from 14 patients who used BBE were obtained.
- Two patients with RDEB severe and one patient with RDEB intermediate discontinued the treatment because no benefit was felt, but rather relapse or worsening of the wounds, and stopped the treatment after 2–6 months. Therefore, for approximately:
 - 73% (8/11) of the DEB patients, BBE as considered beneficial
 - 70% (7/10) of the RDEB patients, BBE as considered beneficial
 - 50% (1/2) of the RDEB intermediate, BBE as considered beneficial
 - 75% (6/8) of the RDEB severe, BBE as considered beneficial
- Eleven patients benefited from the treatment with BBE and used it regularly during an average period of 7 months (range 4–12 months). From those, it was observed:
 - Complete wound closure (in two patients),
 - Partial wound closure (eight patients),
 - Faster wound healing (eight patients),
 - All DEB patients (median age 19 years) experienced partial wound closure and faster wound healing, although blisters and wounds relapsed on the same sites (Figure 11.8).
- The 11 patients continued to use BBE in the 18 months following this evaluation without any adverse events.

	Patient 6 RDEB Before Oleogel-S10 6 m  Patient 8 RDEB Before Oleogel-S10 5 m  Patient 9 RDEB Before 1 m 6 m Oleogel-S10  Figure 11.8: Representative clinical pictures of wounds of patients with RDEB before and under BBE treatment at different time points given in months (m).
Fulchand et al (2025)[35]	<i>Natural history study of recessive dystrophic epidermolysis bullosa wounds and patient reported outcomes using mobile application home photograph</i> Data description: - This is a prospective observational study in which 13 RDEB participants used a mobile application to upload weekly photographs of multiple target wounds for up to 6 months and reported associated wound pain and itch (Photo Cohort, N=69 wounds). A separate dataset of placebo-treated wounds was also used from a previously completed trial (Validation Cohort, N=57 wounds) to validate the 12-week definition of wounds and to determine their rate of spontaneous wound closure. - Chronic wound was defined as to be constantly open (never healed) for ≥ 12 weeks - Spontaneous wound closure was defined as an open area $\leq 0.5\text{cm}^2$ - Target wounds were observed weekly for spontaneous wound closure for an average of 14 weeks (SD=12), with an average of seven days between photo uploads Results: - A total of 734 photos were uploaded for 69 wounds. - In the Photo Cohort, 60.9% (42 out of 69) were classified as chronic open wound type and 27.5% (19 out of 69) as recurrent wounds (Table 11.4) - Compared with recurrent wounds, chronic open wounds were larger at baseline (50 vs. 5 cm^2 and present for a longer duration (21.4 vs. 2 weeks) (Table 11.4) - Only 17% of chronic open wounds achieved spontaneous wound closure during the observation period (Table 11.4) - The median time to wound closure was 5.7 weeks for recurrent wounds (Table 11.4)

- Of the few chronic open wounds that were observed to have spontaneous wound closure (7 out of 42), the median time for wound closure was close to six months (25.7 weeks vs. 6.7 weeks for recurrent wounds, $P < 0.0001$) (Table 11.4)
- Generalized estimating equation models were developed to estimate the odds of spontaneous wound closure during observation period.
 - These regression models used clustering to account for the multiple wounds within the same patient (69 wounds from 13 participants).
 - The only clinical predictor associated with spontaneous wound closure was baseline wound size.
 - From the multivariable analysis, a smaller baseline wound area was defined as wound with an area lower than the median (13.5 cm^2). This median was calculated independently of the wound type (recurrent vs. chronic).
 - A smaller baseline wound area was significantly associated with a 12.8-fold greater likelihood of spontaneous closure (12.8, 95% CI: 3.3–48, $P < 0.01$), adjusting for participant age, wound location, and recent wound infection in the past 3 months.
 - Wounds without recent infection had a 3.8-fold (95%CI: 0.91–15.9) greater likelihood of spontaneous closure; however, this did not reach statistical significance.
 - Patient-level covariates (age, sex, genotype, BMI, hemoglobin, and baseline vitamin D levels) were not significantly associated with spontaneous wound closure in univariate and bivariate analysis adjusting for baseline wound size.
 - In multivariate models, recurrent wound type was associated with a 29-fold higher-odds of spontaneous closure compared with chronic open wound type, adjusting for participant age, wound location, and baseline wound size ($P = 0.0045$)

Table 11.4: Participant and wound characteristics from RDEB participants in the photo cohort and placebo

Wound characteristics	Photo cohort (N=69 wounds, 13 participants)	Validation cohort (N=57 wounds, 57 participants)
<i>Number of wound types following classification, n/N (%)</i>		
Chronic wound	42/69 (60.9%)	42/57 (73.7%)
Recurrent wound	19/69 (27.5%)	13/57 (22.8%)
Unable to classify	8/69 (11.6%)	2/57 (3.5%)
<i>Average baseline wound size in cm^2 (SD)</i>		
Chronic wound	50 (70)	20 (10)
Recurrent wound	5 (6)	14 (5)
Unable to classify	24 (31)	18 (11)
<i>Median age of wounds at baseline in weeks (range)</i>		
Chronic wound	21.4 (2.0–251.4)	12 (3.4–516.6)
Recurrent wound	2.0 (0.4–8.6)	3.9 (3.0–6.0)
Unknown	1.6 (0–4.0)	4.3 (4.3–4.3)
<i>Time to closure in days (median (range)) (n/N, %)</i>		
Chronic wound	180 (90–317) (n=7/17, 17%)	102 (8–45) (n=11/42, 26%)
Recurrent wound	47 (3–78) (n=19/19, 100%)	56 (35–81) (n=12/14, 86%)

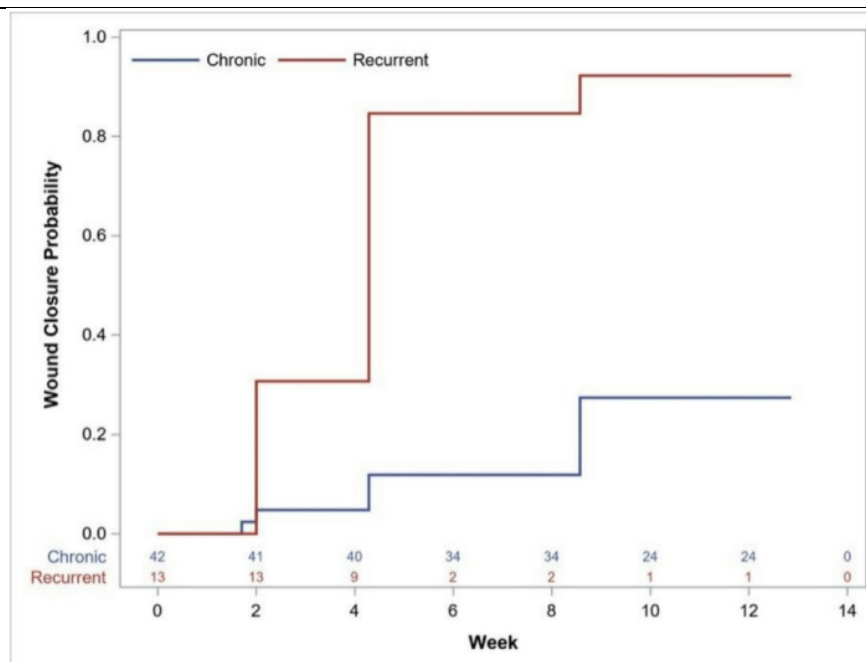


Figure 11.9: Kaplan-Meier curve of spontaneous wound closure probability for chronic open wounds versus recurrent wounds (Validation cohort, N=57 participants)

Karakioulaki et al. (2025) [36]

Beremagene geperpavec (B-VEC) for infantile dystrophic epidermolysis bullosa: Benefit of early intervention

Data description:

- A male infant with severe recessive DEB born with extensive skin defects on the hands and legs with B-VEC for 40 weeks.
- At 9 months of age, when the treatment was initiated, he presented with multiple blisters and wounds, including aplasia cutis congenita on his left leg. He was receiving pain relief therapy with paracetamol, ibuprofen and morphine sulfate.
- The infant exhibited failure to thrive and did not meet the motor milestones.
- B-VEC (1.6×10^9 PFU in 0.8 mL gel) was applied weekly to all wounds.
- A total volume of 0.8 mL allowed the treatment of up to 80 cm² of wound area per week.

Results:

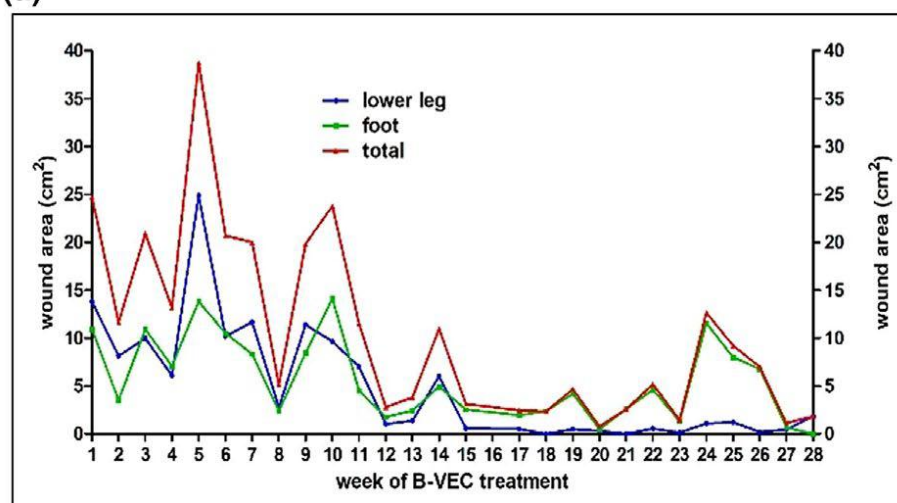
Table 11.5: Genetic, clinical and laboratory values

Parameter	Value	Normal range
COL7A1 (NM_000094.4)	c.3942dup;4018C>T	
Body weight at birth	3.75 kg 78th percentile (WHO ^a)	
Body weight at 2.5 months of age	5.18 kg 13rd percentile (WHO ^a)	

Body weight at treatment start (9 months of age)	7.5 kg 13rd percentile (WHO ^a)	
Body weight at Week 28 of treatment (15 months of age)	9.3 kg 16th percentile (WHO ^a)	
Body weight at Week 40 of treatment (19 months of age)	10.8 kg 38th percentile (WHO ^a)	
Haemoglobin before treatment	94 g/L	100–135 g/L
Haemoglobin at Weeks 8, 10 and 40 of treatment, respectively	10.8, 10.8 and 11.3 g/dL	9.7–13.6 g/dL
C-reactive protein before treatment	24 mg/L	0–20 mg/L
C-reactive protein at Weeks 8, 10 and 40 of treatment, respectively	8.8, 27.2 and 4.9 mg/L	<5 mg/L
Anti-type VII collagen IgG antibodies ELISA at Week 38 of treatment	Ratio: 1.27 9.00 U/mL	<1 <6 U/mL

^a Percentiles were calculated using the online tool <https://www.infantchart.com/>

(a)



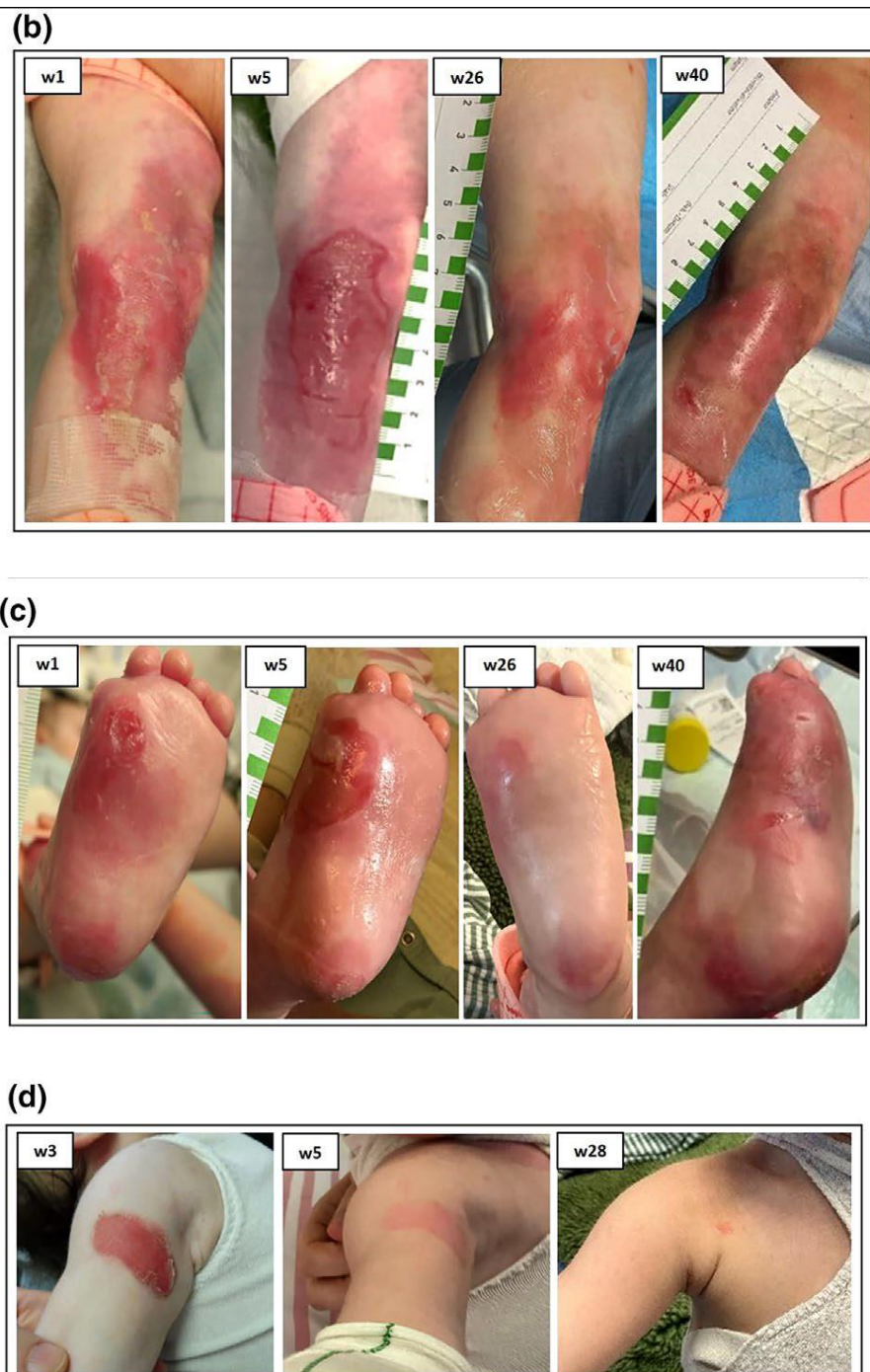


Figure 11.10: Course of wound healing during treatment with beremagene geperpavec (B-VEC). (a) Longitudinal tracking of wound surface area on the infant's left lower leg and foot. Wounds were photographed weekly (w) for 28 weeks, and surface areas were independently quantified by two observers using ImageJ (<https://imagej.net/ij/>). Data were analysed and plotted using GraphPad Prism (version 10.0.0). (b) Representative images of the left lower leg, which exhibited aplasia cutis congenita and had remained unhealed since birth. Following treatment, the wound closed by Week 26 and remained durably healed throughout the 40-week observation period. (c)

	Representative images of the left foot. The wounds fully healed by Week 26 and remained closed through Week 40, despite the child's increased mobility. (d) Representative images of acute wounds that responded rapidly to treatment, achieving complete closure without visible scarring. • The boy was comfortable during the treatment and tolerated it well. • Chronic wounds on his left leg healed within 26 weeks. • Although new blisters appeared in the proximity or in other regions that were not treated before, they healed in 1–2 weeks under B-VEC. • Acute wounds healed in <7 days with almost no scarring and remained closed. • Morphine was discontinued. • Four months after starting treatment, the boy developed his motor skills and was able to stand and walk. • By the end of the observation period, the chronic wounds on the lower extremities were persistently healed, despite the boy's increased physical activity and independent mobility. • He gained weight, showed improved CRP and haemoglobin levels (Table 11.5), with no side effects or loss of efficacy observed. Conclusions: • These real-world observations highlight B-VEC efficacy in congenital skin defects. • The impact of B-VEC in that child was far beyond wound healing: it improved the general development of the child and positively influenced the well-being of the entire family, based on physician assessments conducted during and between clinical consultations. • While the wound area progressively decreased, transient increases were observed due to new blisters (Figure 11.10 a). These fluctuations are common in EB patients, due to the inherently dynamic nature of the disease and external factors such as mechanical trauma, heat and intercurrent infections.

12. Appendix

Appendix A: Clinical trials supplementary information

12.1.GEM-1/2

12.1.1. Eligibility criteria

- Age:
 - Phase 1: aged ≥ 18 years
 - Phase 2a: aged ≥ 5 years
 - Phase 2b: aged ≥ 2 years
 - Phase 2c: aged ≥ 2 years
- Clinical diagnosis of RDEB confirmed by genetic testing, immunofluorescence, and immunoelectron microscopy
- Confirmed RDEB COL7A1 mutations
- LH24 antibody negative (NC2-negative and NC1-positive). (This criterion is applicable to the first 2 adults on the study (phase 1). Subsequent patients could be NC1-positive or NC1-negative)
- Wounds meeting the wound size/surface area entry criteria:
 - Phase 1: 2 wounds up to 10 cm²; 1 randomised to B-VEC and 1 randomised to placebo
 - Phase 2a and 2b: At least 3 wounds up to 20 cm²; 2 wounds randomised to B-VEC and 1 randomised to placebo
 - Phase 2c: At least 2 wounds up to 50 cm²; at least 1 randomised to B-VEC and 1 randomised to placebo
- Willing to comply with study requirements; written informed consent from patient or legal representative

12.1.2. Exclusion criteria

- Medical instability limiting ability to travel to the investigative centre
- Presence of medical illness (e.g., HIV, hepatitis B, or hepatitis C) expected to complicate participation and/or compromise the safety of the technique
- Serum antibodies to COL7 (patients with negative results within 12 months of screening are eligible)
- Active infection in the area that will undergo administration
- Evidence of systemic infection
- Known allergy to any of the constituents of the product
- Current evidence or a history of squamous cell carcinoma in the area that will undergo treatment
- Active drug or alcohol addiction
- Hypersensitivity to local anaesthesia (lidocaine/prilocaine cream)
- Receipt of chemical or biological study product for the specific treatment of RDEB in the past 3 months

- Specific wounds that have previously been administered investigational gene or cell therapy
- Use of systemic antibiotics within 7 days
- Positive pregnancy test or breast-feeding
- Clinically significant abnormalities as determined by the investigator

12.1.3. Method of randomisation

- A complete randomised-block design, with each patient designated as a block to receive all conditions, was used to assign treatment. Investigator-assigned wound numbers were randomised using a pre-generated randomisation schedule. Randomisation schemes were generated via a customised program prior to the study, and randomisation assignments for the treatment sites of each study patient were provided in sealed envelopes. Once the wound pairs were identified and labelled, the randomisation envelope was opened, and the assigned dose was then given.

Intervention(s) and comparator(s)

- GEM-1 enrolled N=12 patients (9 distinct patients enrolled in the study; 3 enrolled in both phase 2a and 2b).
- Wounds were randomly assigned in a 1:1 (phase 1 and 2c) or 2:1 (phase 2a and 2b) ratio to be treated with B-VEC or placebo.
- B-VEC (N=12):
 - Thawed cryopreserved drug product mixed with excipient gel (Velesco Lot [phases 1, 2b, and 2c] or PluroGel® [phase 2a])
 - Topical doses:
 - Phase 1 (n=2 adults): 1×10^8 PFU at Days 0, 2, 28, and 30; additional dose on Day 42 for patient 2
 - Phase 2a (n=2 adults and n=2 paediatric patients): 6×10^8 PFU initially administered on Days 1, 2, 3, 4, and 5
 - Patient 1 had additional administrations at Day 30, Day 44 (unscheduled), and Day 60
 - Patient 3 had an additional administration on Day 30
 - Patient 4 had an additional administration on Day 30 and Day 46 (unscheduled)
 - Phase 2b (n=3 adults and n=2 paediatric patients): 1×10^8 to 1.2×10^9 PFU per administration day dosed approximately every 2–3 days for 2 consecutive weeks and then at Days 30, 60, and 90 if wounds were open during study visits
 - Phase 2c (n=1 paediatric patient): 8×10^8 to 1.57×10^9 PFU per wound per administration. Wounds underwent 2 cycles of treatment:
 - Cycle 1 was 25 days and consisted of 20 administrations
 - Cycle 2 was 24 days and consisted of 21 administrations
 - Placebo (N=12):
 - Isotonic saline mixed with excipient gel

12.1.4. Permitted and disallowed concomitant medication

- Patients were encouraged to restrict topical administration of any therapy to the wounds under study for a minimum of 48 hours following administration of the investigational product.
- Throughout the study, any concomitant medications or treatments deemed necessary to provide adequate supportive care could be prescribed, including medication for the intradermal injections and biopsies to treat pain and/or anxiety (e.g., lidocaine, lorazepam).
- Patients continued routine skin care throughout the study.

12.1.5. Duration of follow-up, lost to follow-up information

- Study period: May 2018 to November 2019
- Up to 2-month intervention (depending on phase) followed by long-term follow-up period consisting of annual telephone contacts (up to 5 years) with the patient and their primary care physician, which began after each patient completed the interventional portion of the study.
- Treatment discontinuation: n=4
- 3 patients were discontinued from phase 2a by the sponsor so they could roll over to phase 2b. These patients are considered to have completed the study.
- 1 patient completed their last dose on Day 61 and was discontinued by the sponsor due to not being able to participate further. This patient is considered to have completed the study.
- Study withdrawal: n=1 (due to inability to travel to study assessments)

12.1.6. Primary outcomes (including scoring methods and timings of assessments)

- Proportion of wounds with complete wound closure (was defined as at least 90% reduction in wound surface from baseline) at Weeks 8, 10, or 12.
- Time to wound closure, defined as the time from the first treatment to complete wound closure (at least 90% reduction in wound surface from baseline).
- Duration of wound closure, defined as the time from the complete closure ($\geq 90\%$ reduction in wound surface from baseline) to the first reopening of the same wound.

12.1.7. Other outcomes used in the economic model/specified in the scope

- Investigator global assessment score (wounds were compared against baseline at Days 3, 5, 15, 30, 60, and 90)
- Patient-reported outcome for pain (wounds were compared against baseline at Days 3, 5, 15, 30, 60, and 90)

12.1.8. Pre-planned subgroups

- No subgroup analysis was planned or performed.

12.2.GEM-3

12.2.1. Eligibility criteria

- Age ≥ 6 months with clinical diagnosis of DEB
- Confirmation of DEB diagnosis (either dominant [DDEB] or recessive [RDEB]) by genetic testing including COL7A1
- Two cutaneous wounds meeting the following criteria:
 - Location: similar in size, located in similar anatomical regions, and similar in appearance
 - Appearance: clean with adequate granulation tissue, excellent vascularisation, and did not appear infected
- Use of reliable birth control throughout the duration of the study and for 3 months after the last dose of B-VEC, if of childbearing potential
- Negative pregnancy test at Visit 1 (Week 1), if applicable
- Willing to comply with study requirements; written informed consent from patient or legal representative

12.2.2. Exclusion criteria

- Medical instability limiting ability to travel to the investigative centre
- Diseases or conditions that could have interfered with the assessment of safety and efficacy of the study treatment and compliance of the subject with study visits/procedures, as determined by the investigator
- Current evidence or a history of squamous cell carcinoma in the area that would undergo treatment
- Actively receiving chemotherapy or immunotherapy at Visit 1 (Week 1)
- Active drug or alcohol addiction as determined by the investigator
- Hypersensitivity to local anaesthesia (lidocaine/prilocaine cream)
- Participated in an interventional clinical trial within the past 3 months (not including B-VEC administration)
- Receipt of a skin graft in the past 3 months
- Pregnant or nursing

12.2.3. Method of randomisation

- Using a pre-generated randomisation schedule, the matched primary wounds were randomised to receive either B-VEC or placebo gel. The randomisation schedule was generated using a block size of 6 for 7 sites with a maximum of 72 randomisations per site. The randomisations were not stratified. The randomisation schedule was generated by an independent statistician and validated by an independent statistical programmer.

12.2.4. Intervention and comparators

- The wounds within each pair were randomly assigned in a 1:1 ratio to receive once-weekly application of either B-VEC or placebo for 26 weeks until wound closure.

- B-VEC (N=31):
 - Thawed cryopreserved drug product mixed with excipient gel (Methocel)
 - Topical dose ranging from 4×10^8 to 1.2×10^9 PFU depending on the baseline wound size
- Placebo (N=31):
 - Normal saline mixed with excipient gel, at a matched volume to B-VEC drug product
- Additional secondary wounds were selected for open-label B-VEC treatment.

12.2.5. Duration of follow-up, lost to follow-up information

- Study period: August 2020 to April 2021
- 7-month follow-up (6-month double-blind period, 30-day safety follow-up)
- Treatment discontinuation: n=0
- Study withdrawal: n=3
 - One patient was lost to follow-up at Week 6
 - One patient relocated at Week 12
 - One patient withdrew at Week 24 because of travel constraints due to COVID 19

12.2.6. Permitted and disallowed concomitant medication

- Topical administration of any medication (other than B-VEC and placebo) to a study target wound was prohibited throughout the study period up to Week 26 unless approved in advance by the medical monitor/sponsor.
- Topical concomitant medications or treatments deemed necessary to provide adequate supportive care to nontarget wounds were permitted (and documented). Although prescription of tacrolimus, clobetasol, or becaplermin was permitted per protocol, none was applied during the study.
- Women of childbearing potential using oral contraception must have consistently been taking their birth control for 3 months prior to Visit 1 (Week 1) and must have committed to continue using contraception throughout the study and for up to 3 months following the last dose of B-VEC.

12.2.7. Primary outcomes (including scoring methods and timings of assessments)

- Proportion of primary wounds with complete wound closure at 6 months (Week 22+24 or Week 24+26).
- Only wounds that were healed for at least 2 consecutive weeks were counted as having had a response.

- Complete wound closure was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin reepithelialisation without drainage, as determined by the investigator.

12.2.8. Other outcomes used in the economic model/specified in the scope

- Key secondary endpoint:
 - Primary wounds with complete closure at 3 months (Week 8+10 or Week 10+12).
- Other secondary end points:
 - Change from baseline to Week 22, 24, and 26 in pain severity during changes in wound dressing. Assessed with the use of:
 - VAS (scores range from 0–10, with higher scores indicating greater pain) for patients aged ≥ 6 years
 - FLACC-R scale for patients aged < 6 years.
- Exploratory endpoints:
 - Change from baseline to Week 26 in general HRQoL assessed using the EQ 5D-5L.
 - Change from baseline to Week 26 in skin-specific HRQoL assessed using the Skindex-29 questionnaire.

12.2.9. Preplanned subgroups

- Subgroup analyses for the primary endpoint were prespecified on the basis of sex, age, and race.

12.3.EASE

12.3.1.

Eligibility criteria

- Male and female patients with the following subtypes of inherited EB: junctional EB (JEB), dystrophic EB (DEB), and Kindler EB aged ≥ 21 days
- Patients with an EB target wound (i.e., EB partial thickness wound of 10 cm^2 to 50 cm^2 in size aged ≥ 21 days and < 9 months)
- Patient and/or his/her legal representative has/have been informed, has/have read and understood the patient information/informed consent form, and has/have given written informed consent
- Patient and/or his/her legal representative must be able and willing to follow study procedures and instructions

12.3.2. Exclusion criteria

- Patient has EB simplex
- EB target wound that is ≥ 9 months old or has clinical signs of local infection
- Use of systemic antibiotics for wound-related infections within 7 days prior to enrolment
- Administration of systemic or topical steroids (except for inhaled, ophthalmic or topical applications, such as budesonide suspension for oesophageal strictures [e.g., Pulmicort respules® 0.25 mg/2 mL or 0.5 mg/2 mL]) within 30 days before enrolment
- Immunosuppressive therapy or cytotoxic chemotherapy within 60 days prior to enrolment
- Patient has undergone stem cell transplant or gene therapy for the treatment of inherited EB
- Current and/or former malignancy including basal cell carcinomas and squamous cell carcinomas
- Enrolment in any interventional study or treated with any investigational drug for any disease within 4 weeks prior to study entry
- Factors present in the patient and/or his/her legal representative that could interfere with study compliance such as inability to attend scheduled study visits or compliance with home dressing changes
- Pregnant or nursing women and women of childbearing potential including postmenarchal female adolescents not willing to use an effective form of birth control with failure rates $< 1\%$ per year (e.g., implant, injectable, combined oral contraceptive, intrauterine contraceptive device, sexual abstinence, vasectomised partner) during participation in the study (and at least 3 months thereafter)
- Patient is a member of the investigational team or his/her immediate family
- Patient lives in the same household as a study participant

12.3.3. Method of randomisation

Subjects were randomised 1:1 to receive either BBE gel or control gel. Randomisation was conducted according to blinded patient number, and the randomisation key was held solely by an independent statistician. [29]

12.3.4. Intervention and comparators

The participants received either BBE (10% birch bark extract in 90% sunflower oil) or control gel (Sunflower oil, Cera flava/yellow wax, and Carnauba wax (matched BBE in terms of texture and visual appearance)) for a double-blind study phase of 90 days and applied each time the wound dressing is changed.

12.3.5. Duration of follow-up, lost to follow-up information

The study had two distinct parts with different durations:

Double-Blind Phase (DBP):

- This was the randomized, placebo-controlled phase where the primary efficacy endpoint was assessed.
- Duration: 90 days (approximately 3 months).
- The primary endpoint focused on target wound closure within 45 days.

Open-Label Phase (OLP):

- This was the single-arm follow-up phase where all patients received BBE.
- Duration: 24 months (2 years).
- The primary rationale for this phase was to obtain long-term safety and efficacy data.

12.3.6. Permitted and disallowed concomitant medication

Permitted Concomitant Medications

The study allowed standard-of-care treatments commonly used in Epidermolysis Bullosa (EB) care, particularly when applied to wounds other than the specifically monitored target wound:

- Liquid Antiseptics: Permitted at each dressing change to clean and/or reduce microbial colonization of all EB wounds, including the target wound, prior to the application of the study gel (Filsuvez or placebo).
- Bathing: Allowed for wound care, such as to aid in dressing changes.
- Standard of Care Wound Dressings: Permitted, specifically non-adhesive wound dressings (e.g., soft silicone or foam).
- Topical Treatments for Non-Target Wounds:
 - Silver sulfadiazine, topical antibiotics, or topical steroids were permitted for the treatment of any EB wound except the target wound or additional wounds matching the target wound criteria (i.e., newly developed partial-thickness wounds of a certain size).

Disallowed Concomitant Medications (Exclusions)

The following medications were generally excluded from the trial, particularly for application directly to the target wound, as they could confound the primary efficacy outcome (wound healing):

- Concomitant Topical Products with Study Gel:
 - Other topical products (other than Filsuvez/placebo gel and permitted liquid antiseptics) were not to be used concomitantly on the target wound or other wounds matching the target wound criteria. The gel should be used alone on the treatment area.
- Systemic Drugs near Enrollment:

- Systemic antibiotics for wound-related infections within 7 days prior to enrollment.
 - Systemic or topical steroids (except for inhaled, ophthalmic, or specific local applications like budesonide suspension for esophageal strictures) within 30 days before enrollment.
 - Immunosuppressive therapy or cytotoxic chemotherapy within 60 days prior to enrollment.
- Other EB-Specific Therapies:
 - Stem cell transplant or gene therapy for inherited EB prior to enrollment. (This specifically refers to newer therapies like Vyjuvek, which were not yet approved or widely used when the trial began, but represent a class of treatment that would be exclusionary.)

12.3.7. Primary outcomes (including scoring methods and timings of assessments)

Proportion of subjects with first complete closure of the EB target wound (defined as EB partial-thickness wound of 10 cm² to 50 cm² in size and ≥ 21 days to < 9 months in age) in subjects with inherited EB (subtypes DEB, JEB, or Kindler EB) within 45 days of treatment with BBE compared to control gel based on clinical assessment by the investigator (the wound was rated as "closed" at first appearance of complete re-epithelialization without drainage).

12.3.8. Other outcomes

- Time to First Complete Closure of the EB Target Wound as Evidenced by Clinical Assessment Until Day 90 (D90) or End of Double-blind Phase (EDBP)
- Proportion of Patients With First Complete Closure of the EB Target Wound at D90 or EDBP Based on Clinical Assessment by the Investigator Until D90 or EDBP
- The Incidence of EB Target Wound Infection Between Baseline (DBP D0) and D90 or EDBP as Evidenced by Adverse Events (AEs) and/or Use of Topical and/or Systemic Antibiotics (Related to Wound Infection)
- The Maximum Severity of EB Target Wound Infection Between Baseline (DBP D0) and D90 or EDBP as Evidenced by AEs
- Change From Baseline (DBP D0) in Total Body Wound Burden as Evidenced by Clinical Assessment Using Section I (Assessment of the Skin Except for the Anogenital Region) of the 'EB Disease Activity and Scarring Index' (EBDASI), at D90 or EDBP
- Change From Baseline (DBP D0) in Itching Using the 'Itch Man Scale' in Patients ≥ 4 Years and up to 13 Years of Age Before Wound Dressing Changes at D90 or EDBP

- Change From Baseline (DBP D0) in Itching Using the 'Leuven Itch Scale' in Patients ≥ 14 Years of Age Before Wound Dressing Changes at D90 or End of Double Blind Phase (EDBP)

Appendix B: General background and mechanism of action of B-VEC

Resource	Description
SmPC[22]	• <i>B-VEC is a gene therapy based on an engineered, replication-defective herpes simplex virus 1 (HSV-1) encoded with COL7A1 gene, addressing the underlying genetic cause of dystrophic epidermolysis bullosa.</i> • <i>Upon cutaneous application to the wounds, beremagene geperpavec can transduce both keratinocytes and fibroblasts. Once in the nucleus, transcription of the encoded human COL7A1 is initiated. The resulting transcripts allow for production and secretion of COL7 by the cell in its mature form. These COL7 molecules arrange themselves into long, thin bundles that form anchoring fibrils. The anchoring fibrils hold the epidermis and dermis together and are essential for maintaining the integrity of the skin.</i> • <i>DEB is caused by mutations in the COL7A1 gene, which results in reduced or absent levels of biologically active COL7. Upon cutaneous application to the wounds, B-VEC can transduce both keratinocytes and fibroblasts. Following entry of B-VEC into the cells, the vector genome is deposited in the nucleus. Once in the nucleus, transcription of the encoded human COL7A1 is initiated. The resulting transcripts allow for production and secretion of COL7 by the cell in its mature form. These COL7 molecules arrange themselves into long, thin bundles that form anchoring fibrils. The anchoring fibrils hold the epidermis and dermis together and are essential for maintaining the integrity of the skin.</i>

Reference list

1. Has, C., et al., *Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility*. Br J Dermatol, 2020. **183**(4): p. 614–627.
2. Petrof, G., et al., *The epidemiology of epidermolysis bullosa in England and Wales: data from the national epidermolysis bullosa database*. British Journal of Dermatology, 2022. **186**(5): p. 843–848.
3. Denyer, J., E. Pillay, and J. Clapham, *Best practice guidelines for skin and wound care in epidermolysis bullosa. An International Consensus*. 2017.
4. Fine, J.D., *Inherited epidermolysis bullosa*. Orphanet J Rare Dis, 2010. **5**: p. 12.
5. Tang, J.Y., et al., *A systematic literature review of the disease burden in patients with recessive dystrophic epidermolysis bullosa*. Orphanet J Rare Dis, 2021. **16**(1): p. 175.
6. Cianfarani, F., et al., *Pathomechanisms of altered wound healing in recessive dystrophic epidermolysis bullosa*. Am J Pathol, 2017. **187**(7): p. 1445–1453.
7. Mellerio, J.E., *Infection and colonization in epidermolysis bullosa*. Dermatol Clin, 2010. **28**(2): p. 267–9.
8. Mellerio, J.E., et al., *Management of cutaneous squamous cell carcinoma in patients with epidermolysis bullosa: best clinical practice guidelines*. Br J Dermatol, 2016. **174**(1): p. 56–67.
9. Nystrom, A., L. Bruckner-Tuderman, and D. Kiritsi, *Dystrophic epidermolysis bullosa: secondary disease mechanisms and disease modifiers*. Front Genet, 2021. **12**: p. 737272.
10. Angelis, A., et al., *Social/economic costs and health-related quality of life in patients with epidermolysis bullosa in Europe*. Eur J Health Econ, 2016. **17**(Suppl 1): p. 31–42.
11. Bruckner, A.L., et al., *The challenges of living with and managing epidermolysis bullosa: insights from patients and caregivers*. Orphanet J Rare Dis, 2020. **15**(1): p. 1.
12. Fulchand, S., et al., *Patient-reported outcomes and quality of life in dominant dystrophic epidermolysis bullosa: A global cross-sectional survey*. Pediatr Dermatol, 2021. **38**(5): p. 1198–1201.
13. Eng, V.A., et al., *Patient-reported outcomes and quality of life in recessive dystrophic epidermolysis bullosa: A global cross-sectional survey*. J Am Acad Dermatol, 2021. **85**(5): p. 1161–1167.
14. National Institute for Health and Care Excellence (NICE), *Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa [ID1505]. Committee papers*. 2023.
15. European Medicines Agency (EMA). *Filsuvez (Oleogel-S10) 0.5g–1.0 g birch bark gel. Summary of Product Characteristics*. 2022 4 July [cited 2022 29 November].
16. European Medicines Agency (EMA). *EPAR Medicine Overview: Filsuvez (birch bark extract)*. 2022 4 July [cited 2022 29 November]; Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/filsuvez>.
17. European Medicines Agency (EMA). *Committee for Medicinal Products for Human Use (CHMP) assessment report: Filsuvez*. 2022 4 April [cited 2022 4 December]; Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/filsuvez>.

18. Medicines and Healthcare products Regulatory Agency (MHRA). *Filsuvez Gel Summary of Product Characteristics*. 2022 18 August [cited 2023 3 April]; Available from: <https://www.medicines.org.uk/emc/product/13971/smpc/print>.
19. Guide, S.V., et al., *Trial of beremagene geperpavec (B-VEC) for dystrophic epidermolysis bullosa*. N Engl J Med, 2022. **387**(24): p. 2211–2219.
20. Gurevich, I., et al., *In vivo topical gene therapy for recessive dystrophic epidermolysis bullosa: a phase 1 and 2 trial*. Nat Med, 2022. **28**(4): p. 780–788.
21. University of Sheffield. *Technical support document 26: Expert elicitation for long-term survival outcomes*. 2025 [cited 2025 18 June]; Available from: <https://www.sheffield.ac.uk/nice-dsu/tsds/expert-elicitation-tsd>.
22. Krystal Biotech, *Summary of product characteristics: Vyjuvek (beremagene geperpavec)*. 2023, Krystal Biotech Netherlands, B.V.: Amsterdam, Netherlands.
23. Krystal Biotech Inc., *GEM-3 Clinical Study Report. A Phase 3 Efficacy and Safety Study of Beremagene Geperpavec (B-VEC, Previously KB103) for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)*. 2022. p. 1–84.
24. Reimer, A., et al., *Natural history of growth and anaemia in children with epidermolysis bullosa: a retrospective cohort study*. Br J Dermatol, 2020. **182**(6): p. 1437–1448.
25. Du Bois, D. and E.F. Du Bois, *A formula to estimate the approximate surface area if height and weight be known*. 1916. Nutrition, 1989. **5**(5): p. 303–11; discussion 312–3.
26. National Center for Health Statistics. *Downloadable Charts - growthcharts*. 2024; Available from: <https://www.cdc.gov/growthcharts/who-charts.html>.
27. Mauritz, P., et al., *Impact of painful wound care in epidermolysis bullosa during childhood: an interview study with adult patients and parents*. Acta Derm Venereol, 2019. **99**(9): p. 783–788.
28. Kern, J.S., et al., *Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: results from the phase III randomized double-blind phase of the EASE study*. British Journal of Dermatology, 2022. **188**(1): p. 12–21.
29. Kern, J.S., et al., *Oleogel-S10 Phase 3 study "EASE" for epidermolysis bullosa: study design and rationale*. Trials, 2019. **20**(1): p. 350.
30. Krystal Biotech Inc., *GEM-3, data on file*. 2023.
31. Krystal Biotech Inc., *GEM-3 OLE, data on file*. 2023.
32. Krystal Biotech Inc., *GEM-1/2, data on file*. 2023.
33. Agence Nationale de Sécurité du Médicament (ANSM), *Résumé de rapport de synthèse. Autorisation d'accès compassionnel [Vyjuvek – beremagene geperpavec (B-VEC)]*. 2025.
34. Davidovic, M., S. Gewert, and C. Has, *Real - World Experience With Oleogel - S10 for Wounds in Epidermolysis Bullosa*. JEADV Clinical Practice, 2025.
35. Fulchand, S., et al., *Natural history study of recessive dystrophic epidermolysis bullosa wounds and patient reported outcomes using mobile application home photography*. Scientific Reports, 2025. **15**(1): p. 28767.
36. Karakioulaki, M., K. Eyerich, and C. Has, *Beremagene geperpavec (B-VEC) for infantile dystrophic epidermolysis bullosa: Benefit of early intervention*. J Eur Acad Dermatol Venereol, 2025.
37. Krystal Biotech Inc., *GEM-3 + GEM-3 OLE*. 2024.
38. Krystal Biotech Inc., *GEM-1 Clinical Study Report: A Phase 1/2 Study of B-VEC, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human*

- Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)*. 2022.
39. Solis, D.C., et al., *Classification of 2 distinct wound types in recessive dystrophic epidermolysis bullosa: A retrospective and cohort natural history study*. J Am Acad Dermatol, 2021. **85**(5): p. 1296–1298.
 40. Krystal Biotech Inc., *OLE Clinical Study Report: Open label treatment of beremagene geperpavec (B-VEC)*. B-VEC-EX-02. 2023.
 41. Kern, J.S., et al., *Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: results from the phase III randomized double-blind phase of the EASE study*. Br J Dermatol, 2022. **188**(1): p. 12–21.
 42. Hon, K.L., et al., *Age and etiology of childhood epidermolysis bullosa mortality*. J Dermatolog Treat, 2015. **26**(2): p. 178–82.
 43. Brena, M., S. Guez, and L. Lospalluti, *Topical gene therapy for severe recessive dystrophic epidermolysis bullosa: clinical outcomes and multidisciplinary management in three patients treated with beremagene geperpavec (B-VEC) in Italy*. Submitted to Journal of Dermatological Treatment, 2025.
 44. Devries, D.T., et al., *Relative extent of skin involvement in inherited epidermolysis bullosa (EB): composite regional anatomic diagrams based on the findings of the National EB Registry, 1986 to 2002*. J Am Acad Dermatol, 2004. **50**(4): p. 572–81.

Single Technology Appraisal

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

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 available 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.

Clinical expert statement

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

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 as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [NICE health technology evaluations: the manual](#) (section 5.4) 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 Thursday 4 December 2025**. 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.

Clinical expert statement

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

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.

Clinical expert statement

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

Part 1: Treating skin wounds associated with dystrophic 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	Dr Anna Martinez and Prof Jemima Mellerio
2. Name of organisation	Great Ormond Street Hospital NHS FT and Guy's and St Thomas' NHS FT
3. Job title or position	Consultant dermatologists
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 skin wounds associated with dystrophic epidermolysis bullosa? ☐ A specialist in the clinical evidence base for skin wounds associated with dystrophic 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.	None

Clinical expert statement

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

8. What is the main aim of treatment for skin wounds associated with dystrophic epidermolysis bullosa? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To speed up wound healing and reduce the time to reopening of those wounds. Also to decrease downstream consequences of wounds such as infections and inflammation which lead to long term sequelae eg anaemia, osteoporosis and skin cancer.
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)	Under 10 year olds: to try and have sustained healing of non-chronic, recurring wounds Over 10 years old: to heal acute and chronic wounds and prevent recurrence
10. In your view, is there an unmet need for patients and healthcare professionals in skin wounds associated with dystrophic epidermolysis bullosa?	Undoubtedly. This is one of the top major challenges in EB care as wounds contribute to symptoms such as itch and pain, reduced quality of life and downstream consequences of systemic inflammation. Current standard of care is limited to dressings, infection prevention and symptom control, and Filsuvez (the only approved treatment for EB) which, although speeding healing in some patients (only around 50% report benefit), and does not reduce wound recurrence.
11. How are skin wounds associated with dystrophic epidermolysis bullosa currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • 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.) • What impact would the technology have on the current pathway of care?	Currently treated with a variety of specialised dressings, antimicrobials and antibiotics, and Filsuvez. Skin care guidelines are available at: https://www.debra-international.org/skin-and-wound-care-in-eb-cpg In general, there is consensus across the UK, however, patient and carer preference has a large influence on specific skin care measures. The technology would have a major impact on current care; it would have a greater impact on healing and on sustained wound closure over time. It would likely be disease-modifying over time by reducing wound burden and secondary consequences.

Clinical expert statement

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

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? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The technology would need to have a pathway to implement treatment ie it would need to be made up and delivered for patient use, ideally at home, on a weekly basis for application during dressing changes. Initial training of carers/patients would be carried out in the respective reference EB centre before moving treatment into the home setting. A pathway for achieving this has already been discussed and agreed between the 4 English UK EB centres involving clinicians and pharmacists, and this plan has been shared with NHSE. The preferred model would involve a centralised (off-EB centre site) aseptic pharmacy and homecare delivery to patients' homes.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • 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?	Yes. The reduction in wound burden and disease severity, especially over years/a lifetime, would be expected to have very significant patient benefit. For example, starting treatment early in life and reducing the numbers of chronic wounds, the sites which develop aggressive skin cancers later in life, could have a really significant impact on increasing life expectancy for the most severely affected patients. Undoubtedly, HRQOL would improve with this technology: reduced wound burden means less pain, less itch, less time spent doing dressing changes, fewer associated morbidities and increased survival.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology is specifically for individuals with recessive or dominant dystrophic EB. It is likely to be of greatest benefit for those with the most severe form (severe RDEB) but all those with DEB could potentially derive great benefit.
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?	EB patients/carers are experts at wound care, usually spending many hours per week on changing dressings and applying topical treatments. It is not expected to be any different from current care following adequate training from the staff at the specialist EB centres, who are very willing and able to do this. No monitoring or additional care is needed above standard of care.

Clinical expert statement

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

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The clinical teams will assess individuals according to disease severity before offering treatment for both DDEB and RDEB. Discontinuation would be decided according to lack of efficacy, side effects or safety concerns.
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	We consider that benefits of treatment would result in considerable patient benefit likely to be captured by calculations of QALYs. However, reductions in time spent doing dressing changes and the number of dressings required is unlikely to be reflected in this calculation.
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?	This technology is a potential game-changer for individuals with DEB; it is the first time that gene replacement therapy leading to meaningful clinical benefits (with a good safety profile) has been available. There are many unmet needs in the management of EB eg pain, itch, wound healing and sustained wound closure as well as a raft of extracutaneous issues. This technology is the only approach to date to address these through improved healing of wounds.
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?	The treatment appears to be well-tolerated. There is a potential for the development of anti-type VII collagen antibodies but, to date, there is no evidence that these, if they do occur, are pathogenic ie there is no evidence for any clinical side effects from these.

Clinical expert statement

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

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?	The patients in the clinical trials are akin to those in the UK with a similar standard of care prior to the clinical trial. To our knowledge, there have not been any AEs that have come to light subsequently.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE highly specialised technologies guidance [HST28]?	No
23. How do data on real-world experience compare with the trial data?	No published data but anecdotal evidence from overseas colleagues with real world experience are encouraging.
24. NICE considers whether there are any equality 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	There are no equality issues with all 4 English NHSE EB centres treating populations with diverse characteristics equitably.

Clinical expert statement

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

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.](#)

Clinical expert statement

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

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

Limited data available on clinical effectiveness of B-VEC in patients with dominant DEB (section 2.3.1 of EAR)	
An ITC between B-VEC and BBE based on a comparison of trial outcomes from the GEM-3 and EASE studies has not been provided	

Clinical expert statement

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

(sections 3.9 and 3.10 of EAR)	
Utility values are based on a vignette study despite there being EQ-5D estimates available (section 4.3.3.2 of EAR)	
Validity of the company's patient level simulation as a source of effectiveness estimates (section 4.3.3.5 of EAR)	
Estimation of vial usage from the patient level simulation (section 4.3.3.5 of EAR)	
The company's preferred four-state model structure is dependent on a mapping algorithm which the EAG considers lacks face validity	

Clinical expert statement

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

(section 4.3.3.6 of EAR)	
The plausibility of reduced clinical manifestations and mortality in patients with reduced wound burden (section 4.3.3.8 of EAR)	
Patients discontinuing treatment are assumed to stay in the state they occupy when discontinuing (section 4.3.3.12 of EAR)	
Uncertainty regarding the feasibility of vial sharing (section 4.3.3.10 of EAR)	
Are there any important issues that have been missed in EAR?	

Clinical expert statement

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

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

B-VEC is a different technology to BBE and differs by having a longer maintenance of wound healing after use

From trial data and real world use to date, B-VEC appears to significantly improve wound healing and patients symptoms eg pain and itch

B-VEC appears to be very safe and well-tolerated

With ongoing use, B-VEC should improve morbidity and mortality in patients with RDEB

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](#).

Clinical expert statement

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

Single Technology Appraisal

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

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (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 you about living with skin wounds associated with dystrophic epidermolysis bullosa or caring for a patient with skin wounds associated with dystrophic epidermolysis bullosa. 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.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

Patient expert statement

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In [part 3](#) 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 appraisal 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.

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.

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.

Your response should not be longer than 15 pages.

Patient expert statement

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 Thursday 4 December 2025**. 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: Living with this condition or caring for a patient with skin wounds associated with dystrophic epidermolysis bullosa

Table 1 About you, skin wounds associated with dystrophic epidermolysis bullosa, current treatments and equality

1. Your name	Claire Mather and [REDACTED]
2. Are you (please tick all that apply)	☐ A patient with skin wounds associated with dystrophic epidermolysis bullosa? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with skin wounds associated with dystrophic 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

	☒ 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 skin wounds associated with dystrophic epidermolysis bullosa? If you are a carer (for someone with skin wounds associated with dystrophic epidermolysis bullosa) please share your experience of caring for them	People living with EB, from birth, live in constant and debilitating pain, and in severe cases it can be fatal. Our member ■ has submitted her testimony to explain what it is like for her to live with EB. <u>"I have suffered with Dystrophic Epidermolysis Bullosa (Recessive) for ■ 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."</u> 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 ■ describes that <u>"It's painful. I have</u>

Patient expert statement

sores on my hands and legs most days. It stings when I have a bath. Its itchy, my skin blister if I itch”.

■, one of our members, is ■ 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.”

On a typical day for EB patients...

- 81% of patients spend time on blister / wound care, taking one hour on average
- 85% spend time on personal hygiene e.g. taking an average 1.2 hours
- 67% spend time on resting / recovery, for an average 4.1 hours
- Severe patients spend more time on blister / wound care, personal hygiene, food preparation, getting dressed and resting daily

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 ■ 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, ■, whose daughter lives with Dystrophic EB says “It is heartbreaking to see her in pain, bottling up her worries so she doesn’t impact

Patient expert statement

	<u>others and doing her best to live her life just as her peers do. Yet often missing out.”</u> Parent/carer perspective <u>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.”</u> Carer health-related quality of life The results of the 2023 DEBRA Insights Study concluded: a total of 78% of carers in the study lived with the person with EB. Carers reported moderate to high impacts on various aspects of their lives, with 61% stating it affected their ability to enjoy life, and 59% citing a mental health impact. Additionally, 61% tried to hide the emotional toll of caregiving. 13% strongly agreed they struggled to access mental health support, and 75% felt carers need more emotional support than is currently available. Costs to the family and society

Patient expert statement

	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. ■■■ worries for her younger daughter who doesn't have EB <u>"Our younger daughter often has to take second place because of the time and support her sister needs. And that is not fair."</u> 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 ■■■ describes <u>"EB impacts our home life; our furniture, our bathroom, clothes we buy, holidays we go on, places we visit – it's endless"</u>. 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, <u>"Understanding the socioeconomic costs of dystrophic epidermolysis bullosa in Europe: a costing and health-related quality of life study,"</u> was published in the <u>Orphanet Journal of Rare Diseases</u>, and shows that on average, the direct nonmedical costs, which include caregiver services, were roughly five times as high

Patient expert statement

	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.
7a. What do you think of the current treatments and care available for skin wounds associated with dystrophic 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?	7a: In August 2023, birch bark extract (Filsuvez® gel) became the first treatment specifically licensed for the treatment of partial-thickness wounds associated with dystrophic epidermolysis bullosa (DEB) and junctional epidermolysis bullosa (JEB) in patients 6 months and older in the UK. NICE recommended Filsuvez through its Highly Specialised Technology evaluation although this comes with a limitation: the number of patients who can be treated with the gel is capped and the controlled access due to its specialised nature. A 2022 study by Petrof et al. reported an EB prevalence of 34.8 per million and 10.7 per million for DEB, suggesting approximately 730 DEB patients in the UK (census 2021). Most are likely not treated with Filsuvez due to strict inclusion criteria and lack of alternative treatment options. To date, there are no publications on the Filsuvez prescribing pattern, so we are unable to provide any data. Ref: Petrof et al., <i>The epidemiology of epidermolysis bullosa in England and Wales: data from the national epidermolysis bullosa database. British Journal of Dermatology</i> (2022) 186, pp843–848 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. There is only one approved drug for EB, but no treatments specifically designed to significantly reduce pain, wound care, or scarring. █ simply says, “<u>I don’t have any treatment.</u>” And another member describes how the treatment available is only wound care. “The daily removal of whole-body

Patient expert statement

	<u>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”.</u> What is more, the care of severe wounds inflicts further pain and distress, as our member describes <u>“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”.</u> Our member fears that this care is likely to become more difficult as pressures on the NHS are exacerbated <u>“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”.</u> 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. The DEBRA Insight study confirmed this, showing only 3% of GPs and 18% of dermatologists had good knowledge of EB. Among GPs, 58% had seen at least one EB patient in the past 5 years, with 52% from suburban practices, 40% from urban, and 8% from rural areas. Dermatologists included 88% consultants and 12% specialist registrars, with 74% working in University Teaching Hospitals and 26% in non-University Teaching Hospitals. None worked at an EB specialist centre, though 82% had seen at least one EB patient in the past 5 years. This limited awareness among healthcare professionals worsens the challenges EB patients and carers face, often requiring them to repeatedly explain the condition and their needs.

Patient expert statement

	Ref: https://www.debra.org.uk/get-involved/members-participation/eb-insights-study/ 7b: As a patient group organisation, following 2023 DEBRA Insights study and other patient/member engagement we believe 7A summarises views from the wider EB population.
8. If there are disadvantages for patients of current NHS treatments for skin wounds associated with dystrophic epidermolysis bullosa (for example, how they are given or taken, side effects of treatment, and any others) please describe these	There is a significant unmet need – In August 2023, NICE approved birch bark extract (Filsuvez® gel) as the first treatment for EB, though its use is limited due to its specialised nature and patients reporting mixed response to treatment. Given its recent approval, it is unknown how many patients have been prescribed it. Additionally, there are no NICE guidance or advice or quality standards products for EB. There is currently no choice of treatment. ████ says “<u>We don’t have treatments. We do have awesome caring medical professionals who help with management of the condition. But that is all.</u>” She goes on to say that the most disappointing element of what is currently available to them is “<u>that nothing helps makes it better. It’s about minimising the damage not improving things.</u>” 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.

Patient expert statement

	Our member worries that her <u>“son has wounds which have not healed in over three years, and we fear the development of squamous cell carcinoma”</u>.
9a. If there are advantages of beremagene geperpavec 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 beremagene geperpavec 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	9a: To our knowledge, there have been no clinical trials or compassionate use of B-Vec in the UK, so we are unaware of any UK patients with experience using it. <u>However, we are aware of a mother in France whose daughter with Recessive DEB and has been prescribed it. Her experiences are as follows:</u> • <u>The application of B-Vec to the wound site is straightforward and painless.</u> • <u>A wound closed after 6 months of first treatment application.</u> • <u>Both mother and daughter have more energy.</u> • <u>Initially, weekly trips to a national EB centre for 4 months required 8 hours of travel for each appointment, but this has now changed as B-Vec is prescribed locally, reducing travel time to 45 minutes.</u> • <u>The treatment should be brought to patients, rather than requiring patients to travel to it.</u> • <u>The application is simple and could be delegated to the family, rather than relying on healthcare professionals.</u> 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 <u>“quicker healing wounds” and “reduction in healing times for wounds, and potential reduction in pain levels”</u> due to <u>“reducing the pain of dressing changes” and “improved ability to undertake activities of daily living”</u>. They hope that there may be <u>“fewer areas with wounds”</u>.

Patient expert statement

	Given the lack of patient choice this additional treatment would provide patients with an alternative therapy if Filzuvez does not work on targeted wound.
10. If there are disadvantages of beremagene geperpavec over current treatments on the NHS please describe these. For example, are there any risks with beremagene geperpavec? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Depending on where parents/carers and patients live in England, the disadvantage of travel cost and time to EB centres on a weekly basis for each appointment before home delivery and/or local prescription system is implemented. There are no comparator treatments. There have been no UK clinical trials of B-Vec in the UK.
11. Are there any groups of patients who might benefit more from beremagene geperpavec 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	Unsure as we are not clinical professionals
12. Are there any potential equality issues that should be taken into account when considering skin wounds associated with dystrophic epidermolysis bullosa and beremagene geperpavec? 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	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. With B-Vec, the travel costs and time required for weekly appointments may create further inequality, limiting access to treatment for those who live far from the centres or lack the financial means to travel

Patient expert statement

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?	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”.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in [table 2](#). We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient 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, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Limited data available on clinical effectiveness of B-VEC in patients with dominant DEB (section 2.3.1 of EAR)	NB: We are not clinical trial experts and are therefore unable to provide a meaningful response
An ITC between B-VEC and BBE based on a comparison of trial outcomes from the GEM-3 and EASE studies has not been provided	NB: We are not clinical trial experts and are therefore unable to provide a meaningful response

Patient expert statement

(sections 3.9 and 3.10 of EAR)	
Utility values are based on a vignette study despite there being EQ-5D estimates available (section 4.3.3.2 of EAR) We consider patient perspectives may particularly help to address this issue Do utility estimates from the vignette study or EQ-5D data better reflect the health-related quality of life of people with skin wounds associated with dystrophic epidermolysis bullosa, and their carers?	NB: We are not health economics experts and are therefore unable to provide a meaningful response
Validity of the company's patient level simulation as a source of	NB: We are not clinical trial experts and are therefore unable to provide a meaningful response

Patient expert statement

effectiveness estimates (section 4.3.3.5 of EAR)	
Estimation of vial usage from the patient level simulation (section 4.3.3.5 of EAR)	NB: We are not clinical trial experts and are therefore unable to provide a meaningful response
The company's preferred four-state model structure is dependent on a mapping algorithm which the EAG considers lacks face validity (section 4.3.3.6 of EAR)	NB: We are not clinical trial experts and are therefore unable to provide a meaningful response
The plausibility of reduced clinical manifestations and mortality in patients with reduced wound burden (section 4.3.3.8 of EAR)	NB: We are not clinical trial experts and are therefore unable to provide a meaningful response

Patient expert statement

We consider patient perspectives may particularly help to address this issue Would you expect non-skin related complications associated with dystrophic epidermolysis bullosa to be affected by beremagene geperpavec treatment?	
Patients discontinuing treatment are assumed to stay in the state they occupy when discontinuing (section 4.3.3.12 of EAR) We consider patient perspectives may particularly help to address this issue How would you expect a patient's health to be	NB: We are not clinical trial experts and are therefore unable to provide a meaningful response

Patient expert statement

impacted after discontinuing treatment with beremagene geperpavec or birch bark extract?	
Uncertainty regarding the feasibility of vial sharing (section 4.3.3.10 of EAR)	NB: We are not health economics experts and are therefore unable to provide a meaningful response

Patient expert statement

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- 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 EB is 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 help wound closer 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.

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](#).

Patient expert statement

Single Technology Appraisal

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

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (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 you about living with skin wounds associated with dystrophic epidermolysis bullosa or caring for a patient with skin wounds associated with dystrophic epidermolysis bullosa. 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.

A patient 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.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In [part 3](#) 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 appraisal 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

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

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.

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.

Your response should not be longer than 15 pages.

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 Thursday 4 December 2025**. 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: Living with this condition or caring for a patient with skin wounds associated with dystrophic epidermolysis bullosa

Table 1 About you, skin wounds associated with dystrophic epidermolysis bullosa, current treatments and equality

1. Your name	Sohana Collins
2. Are you (please tick all that apply)	☒ A patient with skin wounds associated with dystrophic epidermolysis bullosa? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with skin wounds associated with dystrophic epidermolysis bullosa? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Cure EB
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

Patient expert statement

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

	☐ 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 ☒ I have other relevant knowledge or experience (for example, I ☐ am drawing on others' experiences). Please specify what other experience: I have read the case studies & questionnaires that Cure EB conducted with patients & carers as part of their original submission as well as more recently. ☐ 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 skin wounds associated with dystrophic epidermolysis bullosa? If you are a carer (for someone with skin wounds associated with dystrophic epidermolysis bullosa) please share your experience of caring for them	I have always been aware of the fact that I was born into a life completely alien compared to those of the people around me. EB causes me to be in pain all the time and impacts absolutely every aspect of my life. The constant caution and stress of avoiding damage to my skin, eyes, mouth and oesophagus does not prevent constant pain. Since birth my days have been defined by dressing changes; exclusion from or extreme monitoring of everyday activities; adjustments to eating,

	travelling, education, socialising and unpredictable appearances of blisters, ruptures and severe wounds akin to third degree burns. I also have to deal with the growing trauma that accumulates through a lifetime of these experiences and the knowledge that all of this continuous damage will most likely lead to an aggressive skin cancer, which is almost always fatal. After I wake up to take five different medications and allow them to set in before doing dressing changes. It's always difficult to find the balance between doing this procedure as thoroughly as possible while still getting through it quickly. They usually take between one and a half hours to two hours unless I have a full bath change (which I do every other day) which takes between three and five hours. EB has a huge effect on my social life, as I always need to eat specially prepared, supplemented and blended food as well as take medication with every meal. At university if I went out I would usually return home to eat lunch and dinner due to these needs and the fact that I often found it awkward and embarrassing to eat in front of people. Eating takes a long time, often leads to coughing and vomiting when something gets stuck, and when my oesophagus is injured can lead to reflux and vomiting blood. I need to live at home with my family and when I was at university I needed to live with a full-time carer to prepare food and medication and help me with dressings and things like getting dressed. Dressing changes involve removing dressings, pricking blisters, clipping dry skin, creaming wounds, and redressing. So I spend around 5-7 hours a day dedicated to a skincare routine that I would genuinely not survive without. This is all very painful and only just keeps my skin under control, but over time, despite all this care and attention, my condition continues to get worse and there's nothing I can do about it. I have always had to be meticulous about my eye care – applying drops and ointments multiple times a day and wearing sunglasses when outside to avoid any damage from wind, as these can lead to corneal abrasions which lead to temporary blindness for several days.

	My day is painful, challenging and often completely unpredictable apart from the knowledge that I must be constantly vigilant and careful of what I eat, when I take my medicine, how I walk, sit, write and talk. Even sleeping can cause trauma to my ears, and I often wake up on a pillow that is covered with blood from those wounds or even stuck to the fabric due to congealed blood. As it is a genetic condition and therefore the only experience I have ever known it is difficult to describe; I can only imagine an improved quality of life.
7a. What do you think of the current treatments and care available for skin wounds associated with dystrophic 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?	7a. There are no currently available treatments that address the root cause of EB, the genetic defect, and therefore everything that is available only attempts to manage the pain and debilitation caused by the condition. These include multiple surgeries, for example oesophageal dilatations and hand releases which address stricture and mitten deformities caused by constant wounding and scarring and provide temporary relief but need to be repeated throughout a patient's lifetime. The frequency of these surgeries depends on the patient, with some having a regular slot for interventional surgery every few weeks. Chronic anaemia is common because of the chronic open wounds and regular iron infusions are a regular part of life for which hospital visits are necessary. Eye drops and ointments are applied multiple times a day to try to minimise the risk of corneal abrasions for which surgery is occasionally needed. For many people with EB, they will require a gastrostomy tube to receive adequate nutrition due to the difficulties with eating and the high nutrient and calorie needs due to chronic open wounds. We all take laxatives to avoid constipation as anal fissures are a constant concern due to limited diet and the need to take opiates regularly for pain relief. The NHS provides a good supply of the relevant dressings, generic creams, eye drops and ointments, laxatives and painkillers. However, these are just symptom management and do nothing to address the genetic cause of EB so do little to improve and stave off the long-term complications of EB.

	7b. I believe we all feel similar levels of exhaustion at having to take so many different medications and undergo countless dressing changes, hospital appointments and surgeries just to maintain life. Most of us accept the necessity of these treatments but are frustrated that none of them are able prevent skin wounds or other injuries such as ruptures throughout the digestive system and corneal erosions. UK DDEB patient and parent to a 13 year old with RDEB: <i>“At the moment my son has lots of wounds and they drain his immune system. They also have a very big drain on his calorie intake and then his system generally managing and growing. He’s a teenager, so he’s trying to grow and go through puberty because of the drain of his wounds he is later to go into puberty and he is struggling with his weight. And also that affects his energy. The pain from his wounds affects his sleep. And the itch from his wounds affects his happiness and his sleep. The pain definitely impacts his quality of life.”</i> UK parent to a 2 year with RDEB: <i>“The current treatment and care available on the NHS for skin wounds associated with dystrophic EB is minimal.”</i> UK parent to a 3 year old with RDEB: <i>“Very limited. I mean, it’s only Filsuvez, right? In terms of dressings, I think it’s great. I’m not aware of any dressing that I wish I had that I didn’t. And in terms of quantities, I think I’ve always got what I need. Some things might be out of stock, but then they’ll send a replacement, which is great. But in terms of creams and ointments and wound care solutions, I find it very limited. And I don’t think Filsuvez, at least on my son, has been an effective wound care. It’s more of a very gentle moisturiser, which on open, wet wounds, I don’t find helpful Perhaps when it’s turned into a scab it’s quite good. But I haven’t seen any increase in wound closure times since using Filsuvez on my son. And it hasn’t made any difference to the time between wounds as well. Like it hasn’t made the skin stronger, or less scar tissue in that area. I don’t find it on my son very effective.”</i>

	UK parent to a 14 year old with RDEB: <i>“The current treatments available do very little to improve the healing or associated symptoms that come with severe wounds. Some creams/ointments can help wounds prevent infection or can add moisture to dry and crusty areas of skin, or even help to dry up wet wounds but nothing supports healing or pain management.”</i>
8. If there are disadvantages for patients of current NHS treatments for skin wounds associated with dystrophic epidermolysis bullosa (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I find that current treatments are laborious, painful, invasive and ineffective. New treatments that attempt to heal open wounds, such as Filsuvez, can make wounds soggy and irritate the surrounding skin, sometimes making the wound even worse than it was before, and do not provide any benefit for some patients. UK parent of a 14 year old with RDEB said <i>“We tried Filsuvez for a couple of months but the results were terrible. We applied it to the most severe wounds. The skin was immediately irritated. The advice was that it takes a number of weeks before we will start to see improvement and possibly things will seem worse before they get better. My daughter tolerated it for about 8 weeks before we had to stop. The skin saw no improvement, in fact it broke down further and was extremely painful. We only saw improvement once we stopped using it.”</i> US parents of a 17 year old RDEB patient: <i>“We don’t use Filsuvez. We tried it, but my daughter had a side effect of the medicine, her skin got very red and itchy, which made us stop using it.”</i> UK parent of a 2 year old with RDEB <i>“Whilst I don’t necessarily see any disadvantages of the current treatment/care available on the NHS I don’t see any advantages either. None of the treatment have a negative impact however no treatment or care is making any improvement for those living with EB and their quality of life. We found Filsuvez no superior to any of the other wound creams/gels that we use. Instead we found that due to its thick Vaseline like consistency it would cause the wounds to become extremely hot and itchy making it incredibly uncomfortable to leave on the skin for more than 8-12 hours. We found that we had to increase the frequency of dressing changes when using Filsuvez as it was too</i>

	<i>unbearable to leave on the skin for the usual 24 hours. This meant more time spent doing extremely painful dressing changes without any improvement in wound healing and/or wound pain."</i> UK parent of a 3 year old with RDEB: <i>"The lack of effective treatment. I think the wound management is quite good. But in terms of actually moving the needle on the disease, there isn't anything available. In terms of wound closure, I find it [Filsuvez] ineffective. I think once the wound has scabbed over and is almost closed, it just keeps it moist, but nothing Vaseline can't do, if I'm honest."</i> UK DDEB patient and parent to a 13 year old with RDEB: <i>"They are just symptom relief related treatments. And so the way that the condition progresses is that we're expecting just to get more and more wounds and for them to become more and more chronic. And the treatments at the moment aren't addressing or preventing that. And so we can see the disease progression will continue in the way that's expected with the treatments as they currently stand. There's nothing that's trying to interrupt that cycle of injury, scarring, injury, scarring, and then wounds becoming more chronic and then leading to cancer."</i> UK parents of 14 year old with RDEB: <i>"Often items prescribed are temporary solutions to help the wounds become more stable. Steroids can help but are not for prolonged use and the skin often returns to its poor state. Polymem is the most effective wound dressing to support healing but it's not a solution, it absorbs moisture from the wound and doesn't soak into the skin and cause further damage. The skin also gets use to these treatments and over time they become less effective. There is no single treatment that helps the skin heal and we have tried everything available."</i>
9a. If there are advantages of beremagene geperpavec 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?	9a. Wound care is a constant necessity for people with EB but we know that even if a wound heals we will receive more wounds just by living our daily lives. Some wounds don't heal at all but patients who have received beremagene geperpavec have experienced the closure of previously chronic wounds as well as strengthened skin for a long time afterwards. This means less pain every day, less time spent on

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?

9c. Does beremagene geperpavec 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

dressing changes, lowered risk of infection and reduced risk of obtaining more blisters or wounds.

There is a letter to the editor in JEADV about an infant using B-VEC for RDEB which is compelling (pdf sent with this submission).

Cure EB asked parents that are using B-VEC (overseas or privately within the UK) about their experiences.

UK parent to a 3 year old with RDEB who has been using B-VEC for just over 2 years privately: *"I mean, it's not a cure. It doesn't cure the disease, but it has been a complete game changer for my son. Before we started using it, he had a chronic wound on his left leg. It was a birth wound. He had no skin from his knee all the way down to his toes on his left leg and it wouldn't close. And then when I started using B-VEC, it closed. So when he was born, it was completely open, completely raw. And until we started using B-VEC nine months later, I mean, it might shrink and then re-blister and grow, but it was chronic. It was not healing. And it was incredibly red and inflamed. And since started using B-VEC, it will close. It won't stay closed which I think some people think about B-VEC. It won't keep wounds closed forever. It will close for maybe a couple of days, if we're lucky a week or two, but then it will break down, but never the full entire birth wound that he was born with. It will break down in parts. But then I find with B-VEC applied to it, it would heal. I mean, it's a long time since I've been using it, so I can't compare a three year old who's using it now to a three year old who's not using it now. But when I compare him now to when he was nine months old, it heals a lot quicker. And the skin is less red and inflamed. The whole thing just feels a lot calmer and less aggressive and more manageable. And he's walking, which I think, I mean we do a lot of physio and a lot of care, and we're very on it with his care, but I do attribute a lot of his being able to walk to B-VEC. When he was born until about nine months old, we had to use morphine because dressing changes were so painful. And we haven't had to use morphine in a really long time because generally how his skin is much more manageable and much less red and sore. we don't have to use such strong pain*

	<i>relief. And I think that's a huge impact as well, kind of secondary positive of using B-VEC."</i> US parent of a 17 year old with RDEB who has been using B-VEC for around 3 years: <i>"B-VEC works quite well in new wounds and it takes time in more chronic wounds. With that said, it does close up wounds that would normally not heal. We have closed wounds that were greater than 150 sq/cms that had been open for over a year."</i> Those that have not used it believe that it will have significant advantages over current treatments. UK DDEB patient and parent to a 13 year old with RDEB <i>"Lack of collagen/collagen that does not function properly causes the skin of people with EB to be fragile - to split, shear and blister with a slight knock, rub or pressure. As BVEC is a gene therapy treatment it aims to treat the genetic cause of EB, in order to help the body to produce functioning collagen. For the areas treated this will make the skin stronger, and more able to withstand friction, thus avoiding blisters and the skin shearing and splitting. This would be an amazing advantage; avoiding the pain of injuries, requiring less medication for pain and infection. Less scarring means less contractures of the skin; less occupational therapy, physiotherapy and plastic surgery to manage contractures. This would also reduce the toll that constant injuries and fighting infection has on our EB bodies. It would also reduce generalised inflammation in our bodies, and all of the negative effects this has on our current and long term health. It would mean shorter dressing changes and less dressings required - for some no dressings would be needed. This would reduce the cost of medical supplies, costs of prescriptions and paid carers. It would also allow family members who care for those with EB to spend less time carrying out wound care and dressing changes- allowing them more time to work, or allowing families to spend more time together, which would improve the quality of life for the person with EB who now has more free time, less pain and more energy, and also the family members who care for them for fewer hours, and the siblings who would</i>

	<i>gain more time with their parents who are spending less time each day on dressing changes and wound care.</i> <i>The quality of life improvements for the person with EB would be enormous- less pain, more free time, more independence and able to do more and participate in more activities including their own self care as there is less risk of injury. Less itch and discomfort, better sleep (sleep is currently disrupted by pain, itch and discomfort). It would also allow people with EB to consider plans for the future that they had never thought possible- the ability to travel as they have fewer medical needs, careers and occupations they otherwise would not be able to consider. Reduced social isolation as they are able to participate in more activities with their friends and peers."</i> <i>UK parent of a 2 year old with RDEB: "The advantages of B-VEC are endless for the patient and their caregivers. Firstly there is immediate effect of using B-VEC which is significantly improving wound healing and allowing those wounds to remain closed. This will significantly decrease the amount of pain experienced all day every day, reducing the need for strong opioids and other pain killers. The decrease in pain and need for pain relief will significantly improve quality of life. It will allow those living with EB to attend school/work and be more present as they are not exhausted from the fatigue associated with chronic inflammation and wound healing along with the sedative side effects of using opioids. B-VEC will allow for shorter dressing changes each day as less areas of skin will be wounded. Dressing changes for those living with EB can take anywhere from 3-5 hours to complete every single day. Meaning there is little to no opportunity to work; children have to miss out on socialising with friends as there's simply not enough time in the day between dressing changes and school. B-VEC therefore will also reduce the burden on care givers due dressings changes either being quicker or less frequent."</i>

	9b. I think that the long term effect of beremagene geperpavec is the biggest advantage as there are no other treatments that even approach achieving anything similar. UK DDEB patient and parent to a 13 year old with RDEB: <i>“More robust skin would mean fewer injuries to the skin. The risk of aggressive Squamous Cell Carcinoma for people with Dystrophic EB is very high and feels almost like a certainty hanging over the heads of people with EB and their loved ones. If there are fewer chronic wounds, fewer injuries to the skin, skin that heals more quickly as the body is better able to heal as there are fewer open areas, I would anticipate this greatly reducing the risk of cancer. At worst it would delay the onset of cancer, and allow for more years of happy, healthy living.”</i> UK parent to a 14 year old with RDEB: <i>“The closure of chronic wounds as hopefully this will result in reduced pain. Our daughter is plagued with constant pain and it controls hers and our families daily lives. It is debilitating in every way possible. When her pain is at its worse it is completely paralysing.”</i> UK parent to a 2 year old with RDEB <i>“By prolonging the healing of wounds it has the ability to minimise the chronic scarring associated with Dystrophic EB in turn this will improve independence for patients living with EB as it will reduce contractures in hands, fingers and other joints allow them to remain mobile.</i> <i>As B-VEC enables wound closure by delivering genes directly into the missing cells it reduces the risk of severe infections which is the leading cause of death in children with Dystrophic Epidermolysis Bullosa. Alongside sepsis, Squamous Cell Carcinoma is responsible for a large majority of deaths in EB due to the presence of chronic wounds and repetitive skin breakdown. Because B-VEC supports wound closure by directly delivering the missing gene into the wounds it had the ability to significantly reduce these risks. B-VEC also has the ability to reduce the inflammation in the body. Chronic inflammation often leads to anaemia which comes with a wide range of symptoms however with B-VEC’s ability to promote wound healing significantly reduces this risk. With the significant increase in wound</i>

	<i>closure, B-VEC has the ability to reduce pain, which reduces the need for opioids on a regular basis. Long term opioid use carries significant risks alongside the day to day side effects of using opioids which includes symptoms such as sedation, nausea and constipation these side effects significantly reduces the quality of life for those living with EB yet there is no treatment on the market in the UK that is targeting wound healing with gene therapy which in turn will reduce pain."</i> UK parent to a 3 year old with RDEB who has private access to B-VEC: <i>"A new wound, because for example he's done something at school, is so much easier to manage with B-VEC than without B-VEC. And that will heal and stay closed."</i> 9c. Beremagene geperpavec addresses the genetic defect that causes DEB and therefore has long term healing effects while all other treatments are palliative. Parents with current access to B-VEC: UK parent to a 3 year old with RDEB who has been using B-VEC for just over 2 years privately: <i>"I think there's nothing else available in the UK on the NHS that comes close to not only managing the disease but improving the quality of life of the patient and having any long-term impact. It's not long-term forever, but it's longer-term than anything else on the NHS. I think it's the best medicine available."</i> French parent to an 11 year old with RDEB: <i>"B-VEC is the only available treatment we have tried that tackles the cause of the disease."</i> US parent to a 17 year old with RDEB: <i>"Yes there are very significant advantages of B-Vec over other currently available treatments and especially over just standard of care."</i> Italian parent of RDEB teenager: <i>"The main difference lies in effectiveness: B-Vec has shown a clear and significant improvement in wound healing, whereas Filsuvez did not prove to be particularly effective in our case. In terms of ease of use, Filsuvez is simpler to apply since it is a topical cream that can be used at home,</i>

	<i>while B-Vec requires weekly administration in a hospital setting by a healthcare professional. Overall, B-Vec has had a much greater impact on symptom improvement and wound closure, making it the more beneficial treatment despite being less convenient to administer.”</i> Parents with no access to B-VEC: UK DDEB patient and parent to a 13 year old with RDEB: <i>“BVEC would help the skin to produce the collagen that it currently lacks. This would make the skin more robust and able to manage friction without splitting or blistering as it currently does. The other treatments currently available only manage the injuries that have been caused by having weaker skin. BVEC would help the skin to be more robust; to produce its own working collagen. This would prevent the injuries from occurring in the first place. Fewer injuries would mean less pain, less dressing changes, less scarring, less inflammation for the body, less infections to fight off. Less medical intervention and dressings required. The body will then be more able to grow and respond to other'normal' illnesses, puberty etc.”</i> UK parent to a 2 year old with RDEB: <i>“I consider the reduction in time it takes to do dressings changes to be the most important advantage of B-VEC as I feel it will significantly increase the quality of life with those living with EB as it will allow more time for self care such as socialising and hobbies which will also have a significant improvement on the mental health of those living with EB.”</i> UK parent to a 14 year old with RDEB: <i>“We feel extremely positive that B-VEC could make a considerable improvement to our daughter’s skin. To have have a treatment that could support the healing of her most chronic wounds would be life changing. She lives in constant pain from these wounds and even the smallest difference would improve her quality of life. Being able to do more socially, physically have more energy instead of being drained by the constant pain, sleep better, improve attendance at school, improve attention as the pain is so distracting,</i>

	<i>reduce itch, the list is endless! We also think time could even be saved on dressing changes which would impact her daily life greatly in a positive way as hours of the day are spent on dressings."</i>
10. If there are disadvantages of beremagene geperpavec over current treatments on the NHS please describe these. For example, are there any risks with beremagene geperpavec? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I have no personal experience of beremagene geperpavec but don't know of any disadvantages. Parents that had access to B-VEC for their children reported no disadvantages or side effects. UK parent to a 3 year old with RDEB who has been using B-VEC for just over 2 years privately: <i>"No. I mean, they, they teach you how to dispose of it correctly. You just have to double bag it and then put it in the bin. But I think, no, there's zero risk and we have not had any side effects."</i> US parent to RDEB teenager: <i>"In my experience, there are no risks associated with using B-Vec. I understand that some people have developed antibodies to the treatment and thus it is not as effective. With that said, it seems to be a smaller percentage of users who experience this."</i> US parent to a 17 year old with RDEB: <i>"No significant risks and we have not experienced any negative side effects of the therapy."</i> UK DDEB patient and parent to a 13 year old with RDEB: <i>"I assume that if it's gone through all of the regulatory approvals required, those are very strict and stringent, but then those side effects would have been noted and the safety, you know, will have met the safety thresholds required. Ultimately, at the moment, there are many dangerous side effects of the condition that we're managing. And so I think we need to make a kind of risk benefit weighing up of treatments. And ultimately at the moment, we don't have any, anything that's addressing the cause of the condition itself. So we'd be very willing to try something that's likely to have a positive impact</i>

	<i>because it's gene based. I would prefer to try B-VEC for its potential gene therapy benefits rather than continue to allow EB to affect mine and my son's long term health."</i>
11. Are there any groups of patients who might benefit more from beremagene geperpavec 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	B-VEC will only help patients with dystrophic EB – that is dominant dystrophic and recessive dystrophic EB – not other types of EB. DEB is caused by mutations on the collagen VII gene which leads to a reduction or complete lack of collagen VII protein which this technology addresses. Patients with acute and chronic open wounds will benefit most from beremagene geperpavec due to its impressive long term healing effects unlike any other treatment available, this covers all DEB patients as, without gene correcting intervention, the skin worsens over time and chronic wounds become almost inevitable.
12. Are there any potential equality issues that should be taken into account when considering skin wounds associated with dystrophic epidermolysis bullosa and beremagene geperpavec? 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	I believe the main cause of inequality among patients to be the financial status of the patient (or more accurately their family) and proximity to hospitals with EB specialists. This is particularly important if considering how this is to be administered. If patients have to travel to hospitals weekly this would be very difficult for some.

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?	I would much prefer to receive this treatment at home, as going to hospital every week would be really time consuming, and I already have so much of my day taken over by EB care. I live in London and there is an EB centre in London; it would be even worse for people that live further afield. UK parent to a 3 year old with RDEB who has been using B-VEC for just over 2 years privately: <i>"EB parents have to lance blisters and be incredibly precise with needles. This, applying B-VEC, you do have to be precise. It's using a syringe and putting droplets on the wound, but it's nothing an EB parent can't do. I genuinely believe that whoever is looking after an EB patient can apply B-VEC because we've got to do much worse and much more precise work with a lot higher stakes."</i>

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in [table 2](#). We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient 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, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Limited data available on clinical effectiveness of B-VEC in patients with dominant DEB (section 2.3.1 of EAR)	I'm sure the company will be addressing the data issue but patients and patient representatives see the value of B-VEC to the whole dystrophic EB population, both recessive and dominant DEB. Executive Director, Debra America <i>"There has been strong market penetration in the RDEB and DDEB populations. I see explicit value to using B-VEC within both populations. DDEB can present like RDEB but tends to have different kind of wounds. Without B-VEC they would still be susceptible to downstream negative consequences and comorbidities."</i> DDEB patient UK and parent of a 13 year old with RDEB: <i>"My experience of RDEB is that it's much more widespread and with wound healing needed across the whole body."</i> <i>From my experience of dominant dystrophic, it's more in zones, so things like feet, knees, elbows, hands. And that means that BVEC could really be helpful with this because it will be treating those areas specifically. You don't necessarily have the same systemic difficulties that you might have with RDEB and internal skin is affected, but not to such an extent, potentially. So, the opportunity to use B-VEC, because it can be applied topically to the areas that are needed, I feel like it can have a really positive impact for managing areas that are really fragile for people. And because of that, DDEB patients are likely to need a lot less of the product and need it potentially less often. So, thinking of myself, there are areas like my feet, my knees, my hands, my elbows that I would want to use the treatment on. And it might be that I don't need to use it very much, or I'm only using it on very small areas. And so, that would also impact the cost, it would be less. So I think there'd be quite a lot of benefit, but because it would be treating small areas, there should be less financial implication for that, too. But the possibility of treating areas for me that are a problem would have a really big impact because then it would make those areas more normal.</i> <i>I suppose I try to lead a very normal life and I'm held back by my EB on the areas that it affects. If those affected areas can be improved or can be treated with a gene therapy topically, it feels like a very low risk way of managing my condition because it's topically applied to the areas that are needed rather than applied systemically. And then I wouldn't need as much of it because the areas that I would need to treat would be quite small. I find it's the same areas that tend to get damaged each time. So, it doesn't mean I have very large, clear areas of skin. So, if I can fight to those small areas that often get injured, it feels like that would make a really big difference. I feel as somebody with dominant dystrophic, I fall into a bit of a black hole treatment-wise in that I am not severely and systemically affected enough to be managed in the way that a person with RDEB would be. But I'm more impacted</i>

	<i>than somebody who doesn't feel like they are affected by their condition at all. So, actually, something like B-VEC, where there's a gene treatment, feels very low risk to apply to those small areas and would be really helpful for me."</i>
An ITC between B-VEC and BBE based on a comparison of trial outcomes from the GEM-3 and EASE studies has not been provided (sections 3.9 and 3.10 of EAR)	From my understanding, the end points of the trials were very different. They are also completely different products – Filsuvez is just a cream, without a real understanding of its underlying mechanism of action, B-VEC is a gene therapy. Anecdotally, patients that have had access to both Filsuvez and B-Vec overwhelmingly say that B-VEC is the most effective, with many saying that Filsuvez is not effective at all. UK parent to a 3 year old with RDEB who has been using B-VEC for just over 2 years privately: <i>"Filsuvez I find to be completely ineffective. B-VEC I find moves the needle and actually makes a difference. On some wounds, I can see a difference the next day. You can't compare them; one is an expensive Vaseline, and the other one is actually providing what's missing to the wound, to the skin."</i> French parent of an 11 year old with RDEB: <i>"Can we really call Filsuvez a treatment?"</i> US parent of a teenager with RDEB: <i>"For us, B-VEC has been much more efficacious than Filsuvez."</i> Italian parent of a teenager with RDEB: <i>"The main difference lies in effectiveness: B-VEC has shown a clear and significant improvement in wound healing, whereas Filsuvez did not prove to be particularly effective in our case. In terms of ease of use, Filsuvez is simpler to apply since it is a topical cream that can be used at home, while B-VEC requires weekly administration in a hospital setting by a healthcare professional. Overall, B-VEC has had a much greater impact on symptom improvement and wound closure, making it the more beneficial treatment despite being less convenient to administer."</i>
Utility values are based on a vignette study despite there being EQ-5D estimates available (section 4.3.3.2 of EAR)	I cannot say whether the vignette study or EQ-5D is better but I think it clearly reflects the poor quality of life endured by people with dystrophic EB and that there is a desperate need for treatment that starts to address the root cause of the condition. I've alluded to the potential quality of life improvements in other parts of this document.

We consider patient perspectives may particularly help to address this issue Do utility estimates from the vignette study or EQ-5D data better reflect the health-related quality of life of people with skin wounds associated with dystrophic epidermolysis bullosa, and their carers?	
Validity of the company's patient level simulation as a source of effectiveness estimates (section 4.3.3.5 of EAR)	
Estimation of vial usage from the patient level simulation	

(section 4.3.3.5 of EAR)	
The company's preferred four-state model structure is dependent on a mapping algorithm which the EAG considers lacks face validity (section 4.3.3.6 of EAR)	
The plausibility of reduced clinical manifestations and mortality in patients with reduced wound burden (section 4.3.3.8 of EAR) We consider patient perspectives may particularly help to address this issue	As far as I am aware there has not been a comprehensive study on the actual benefits of B-VEC over and above wound healing but I would guess that with quicker and sustained wound healing, there would be • Less pain as wounds would have closed, less opiate use which in themselves carries risks • Weight gain, as the skin is fighting less hard to heal itself so nutrition could go to growth/weight • Reduction in anaemia – open wounds lead to blood loss and iron deficiency. Treatment should reduce chronic anaemia. • Reduction in itch • Reduction in or delay in onset of skin cancer due to less wounds/less chronic wounds • Reduced scarring – improved healing would mean less scarring and contractures leading to mitten deformities etc • Reduced inflammation due to improved skin healing • Better sleep due to less pain and itch from wounds • Fewer eye abrasions - eye abrasions often happen at night with disordered sleep so less pain etc could lead to fewer eye abrasions UK parent 3 year old with RDEB who has private access to B-VEC: <i>“Definitely an improvement in pain. I think his general mobility is much better because the skin is less sore. Weight gain also because with less open wounds,</i>

Would you expect non-skin related complications associated with dystrophic epidermolysis bullosa to be affected by beremagene geperpavec treatment?	<i>you have more calories, more nutrients going towards putting on weight rather than going to the wound. In general, dressing changes used to be a horrific experience for everyone involved. It was just torture especially for him. But now, most of the time, it's manageable and, and, and he can be quite chill."</i> UK parent to a 2 year old with RDEB: <i>"Despite not being a systemic treatment I think that B-VEC could significantly help with non-skin related complications of Dystrophic EB due to the indirect benefits of prolonged wound healing.</i> <i>By prolonging the healing of wounds it has the ability to minimise the chronic scarring associated with Dystrophic EB in turn this will improve independence for patients living with EB as it will reduce contractures in hands, fingers and other joints allow them to remain mobile.</i> <i>As B-VEC enables wound closure by delivering genes directly into the missing cells it reduces the risk of severe infections which is the leading cause of death in children with Dystrophic Epidermolysis Bullosa. Alongside sepsis, Squamous Cell Carcinoma is responsible for a large majority of deaths in EB due to the presence of chronic wounds and repetitive skin breakdown. Because B-VEC supports wound closure by directly delivering the missing gene into the wounds it had the ability to significantly reduce these risks.</i> <i>B-VEC also has the ability to reduce the inflammation in the body. Chronic inflammation often leads to anaemia which comes with a wide range of symptoms however with B-VEC's ability to promote wound healing significantly reduces this risk.</i> <i>With the significant increase in wound closure B-VEC has the ability to reduce pain, which reduces the need for opioids on a regular basis. Long term opioid use carries significant risks alongside the day to day side effects of using opioids which includes symptoms such as sedation, nausea and constipation these side effects significantly reduces the quality of life for those living with EB yet there is no treatment on the market in the UK that is targeting wound healing with gene therapy which in turn will reduce pain."</i>
Patients discontinuing treatment are assumed to stay in the state they occupy when discontinuing	In a poster submitted by Great Ormond Street Hospital for the 2026 European Wound Management Association Conference in 2026, 21 of 44 patients stopped treatment with Filsuvez due to side effects. Among patients who discontinued Filsuvez, 61% felt it made wounds larger or did not improve them, 44% reported increased itching, 28% reported more pain, 33% reported more exudate, 33% reported overall worsening and 22% reported increased inflammation. GOSH reported that most patients still using Filsuvez have a milder presentation of EB.

(section 4.3.3.12 of EAR) We consider patient perspectives may particularly help to address this issue How would you expect a patient's health to be impacted after discontinuing treatment with beremagene geperpavec or birch bark extract?	Of the patients that had tried Filsuvez and discontinued use, they reported no impact or positive impact upon discontinuation: (attached to submission) <i>"There was no impact of stopping using Filsuvez; after using the majority of wound healing creams/gels on the market Filsuvez is no superior than any of the alternatives available. Despite Filsuvez being labelled as a EB specific wound healing cream it isn't gene therapy so it cannot replace the missing protein (Collagen 7)." Mum to a 2 year old with RDEB</i> <i>"We saw minimal wound closure so there was no impact on stopping."</i> Mum to 17 year old RDEB patient. <i>"The medication is easy to use as it is a cream; however, I do not consider it very effective in terms of wound closure. In our case, it did not prove to be an effective or particularly useful treatment overall. We discontinued the use of Filsuvez after about 4 months, without any consequences."</i> Dad, Italy teenager Of patients that have continued to use Filsuvez: <i>"We would lose that extra maybe 10% quicker healing that we've got at the moment. But I would hope that there would be the opportunity for something that works better and is more effective than 10% improvement we're getting from Filsuvez. Something that tries to manage and address the root cause of EB and not just relieving symptoms and avoiding infection."</i> Mum to 13 year old RDEB patient. For those that are currently using B-VEC, they felt they would be negatively impacted by discontinuing treatment: UK parent to a 3 year old RDEB patient in UK with private access to B-VEC: <i>"I don't want to think about it. I think his skin would, at least on the left leg, break down to how it was on day one. I think his whole care would just be incredibly different. When he was born until about nine months old, we had to use morphine because dressing changes were so painful. And we haven't had to use morphine in a really long time because generally how his skin is much more manageable and much less red and sore. we don't have to use such strong pain relief. And I think that's a huge impact as well, kind of secondary positive of using B-VEC."</i>

	US parent to a 17 year old RDEB patient: <i>“If we stopped using B-VEC it would very negatively effect the future of our daughter. Like I said, it has been effective at closing many different kinds of wounds and has become quite important in our care routine.”</i> Italian parent to a teenager with RDEB: <i>“Stopping the treatment would be a major issue, as it is the only medication that is effective in promoting wound closure. There are no associated risks, side effects, or complications. In summary, B-VEC represents the only truly effective treatment (we have been using it for about two years).”</i>
Uncertainty regarding the feasibility of vial sharing (section 4.3.3.10 of EAR)	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- B-VEC is currently the only treatment that addresses the cause of Dystrophic EB (DEB).
- DEB causes constant pain and long-term damage, and impacts every aspect of life.
- Currently it is impossible for anyone with severe DEB to live independently or experience freedom – there is a huge unmet need.
- I have witnessed B-VEC's remarkable impact on patients' quality of life in Europe and America.
- Home administration would be far better for patients than hospital administration as it would not require travel on top of already laborious daily care and carers are well equipped with the skills to administer.

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](#).

Natasha Hersham

[REDACTED]

[REDACTED]

[REDACTED]

Email: [REDACTED]

15 May 2026

Dr Paul Arundel

Chair, Highly Specialised Technologies Evaluation Committee

[REDACTED]

National Institute for Health and Care Excellence (NICE)

Level 1A, City Tower, Piccadilly Plaza

Manchester M1 4BT

United Kingdom

Re: ID3959 / GID-TA10868 – beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa – HSTEC meeting, 21 May 2026 – Submission and request to provide patient-family testimony

Dear Dr Arundel and [REDACTED],

We are writing as the parents of [REDACTED], a three-year-old boy with Recessive Dystrophic Epidermolysis Bullosa – Generalised Severe (RDEB-GS, ICD-10 Q81.2). [REDACTED] carries two pathogenic null mutations in COL7A1 (c.3942dup p.(Asn1315Glufs*45) and c.4018C>T p.(Arg1340*)), confirmed by SYNLAB Mannheim and Synnovis at Guy's Hospital. Neither allele produces functional type VII collagen. This is the most severe end of the dystrophic EB spectrum.

[REDACTED] began treatment with beremagene geperpavec (B-VEC, Vyjuvek) on 19 January 2024 at the EB Centre, University Hospital Freiburg, under Prof. Dr. Cristina Has. He transitioned to weekly treatment at Great Ormond Street Hospital under Dr Anna Martinez in November 2024. To the best of our knowledge, [REDACTED] is the only paediatric patient in the United Kingdom with sustained, real-world clinical experience of Vyjuvek – now exceeding two years of continuous treatment. We are aware that Cure EB and DEBRA UK are also engaging with the committee on ID3959. Our family supports their submissions and writes separately because we hold a clinical experience base that no other UK family can offer.

We respectfully request the opportunity to be heard by the committee – in writing, in person, or both – before the appraisal concludes.

Why our perspective is unique

We are not commenting on Vyjuvek in the abstract. We have lived with it. We have also lived with the alternative. Our experience with Filsuvez (oleogel-S10) – the only other recently licensed topical for DEB – preceded our access to Vyjuvek and continued in parallel for a period. The two are not clinically interchangeable in our hands, and our judgement is based on direct comparator use, not extrapolation.

Life before Vyjuvek

Before Vyjuvek, [REDACTED]'s day-to-day was defined by open, non-healing wounds, infection cycles, and pain that was managed with morphine. His chronic wounds on the lower legs, feet and hands did not close. New blistering occurred faster than existing sites could re-epithelialise. He was failure-to-thrive: by October 2024 his weight had dropped to the seventh percentile and a PEG gastrostomy was placed for nutritional support.

Filsuvez was used repeatedly during this period at the recommendation of his treating teams. We persisted because we had no other option. In our experience it provided no meaningful effect on healing or on wound burden for [REDACTED]. We retain technical access to Filsuvez today and we do not use it. It is not a substitute for Vyjuvek and it would not allow us to operate the wound-care regime we currently run.

As parents, life in this period was equally severe. We watched our child in continuous physical agony with no developmental trajectory. Sleep, work, and any version of normal family life were not possible. The clinical and the human collapsed into the same picture.

Documented response under Vyjuvek – Freiburg report (attached)

We attach the clinical report compiled by Prof. Has's group at the University Hospital Freiburg covering [REDACTED]'s first ten months of Vyjuvek treatment (January – November 2024; Karakioulaki et al., submitted). The report is concise and visual; we summarise the key findings here:

- Total weekly wound area on the lower legs and feet falls from approximately 25–38 cm² in the first weeks of treatment to near zero by week 15 and remains durably low through week 28.
- Chronic wound sites on the lower leg and foot, photographed at weeks 1, 5, 20 and 26, show progressive re-epithelialisation and near-complete closure of long-standing wounds that had not closed under prior care.
- Acute fresh blisters treated with Vyjuvek at the point of opening resolve cleanly by week 28 with no chronic conversion.

- Hands – initially severely affected, with pseudosyndactyly risk and complete loss of skin integrity – show transformative improvement after 10 months of Vyjuvek, restoring grip, function and the ability to use the hands in normal play.

The wound-area trajectory in the Freiburg dataset is, in our view, more clinically informative than the binary endpoint used in GEM-3 (NEJM 2023). It captures sustained burden reduction, durable healing, and the ability to extend therapy strategically to new sites – outcomes that translate directly into quality of life and into avoided long-term harm (chronic non-healing wounds, infection, sepsis, and ultimately squamous cell carcinoma, the leading cause of death in adult RDEB).

Where [REDACTED] is today

Over two years on, [REDACTED] is a different child – and we are a different family. He walks, which is not a given for a child with RDEB-GS. He talks. He attends pre-nursery school. His weight has moved from the seventh percentile to the fiftieth. His pain burden is markedly reduced and morphine is no longer part of his routine care. He plays. He develops.

Sustained Vyjuvek treatment has done two things that the trial endpoint cannot fully convey. First, it closed wounds that had been open from birth. Second, and equally important, it gave us the clinical headroom to begin treating new sites strategically – the hands in particular – and to keep new acute blisters from converting to chronic wounds. The therapy is not a one-time fix; it is a platform on which the rest of his care now stands.

Filsuvez and Vyjuvek are not interchangeable

We anticipate that the appraisal will consider whether existing treatments – including Filsuvez – meaningfully address the same need. From our direct comparator experience, they do not. Filsuvez delivered limited value for [REDACTED] and we discontinued routine use. Vyjuvek is mechanism-based: it restores the missing collagen at the wound site. It is the only available therapy that has produced durable, repeatable wound closure in our son. Removing or restricting access to Vyjuvek would not return us to a steady state on Filsuvez. It would return us to morphine, non-healing wounds, failure to thrive, and the loss of every developmental gain of the past two+ years months. Our treating clinicians have been explicit that discontinuation in a child with active disease of this severity carries a real risk of rapid deterioration, infection and sepsis.

Quality of life – the family dimension

Quality-of-life evidence in EB tends to focus on the patient. We would ask the committee to also weight the family burden, which in RDEB-GS is extreme. Before Vyjuvek, our household existed in continuous medical crisis. Today, while [REDACTED] still requires intensive daily wound care and skilled nursing support, the qualitative shift is total. He is a developing child with a future and we are parents to that child rather than full-time crisis managers. This shift is, in our experience, the single most important real-world endpoint of this therapy.

The equity argument

We have been fortunate. Through circumstance – initial residence in Germany, private insurance cover, and willingness to navigate cross-border supply – [REDACTED] gained early access to Vyjuvek. Almost no other UK family with a child on the RDEB-GS spectrum has had this option. The outcome we have witnessed should not depend on geography or insurance status. We hope very much that the committee's decision allows other UK families to access the same therapy and the same outcome on the NHS.

Request

We would be grateful for the opportunity to participate in the committee's deliberations on ID3959. Specifically, we would welcome:

- Acceptance of this letter and the attached Freiburg clinical report as a written submission from the patient family for the ID3959 evidence base.
- Consideration of Natasha Hersham as a patient expert for the appraisal, in coordination with Cure EB and DEBRA UK, so that our family-level evidence complements rather than duplicates the patient-organisation submissions.
- The opportunity to provide oral representations to the committee, in person or remotely, via whichever channel the committee considers appropriate – as a patient expert at the 21 May meeting if possible, or at any subsequent meeting on this appraisal.

We are available at the contact details above and will make ourselves available on whichever date the committee meets.

Thank you for your time and for the work the committee is doing on this appraisal.

Yours sincerely,

Natasha Hersham

Parents of [REDACTED] (DOB [REDACTED] 2023)

Attachment

Karakioulaki M et al. – [REDACTED], B-VEC (Vyjuvek) treatment Jan – Nov 2024. Clinical report, EB Centre, University Hospital Freiburg (submitted). Five pages, including weekly wound-area trajectory, chronic and acute wound photographic series, and ten-month hand outcomes.

Single Technology Appraisal

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

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.

Technical engagement response form

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 as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [NICE health technology evaluations: the manual](#) (section 5.4) for more information.

The deadline for comments is **5pm on Thursday 4 December 2025**. 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.

Technical engagement response form

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)	British Association of Dermatologists (BAD)
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: - the name of the company - the amount - the purpose of funding including whether it related to a product mentioned in the stakeholder list - whether it is ongoing or has ceased.	Krystal Biotech Medical advisory board and consulting () Ongoing
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
Limited data available on clinical effectiveness of B-VEC in patients with dominant DEB (section 2.3.1 of EAR)	No	Although the clinical trial data is limited in dominant DEB, mechanistically, there is a good rationale why this would be an effective treatment option for this patient group (i.e. increased expression of collagen VII and the resultant clinical benefits this would confer). However, many patients with dominant DEB have limited wound burden and, therefore, it may not be appropriate to offer the technology, given costs and logistical considerations. We would suggest that the English EB centres agree on a body surface area percentage of wounds that would make patients with dominant DEB eligible for treatment. It is likely that <10% of the centres' dominant DEB cohort would be eligible.
An ITC between B-VEC and BBE based on a comparison of trial outcomes from the GEM-3 and EASE studies has not been provided (sections 3.9 and 3.10 of EAR)	No	BBE and B-VEC are very different products with different mechanisms of action and different clinical outcomes, although both products may speed wound healing. B-VEC, through increased expression of collagen VII, leads to longer-lasting wound healing. The EASE and GEM-3 clinical trials had different designs and outcome measures, making direct comparison impossible.
Utility values are based on a vignette study despite there being EQ-5D estimates available	No	Unable to comment

Technical engagement response form

(section 4.3.3.2 of EAR)		
Validity of the company's patient level simulation as a source of effectiveness estimates (section 4.3.3.5 of EAR)	Yes/No	Unable to comment
Estimation of vial usage from the patient level simulation (section 4.3.3.5 of EAR)	Yes	Under 3 years of age this may be possible but above this age it is anticipated that whole vials would be needed.
The company's preferred four-state model structure is dependent on a mapping algorithm which the EAG considers lacks face validity (section 4.3.3.6 of EAR)	Yes/No	Unable to comment
The plausibility of reduced clinical manifestations and mortality in patients with reduced wound burden (section 4.3.3.8 of EAR)	Yes	Yes – chronic wounds are the main factor in morbidity and probably mortality. Chronic wounds lead to chronic colonisation and infection of wounds, which create a pro-inflammatory state, leading to sequelae such as anaemia, osteoporosis and the development of aggressive squamous cell carcinomas, which are the leading cause of death in early adulthood in people with severe, recessive DEB.
Patients discontinuing treatment are assumed to stay in the state they occupy when discontinuing (section 4.3.3.12 of EAR)	No	We would anticipate that patients would return to their former health state on discontinuation, although this may take many months to do so.
Uncertainty regarding the feasibility of vial sharing (section 4.3.3.10 of EAR)	Yes	Vial sharing may be possible for very young patients - for example, patients under the age of 3 years can only use half vial. If further stability data becomes available, it may be that this is less important as patients may be able to store vials for later use, and to use less frequently if the wound burden is diminished.

Technical engagement response form

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: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	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: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	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 N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	...	...	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case

PLEASE DESCRIBE HERE

Technical engagement response form

Single Technology Appraisal

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

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.

Technical engagement response form

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 as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [NICE health technology evaluations: the manual](#) (section 5.4) for more information.

The deadline for comments is **5pm on Thursday 4 December 2025**. 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.

Technical engagement response form

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)	Chiesi Ltd.
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: - the name of the company - the amount - the purpose of funding including whether it related to a product mentioned in the stakeholder list - whether it is ongoing or has ceased.	Chiesi manufactures a comparator treatment (Filsuvez®)
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	N/A

Technical engagement response form

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

3 of 9

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
Limited data available on clinical effectiveness of B-VEC in patients with dominant DEB (section 2.3.1 of EAR)	No	Nothing to add.
An ITC between B-VEC and BBE based on a comparison of trial outcomes from the GEM-3 and EASE studies has not been provided (sections 3.9 and 3.10 of EAR)	No	While we recognize the importance of including all relevant options, including BBE, in the economic evaluation of B-VEC, we also concur with the company's position that a robust indirect treatment comparison (ITC) between B-VEC and BBE is not feasible based on the currently available evidence. This limitation primarily stems from key differences highlighted by the company.
Utility values are based on a vignette study despite there being EQ-5D estimates available (section 4.3.3.2 of EAR)	No	We agree with the EAG that the EQ-5D estimates from the EASE OLE are appropriate and using utility values from a vignette are not justified. The EASE trial EQ-5D data were sufficient and, as stated in NICE's reference case hierarchy, these should therefore be used as the primary source over utilities generated from the vignette study. Vignette studies should only be used if no suitable trial-based EQ-5D data are available and this is not the case with this submission. Use of utilities from the vignette study superficially inflates the incremental QALY gain of B-VEC vs. BBE.

Technical engagement response form

Validity of the company's patient level simulation as a source of effectiveness estimates (section 4.3.3.5 of EAR)	Yes	The validity of the patient level simulation (PLS) as a source of effectiveness estimates is very uncertain. The use of a small phase 1/2 study (GEM-1 trial) as the primary source of data for the PLS creates a lot of uncertainty and is a weak evidence base for a pivotal economic model. There are also a number of questionable assumptions. For example, the PLS assumed that chronic wounds close as quickly as recurrent wounds when treated with B-VEC and that chronic wounds never heal in patients receiving BSC. EB wounds are highly dynamic; they are in a constant cycle of healing and re-opening and there are multiple factors that can affect this such as, fresh trauma and infection. In reality, all wounds, whether they are receiving BSC, BBE or BVEC, have the potential to heal fully. The EASE study clearly demonstrated that when treated with BBE, chronic wounds were more likely to fully heal and that over time overall wound burden decreased by approximately 50%. The PLS also predicts that patients on B-VEC reach very mild states and stay there which is not supported by clinical evidence. There is more robust evidence than GEM-1 available that could be used to inform the analysis including the GEM-3 trial.
Estimation of vial usage from the patient level simulation (section 4.3.3.5 of EAR)	No	The company's estimation of vial usage is likely to be unrealistically low as it is lower than the usage observed in their open-label extension. In addition, the PLS assumes that after initial treatment, patients remain in a very mild disease state. This would mean that vial usage would drop to virtually 0 as patients would require almost no further treatment. This assumption has limited support from clinical trial data and is unlikely in a dynamic disease such as EB where wounds are constantly healing and reopening.
The company's preferred four-state model structure is dependent on a mapping algorithm which the EAG considers lacks face validity (section 4.3.3.6 of EAR)	Yes	We agree that the company's approach of using a mapping algorithm to convert transition probabilities from the six-state HST28 model into the company's four-state structure lacks face validity. There is a great deal of clinical uncertainty regarding whether combining multiple health states into one appropriately represents disease progression, wound healing and the treatment effect. DEB is a very heterogeneous disease and there is a risk that wound burden in some patients

Technical engagement response form

		could be underrepresented in the model due to the lack of granularity and this could translate into inflating QALYs and reducing costs in favour of BVEC. Furthermore, the company's model relies heavily on BSAP outcomes; however, as outlined in Section 4.2.4, these were not addressed in either the GEM-1 or GEM-3 trials, which serve as the foundation for assessing the effectiveness of B-VEC. Under its current label, B-VEC is not intended for the treatment of all wounds, as its use is restricted to a limited surface area of the body. Consequently, BSAP cannot be considered a relevant endpoint for B-VEC, since the treatment is not designed to address the overall wound burden as BBE does. This is a critical consideration because, beyond the intended population (DEB), the model should reflect the potential for wound healing—the primary outcome measured in the pivotal trials rather than the overall burden of wounds, which was never intended to be evaluated in the trial design. This aspect could significantly influence certain modelled benefits, such as bandage-related costs and the overall gain in QALYs
The plausibility of reduced clinical manifestations and mortality in patients with reduced wound burden (section 4.3.3.8 of EAR)	No	Nothing to add
Patients discontinuing treatment are assumed to stay in the state they occupy when discontinuing (section 4.3.3.12 of EAR)	Yes	This assumption is not reflective of what is observed in clinical practice as wound healing and re-opening are a dynamic and ongoing process in EB. The assumption that patients maintain the improved state post B-VEC discontinuation does not reflect real-world patterns, where individuals typically experience gradual deterioration and revert toward their baseline condition seen with best supportive care. Ultimately, this assumption likely biases results in favour of B-VEC and goes against what is seen in clinical practice.

Technical engagement response form

Uncertainty regarding the feasibility of vial sharing (section 4.3.3.10 of EAR)	No	We are unclear on whether vial sharing is plausible for B-VEC as it is very hard to say if assumptions regarding vial sharing would translate into clinical practice. There is also no guidance in the SmPC on vial sharing so we agree that there is a lot of uncertainty on this topic.

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: Combined use of B-VEC and BBE	Not discussed	Yes	There is no mention or consideration that B-VEC and BBE may be used in combination for some. This is a very important consideration as B-VEC is restricted in the size of wound that can be treated at any one time. Therefore, if there were patients with moderate to large wound BSAP solely treated with B-VEC, there would, in theory, be a number of wounds that were only being treated with standard of care (and not BBE). Also, as B-VEC has to be applied in a hospital setting there may be times when this is not practical, and patients may need treatment at home for which BVEC is not an option.

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)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	...	...	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case

PLEASE DESCRIBE HERE

Technical engagement response form

Single Technology Appraisal

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

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.

Technical engagement response form

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 as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [NICE health technology evaluations: the manual](#) (section 5.4) for more information.

The deadline for comments is **5pm on Thursday 4 December 2025**. 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.

Technical engagement response form

About you

Table 1 About you

Your name	Medicines Value and Access
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	NHS England
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: - the name of the company - the amount - the purpose of funding including whether it related to a product mentioned in the stakeholder list - whether it is ongoing or has ceased.	Nil
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	Nil

Technical engagement response form

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

3 of 13

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
Limited data available on clinical effectiveness of B-VEC in patients with dominant DEB (section 2.3.1 of EAR)	No	We agree with this issue as identified by the EAG.
An ITC between B-VEC and BBE based on a comparison of trial outcomes from the GEM-3 and EASE studies has not been provided (sections 3.9 and 3.10 of EAR)	No	No additional comment.
Utility values are based on a vignette study despite there being EQ-5D estimates available (section 4.3.3.2 of EAR)	No	No additional comment.
Validity of the company's patient level simulation as a source of effectiveness estimates	No	No additional comment.

Technical engagement response form

(section 4.3.3.5 of EAR)		
Estimation of vial usage from the patient level simulation (section 4.3.3.5 of EAR)	Yes	We agree with the EAG comments- the clinical feedback we had are patients are likely to have areas of skin to treat for significantly longer than suggested by the company model. Clinicians have fed back that the usage of b-vec is be limited to the maximum surface area of wounds which they are allowed to treat as per SmPC. Clinicians may choose to treat other wounds for the same patient, therefore the actual usage per patient could be higher than predicted in the simulation.
The company's preferred four-state model structure is dependent on a mapping algorithm which the EAG considers lacks face validity (section 4.3.3.6 of EAR)	No	No further comment.
The plausibility of reduced clinical manifestations and mortality in patients with reduced wound burden (section 4.3.3.8 of EAR)	No	We agree with the EAG comments in relation to non-cutaneous impact.
Patients discontinuing treatment are assumed to stay in the state they occupy when discontinuing (section 4.3.3.12 of EAR)	No	We strongly agree with the EAG comments. Real-world clinical evidence with longer term follow-up would be useful to validate this assumption.
Uncertainty regarding the feasibility of vial sharing (section 4.3.3.10 of EAR)	No	There is little potential to vial share, at least initially. Expectations to vial share at this point would be towards to lower end of the modelling. This would require a lot of co-ordination and dependent on: - the mode of reconstitution (hospital pharmacy or commercial aseptic reconstitution services). While commercial aseptic reconstitution services exist, the

Technical engagement response form

		service delivery model to send the product to patients' home is still in progress, so would take time to set up. (see also "additional section") - the number of vials which is required for the patient (we expect most patients especially in adults would be on maximum dose) - capacity of reconstitution services (hospital pharmacy or commercial aseptic services).

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

Technical engagement response form

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

8 of 13

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response

Technical engagement response form

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

9 of 13

Additional issue 1: Administration costs	section 2.2 of the EAG and clarification questions B46 and B47	Yes/No	Admin time for nurses For administration, it assumes that only 0.5 hours of band 6 nursing care is required. This seems a significant underestimate based on experience at GOSH. Costings for homecare B-vec is likely will be delivered at home via homecare (esp from Year 2 onwards), but due to uncertainty around homecare set up, unable to provide homecare costings estimates. Our initial estimates for homecare delivery alone is XXXX per patient per year, and this is based on standard NHSE homecare delivery charges which do not account for compounding for gene therapies. This is likely to be an underestimate. Admin training requirements The modelling assumes that patients' carers would be sufficiently trained to administer after 1 visit. Based on NHSE site visit, we estimate the Year 1 costs would be higher due to additional training and clinical time for newly initiated patients. Unable to provide estimates of the costs involved at this point due to uncertainty of delivery. Administration costings (HRG coding) Unclear from the modelling the outpatient costs used for B-Vec. We would recommend using the procedure costs of "combined day case/ ordinary

Technical engagement response form

			elective spell” for B-vec. This would apply to each administration visit per patient (see table below). This is because there will be at least 2 nurses involved in administration of B-vec and it can be a time-consuming process. <table><tr><th>HRG Code</th><th>HRG Name</th><th>Combined day case /ordinary elective spell (£)</th></tr><tr><td>JC42C</td><td>Intermediate Skin Procedures, 19 years and over</td><td>1,111</td></tr><tr><td>JC42D</td><td>Intermediate Skin Procedures, 18 years and under</td><td>1,186</td></tr></table>	HRG Code	HRG Name	Combined day case /ordinary elective spell (£)	JC42C	Intermediate Skin Procedures, 19 years and over	1,111	JC42D	Intermediate Skin Procedures, 18 years and under	1,186
HRG Code	HRG Name	Combined day case /ordinary elective spell (£)										
JC42C	Intermediate Skin Procedures, 19 years and over	1,111										
JC42D	Intermediate Skin Procedures, 18 years and under	1,186										
Additional issue 2: Reconstitution costs		Yes	Pharmacy aseptic reconstitution is required. Hospital aseptic pharmacies have indicated that they do not have capacity to reconstitute b-vec in the longer term. Costs of reconstitution (hospital aseptic pharmacies or commercial aseptic reconstitution) is not available and needs to be considered as part of the appraisal.									
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]									

Technical engagement response form

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)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	...	...	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case

PLEASE DESCRIBE HERE

Technical engagement response form



Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]. A Single Technology Appraisal

EAG critique of the company's technical engagement response

Produced by	Sheffield Centre for Health and Related Research (SCHARR), The University of Sheffield
Authors	Andrew Metry, Research Fellow, SCHARR, University of Sheffield, Sheffield, UK Sarah Davis, Senior Research Fellow, SCHARR, University of Sheffield, Sheffield, UK Kate Ren, Professor of Statistical Health Technology Assessment, SCHARR, University of Sheffield, Sheffield, UK
Correspondence Author	Andrew Metry, Research Fellow, SCHARR, University of Sheffield, Sheffield, UK
Date completed	31/03/2026

1. Introduction

In February 2026, the company submitted their response to technical engagement (TE) for the appraisal of beremagene geperpavec (B-VEC) for treating skin wounds associated with dystrophic epidermolysis bullosa (DEB).¹ The company's TE response includes a written response form which presents a brief discussion of each of the key and additional issues identified in the External Assessment Group (EAG) report² with a new company base case and a new Patient Access Scheme (PAS) discount. The company also submitted updated versions of the Markov model that it used to generate updated cost-effectiveness estimates, and the patient level simulation (PLS) that it used to derive the transition matrices and treatment consumption estimates for the Markov model.

The company's TE response also includes a structured expert elicitation (SEE) where clinical experts were consulted regarding input parameters needed for the PLS model where evidence was lacking. This was mainly to estimate outcomes for chronic wounds, which were not sufficiently represented in the GEM-1 trial, the main source for healing rates used in the PLS, and to facilitate the addition of birch bark extract (BBE) as a comparator in the PLS.

This addendum provides a brief commentary on the company's TE response and should be read in conjunction with the EAG report. Section 2 provides a summary of the company's response and the EAG's critique of these points; whilst Section 3 presents a fuller description of the EAG's critique on the company's response to particular issues and new analyses presented by the company. Section 4 provides a brief description of the changes in the updated model submitted by the company. Section 5 presents the methods for additional exploratory analyses undertaken by the EAG. Section 6 presents the results of additional exploratory analyses undertaken by the EAG.

All results presented in this document include the PAS discount which reduces the cost per one 2.5ml vial from a list price of £21,500 to £[REDACTED]. A PAS discount was not previously provided at the time of the original company submission (CS).³

2. Summary of company's TE response and EAG comments

The main points discussed in the company's TE response and the EAG's comments on these points are summarised in Table 1, whereas Section 2.1 highlights additional issues presented by the company. Where further critique by the EAG was considered necessary, this is provided in Section 3.

Table 1: Summary of company's TE response and EAG comments

Key issue	Headline points in company's TE response	EAG comments
Key issue 1: Limited data available on clinical effectiveness of B-VEC in patients with dominant DEB (DDEB)	• The mechanism of action of B-VEC is expected to work regardless of the DEB subtype due to the functional loss of type VII collagen (COL7). The company only noted anecdotal evidence from clinical use in the US to support this claim. • BBE was recommended for both recessive DEB (RDEB) and DDEB, although its pivotal trial (the EASE trial) did not show differences in DDEB patients treated with BBE compared to placebo for the outcome of proportion of patients with first complete closure of the target wound. • In GEM-3 (the pivotal trial for B-VEC), the one DDEB patient who was recruited, achieved complete closure of the B-VEC-treated wound by Month 6, while the placebo-treated wound did not heal. • Several regulatory bodies (e.g. the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), the Japanese Pharmaceuticals and Medical Devices Agency (PMDA)) have granted B-VEC marketing authorisation for both subtypes.	The EAG considers the anecdotal evidence from clinical use in the US to be limited and potentially subject to bias and would have liked to have seen this evidence, however this was not provided by the company. Patients with DDEB have one non-mutated allele of COL7 but retain one mutated allele, and these mutations can lead to varying severities of the collagen structure abnormalities.^{4, 5} Therefore, the EAG believes robust evidence is required to demonstrate whether B-VEC would have a comparable efficacy in the DDEB population versus that of the RDEB patients as shown in GEM-3. In addition, although the EASE trial did not find a statistically significant difference between the DEB subtypes, there was no clinical rationale on why the efficacy of BBE would differ across the subtypes. The EAG considers that the subgroup analysis for BBE does not provides evidence on whether a consistent treatment effect should be expected across the RDEB and DDEB subtypes for B-VEC as BBE does not replace COL7, therefore the efficacy of BBE would not be expected to be affected by the presence in DDEB patients of a non-mutated copy of the COL7A1 gene.

Key issue	Headline points in company's TE response	EAG comments
		The EAG maintains its position that there is not sufficient evidence to support a similar efficacy of B-VEC across the two subtypes. Further, as mentioned in the EAG report Section 2.3.5, “<i>The EAG’s clinical expert also noted that there is a good biological rationale to expect treatment effectiveness might differ in DDEB compared with RDEB due to patients with DDEB having one non-mutated copy of the COL7A1 gene.</i>”
Key issue 2: An indirect treatment comparison (ITC) between B-VEC and BBE based on a comparison of trial outcomes from the GEM-3 and EASE studies has not been provided	• The company had concerns related to the ITC conducted by the EAG, and on how it was implemented within the Markov model. These included concerns related to the treated open wound area in EASE and a potential disconnect between this and the estimated number of BBE tubes required. This is based on the assumption that a mean BSA for a 16-year-old RDEB patient is approximately 12,000 cm², 12% of which was the BSAP treated in EASE (equivalent to 1,450 cm²). However, the reported treated area is 735 cm², which the company infers means that not all the wounds were treated in EASE, and that tube consumption is underestimated compared to a real-world scenario where the gel should be applied to all open wounds. • The transition probabilities for BBE adopted by the EAG, and to which the ITC estimate was applied to derive the	The EAG notes that the 735 cm² reported as treated in EASE is a median value and finds the FDA multi-discipline review of Filsuvez reporting mean treatment area in EASE to be of “12% body surface area or affected wound surface area of 1100 cm² at baseline”.⁶ The EAG has serious concerns regarding using the numbers estimated from the PLS (as described in Section 3.1). The EAG understands the company’s concerns regarding the use of the company’s transition probabilities from HST28, however it highlights that the redacted transition probabilities adopted by the EAG/Committee for HST28 were less favourable to BBE than the unredacted transition probabilities available for use here. Therefore, if the ITC estimate had been applied to the redacted transition probabilities, the B-VEC transitions would be worse compared to the ones being used in the EAG report of this appraisal. To address the

Key issue	Headline points in company's TE response	EAG comments
	probabilities for B-VEC, were not considered appropriate by the EAG and the Committee during the HST of BBE (HST28). • The transition probabilities used for BBE and best supportive care (BSC) in HST28 allows all patients in the most two severe health states to move to a less severe state and never return. This prevents any incremental benefit provided by B-VEC to be shown for patients starting in the severe states. • The ITC only captures wound closure rates, but not the duration of closure. • Based on these issues, the company only used the ITC estimate to derive the weekly proportion of recurrent wounds closed for patients on BBE in the company's PLS. The PLS outputs include transition probabilities for B-VEC, BBE, and BSC in the company's updated PLS model.	company's other concerns, the EAG applied a continuity correction to the company's transition probabilities from HST28 as described in exploratory analysis (EA) 2 (Section 5.2.1). While the ITC only captures wound closure rates, the EAG notes that duration of closure is highly uncertain for B-VEC as illustrated in the EAG report Section 4.3.3.5. The EAG still remains highly sceptical of how the condition is modelled in the updated PLS as described and critiqued in Section 3.1.
Key issue 3: Utility values are based on a vignette study despite there being EQ-5D estimates available	• The company's TE base case adopts the Generalised Linear Model (GLM) based on EuroQol 5-Dimension (EQ-5D) estimates from the EASE trial, which is preferred by the EAG. The company also corrected the age-adjustment for carer utility.	The EAG considers this issue to now be resolved.

Key issue	Headline points in company's TE response	EAG comments
Key issue 4: Validity of the company's patient level simulation as a source of effectiveness estimates	• The company's base case PLS is now updated to reflect the six health states used in the HST28 model rather than the four states used in the company's original model. • The TE PLS uses different closure rates for each of recurrent and chronic wounds on B-VEC. The closure rate for recurrent wounds was sourced from GEM-1, with a lower rate for chronic wounds elicited from the SEE. Previously the same rates were applied for recurrent and chronic wounds from GEM-1. • The company only used the ITC estimate to derive the closure rate of recurrent wounds for patients on BBE in the TE PLS. The closure rate of chronic wounds on BBE was estimated from Davidovic <i>et al.</i>⁷ instead of the SEE. • Chronic wounds on BSC are allowed to close in the updated PLS (a closure rate of 0 was assumed previously) based on the closure rate used for recurrent wounds and an odds ratio of the likelihood of closure for recurrent wounds compared to chronic ones published in Fulchand <i>et al.</i>⁸ This is described in Section 3.1. • A portion of chronic wounds is assumed not to respond to active treatment either by B-VEC or BBE. This is described in Section 3.1.	The detailed critique of the company's updated PLS (company's TE PLS) and the company's SEE can be found in Sections 3.1 and 3.2, respectively. Overall, the EAG still considers that the PLS is not a reliable source of transition probabilities and continues to use the transitions for BBE and BSC as reported in HST28. A continuity correction is now applied to these matrices as described in EA2 before applying the ITC estimate to derive the transitions for B-VEC.

Key issue	Headline points in company's TE response	EAG comments
Key issue 5: Estimation of vial usage from the patient level simulation	• Vial usage cannot be estimated from the GEM trials (GEM-1 and GEM-3) as no patient received B-VEC for all their open wounds. • Wounds remain closed on B-VEC for a median of █ days which the company has estimated based on data from GEM-3 and its open label extension (OLE). Therefore, after treating all open wounds for a patient, only minimal B-VEC is needed for reopened wounds which would rapidly be retreated and managed, leading to a sustainable low body surface area percentage covered with wounds (BSAP).	As described in the EAG report Section 4.3.3.5, the design of the GEM-1 study, as described by Gurevich <i>et al.</i>,⁹ was predicated on the assumption that the treatment effect of B-VEC would not persist beyond 3 months due to the half-life of COL7. This implies that the expected duration of wound closure is much less than the █ days estimated by the company using data from GEM-3 and its OLE. The EAG has previously critiqued this estimate (see EAG report Section 4.3.3.5) as being unsuitable because it relies on assumptions regarding wound closure between the GEM-3 and OLE studies. It also noted that the wound closure duration estimate from the GEM-1 study of 103 days was much closer to the 3 months quoted as the half-life of COL7. Moreover, health state (HS) 1 in the updated PLS (based on the six-state structure) contains more severe patients compared to HS1 in the old PLS (based on the four-state structure). This is because HS1 in the six-state structure covers patients with BSAP 0-4% compared to 0-2.1% in the four-state structure. However, the updated PLS estimates vial consumptions of ~█ vials every 13 weeks from year 3 onwards compared to █ vials in the CS original PLS. This lacks face validity.

Key issue	Headline points in company's TE response	EAG comments
		Therefore, the EAG adopted similar assumptions on vial usage to the ones it used in its base case (and described in the EAG report Section 4.4.2 EA5). This is further described in EA3.
Key issue 6: The company's preferred four-state model structure is dependent on a mapping algorithm which the EAG considers lacks face validity	- The company's TE base case adopts the six-state structure in line with HST28 and the EAG preference. - A scenario analysis is presented using seven states to capture <i>"the granularity in the milder health states, where there is a smaller affected BSAP"</i> where relative efficacy of B-VEC can still be demonstrated.	The EAG considers this issue to now be resolved as the company has adopted the six-state structure from HST28 in its base case. The EAG understands the rationale behind the seven-state scenario analysis, however the transitions for seven states are not available except from the PLS, which the EAG does not consider as a reliable data source (as discussed in Section 3.1). Moreover, moving from the six- to seven-state structure adds an extra layer of face validity concerns. The company's submitted six-state TE base case model shows incremental discounted patient QALYs for B-VEC of 7.32 versus BSC, compared to 7.14 in the seven-state scenario. The EAG believes that if the introduction of the seventh state would show more benefit for B-VEC as the company claims, incremental QALYs should increase which is not the case. The EAG is unclear of the cause of this discrepancy.
Key issue 7: The plausibility of reduced clinical	The company maintains the assumption that the inclusion of clinical manifestations varies by health state based on Eng <i>et</i>	As described in detail in Section 4.3.3.8 of the EAG report, <i>"there was no evidence presented to support that disease severity as described in Eng et al. would reduce by wound healing,"</i> and this

Key issue	Headline points in company's TE response	EAG comments
manifestations and mortality in patients with reduced wound burden	<i>al.</i> , ¹⁰ although this is now being controlled via simpler formulae in the Markov Excel model.	remains the case. Whilst the EAG acknowledges that lowering wound burden may have some systemic benefit from lowering the level of systemic inflammation, it is not expected to address all non-cutaneous manifestations. The EAG considers that the simpler formulae used in the TE response still lead to implausible prevalence results, as shown in Section 3.3.
Key issue 8: Patients discontinuing treatment are assumed to stay in the state they occupy when discontinuing	The company updated its model to redistribute patients discontinuing treatment with B-VEC or BBE across health states in line with the health state distribution observed in the BSC arm. This is in line with HST28 and the EAG preference.	The EAG considers this issue to now be resolved.
Key issue 9: Uncertainty regarding the feasibility of vial sharing	- Suzuki <i>et al.</i> reported that vial optimisation is practiced in approximately 83% of countries.¹¹ - The company also cites, “<i>a study from the UK, where vial sharing strategies resulted in cost savings in 74% of cases.</i>” - Vial optimisation helps reduce vial consumption resulting in cost savings	The EAG agrees with the company regarding the rationale behind vial optimisation, however it questions its applicability in a rare condition such as DEB. The EAG notes that Suzuki <i>et al.</i> only included 12 countries, and was concerned with the use of anticancer injection drugs, which may be easier to optimise considering the relatively large number of patients and the multi-use indication of some of these drugs compared to B-VEC in DEB. Furthermore, the cited study described by the company as being “ <i>from the UK</i> ” was in

Key issue	Headline points in company's TE response	EAG comments
		fact an international survey in which 34% of participants were from the UK and was again concerned only with oncology drugs.¹² The EAG uses 80% vial optimisation in line with the company's base case but provides the same scenarios of 0% and 50% as provided in the EAG report.

Abbreviations: BBE - birch bark extract; BSAP - body surface area percentage; BSC - best supportive care; DEB - dystrophic epidermolysis bullosa; EA - exploratory analysis; EAG - evidence assessment group; EQ-5D - EuroQOL quality of life measure, 5 Dimensions; HS - health state; HST - highly specialised technology (submission); ICER - incremental cost-effectiveness ratio; ITC - indirect treatment comparison; PLS - patient-level simulation; SEE - structured expert elicitation; TE - technical engagement

2.1. Additional issues listed by the company in the TE response

The company's TE base case uses the Gompertz model for both severe and non-severe RDEB in line with the EAG preference. The EAG is content with the amendment, however there was an implementation error in the model as discussed in EA1. The company also corrected the error regarding the RDEB/DDEB split as suggested by the EAG.

Other assumptions regarding how some inputs such as rates of clinical manifestations and concomitant treatment use by health state were derived for the six-state structure are described in an appendix to the company's TE response. These were sourced from Eng *et al.*¹⁰ where mild state was assumed to correlate with HS1, moderate with HS2 to HS5, and severe with HS6. The EAG reiterates their critique of this publication as provided in its report Section 4.3.3.8. It notes in particular that the definitions of a health state do not align between the Eng *et al.* and the modelled states. In terms of the severity modifier in the company's TE response, the company agrees with the EAG calculations where a QALY multiplier of 1.2 is suggested.

During the technical engagement, NICE was interested to see the results for an additional arm in the model where B-VEC and BBE could be used concurrently due to the dose limitations for a single B-VEC application. However, the company did not find this feasible with the limited timeframe available and noted that incorporating this arm "*would introduce substantial additional uncertainty into the model*" due to lack of supporting data, which the EAG agrees with.

3. EAG's critique on key issues 2, 4, 6 and 7.

The EAG has already made brief comments on issues 1, 3, 5, 8, and 9 in Table 1 and does not consider it necessary to provide further commentary on these issues. However, additional critique is provided below on the company's responses to issues 2, 4, 6, and 7.

3.1. Description and critique of the updated patient-level simulation (PLS) adopted by the company (Key issues 2, 4 & 6)

As described in Section 4.2.5.1.1 of the EAG report,³ the company built a PLS to inform the economic evaluation of B-VEC versus BSC in the treatment of DEB where wound-level clinical evidence from GEM-1 was used to simulate the disease progression based on body surface area percentage covered with wounds (BSAP).

The simulation is implemented in R and estimates health state transitions and B-VEC vial consumption, within a hypothetical cohort. The PLS model submitted at the start of the appraisal did not include BBE, however the company added it to estimate the related health state transitions and BBE tube consumption per health state at the technical engagement stage.

The company's TE PLS model structure and assumptions differ from the one submitted in the original CS in the following aspects:

1. Six health states are used to model the different severity levels of DEB as explained in key issue 6 in Table 1 (instead of the initially submitted four-state structure) to align with the modelling conducted in the HST28 of BBE, which was preferred by the EAG.
2. Time horizon is extended to 10 years (instead of 3 years) given the reduced rate of closure of chronic wounds compared to recurrent wounds (as discussed in the next point) and inclusion of BBE within the PLS. This was to ensure further transitions are captured until equilibrium is reached.
3. The company updated the closure rates of chronic wounds for B-VEC and BSC as explained in Key issue 4 in Table 1. In the original CS PLS, it was assumed that 42.54% of the treated open wound area closes each week for wounds treated with B-VEC regardless of wound type. This rate is kept the same in the TE PLS for recurrent wounds, however a slower rate of 36.7% is used for chronic wounds.

For BSC, chronic wounds were never assumed to close (i.e., a 0% rate was assumed) in the original CS PLS. This is updated in the TE PLS to a 0.57% weekly closure rate calculated from the weekly rate used for recurrent wounds treated with BSC (14.17%) and information from Fulchand *et al.* which reported that "*recurrent wounds had a 29-fold greater likelihood to close spontaneously*" compared to chronic ones.⁸

Another parameter change was using a lognormal distribution to sample the size of reopened wounds (instead of the normal distribution which allowed the predicted size to be negative).

4. The company updated the PLS to include BBE. Table 2 summarises the parameters used for modelling healing dynamics for wounds on BBE.

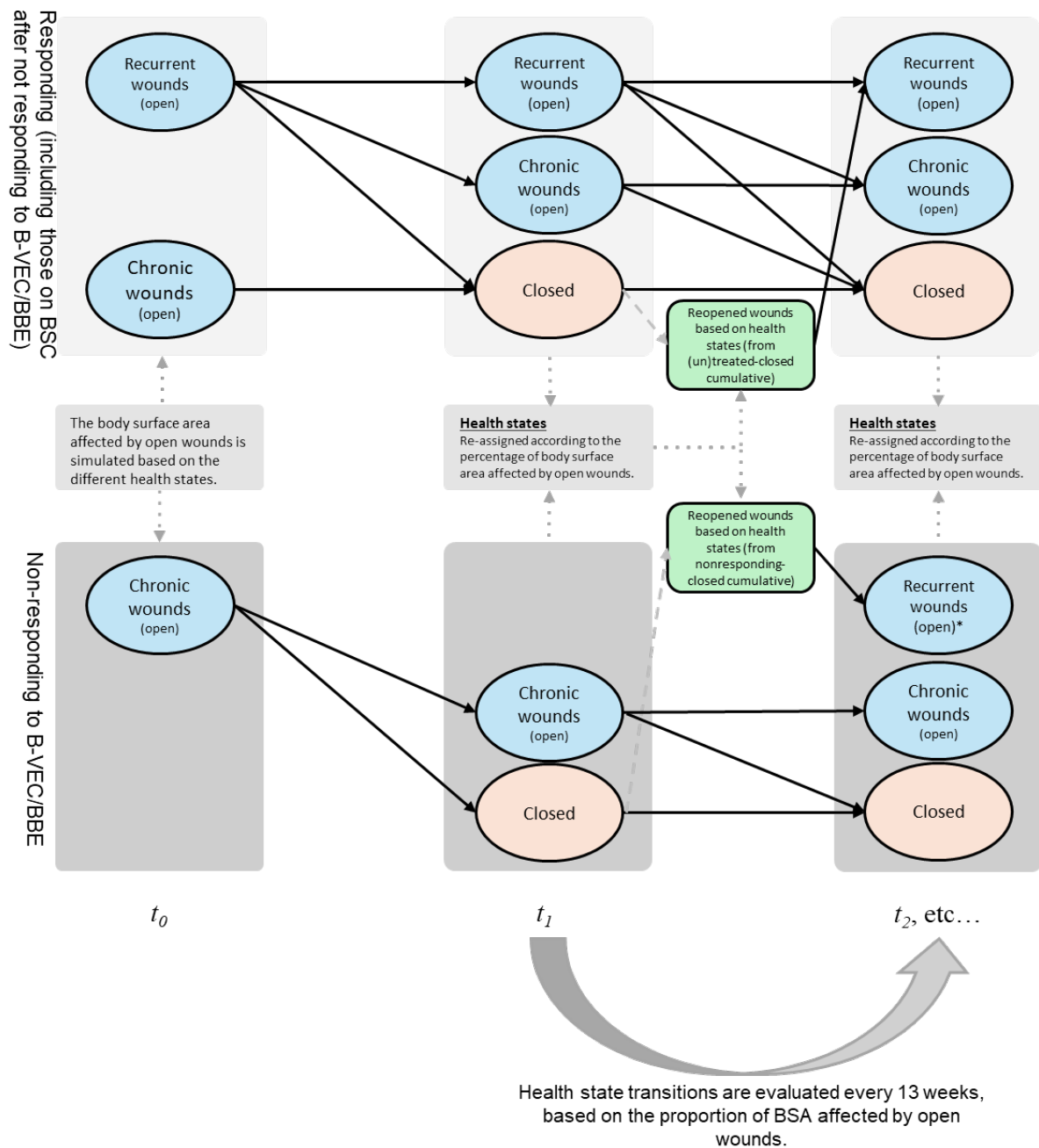
Table 2: Summary of parameters for modelling wound dynamics for BBE

Parameter	Value	Source
Recurrent wound closure per week	16.27% (if treated)	The EAG's ITC estimate (that patients receiving B-VEC were 3.12 times more likely to have complete wound closure at 3 months compared to those receiving BBE) was applied to the closure rate of B-VEC
Chronic wound closure per week	3.17% (if treated)	Davidovic <i>et al.</i> ⁷ and the company's calculations in Key issue 4 of its TE response ¹
Reopening probability per week	█████%	Based on a duration of closure of █████ days elicited from the SEE exercise and the equations reported in the EAG report p108.
Reopened wound size	Lognormal distribution (Mean: █████, SD: 0.96) increased by ratio of 4.5	Assumed the same as BSC Based on an observed maximum wound size of █████ cm ² for placebo wounds in GEM-1
Recurrent → Chronic transition per week	24.16%	Calculated based on recurrent wound closure rates and the assumptions that wounds not closed at eight weeks become chronic
Max area treated per tube	250 cm ²	Assuming the thickness of applied gel layer of 1 mm (The tube size is 25 ml)
Number of applications per week	Three	Davidovic <i>et al.</i> ⁷
Compliance	100%	Assumption

Abbreviations: BBE - birch bark extract, BSC - best supportive care, EAG - evidence assessment group, ITC - indirect treatment comparison, SEE - structured expert elicitation

5. The original CS PLS assumed that all chronic wounds would respond to B-VEC. The company updated this assumption to artificially slow the closure rates for this kind of wound and extend the time needed for chronic wounds to fully close (Key issue 4 in the company's TE response). This was achieved by assuming that a proportion of chronic wounds would not respond to active treatment either by B-VEC or BBE. This responding proportion was elicited for B-VEC via the SEE (█████%) and calculated from Davidovic *et al.* for BBE (73%).⁷ The non-responding proportion is assumed to discontinue active treatment after four weeks, however the efficacy parameters of BSC (such as closure rate, reopening size) were applied to this proportion from the model start. Figure 1 illustrates the updated model structure.

Figure 1: The TE PLS model (EAG interpretation of the PLS R code)



*These wounds follow the same wound healing dynamics of wounds on BSC

The EAG still views the PLS as an unreliable source for deriving the transition probabilities for the Markov model for the reasons mentioned in the EAG report Sections 4.3.3.4 and 4.3.3.5. Moreover, the inclusion of BBE and the assumption of a proportion of chronic wounds that are non-responding added more discrepancy and uncertainty as described below.

1. Transitions for BBE

The inclusion of BBE in the PLS helped in validating the model outputs because the transition probabilities for BBE between the six health states of the Markov model were also available from HST28. While the transition matrices cannot be compared directly because of the difference in cycle length (HST28 used a monthly cycle length compared to 13 weeks in the current appraisal), the EAG compared the health state occupancy from the Markov model for alive patients who are still on BBE using the two sets of transition matrices. The EAG highlights that the HST28 matrices it used were not favoured at the time by the EAG or the Committee for HST28 as they were approximated and were not directly counted from the EASE trial. The EAG/Committee preferred the transitions estimated using EASE directly (Table 27 of the EAG report for HST28¹³), however these were redacted. The EAG notes that the unredacted transition matrices used here for the comparison and in the current EAG base case of the current appraisal were described in HST28 as being favourable to BBE relative to the ones preferred by the HST Committee.

The EAG used the baseline distribution as per EASE and compared the health state occupancy at 90 days/13 weeks (this was the point in the HST28 model after which the last matrix was used to estimate the transitions for the modelled time horizon) and at three years (the HST28 Markov trace achieved state equilibrium by this point). Table 3 shows the results of this comparison.

Table 3: Health state occupancy (Markov model) of alive patients who are on BBE using the two sets of transition probabilities

Time point	Source of transitions applied	HS1	HS2	HS3	HS4	HS5	HS6
Baseline	-	20.8%	27.8%	13.8%	15.8%	8.8%	12.8%
Day 90	HST28 company's optimistic transitions*	21.9%	32.1%	15.0%	30.7%	0.2%	0.0%
Week 13	The PLS	46.4%	16.7%	10.8%	13.0%	8.1%	5.0%
Year 3	HST28 company's optimistic transitions*	20.2%	43.5%	20.7%	15.6%	0.0%	0.0%
Year 3	The PLS	75.3%	9.0%	5.5%	8.9%	0.0%	1.2%

*The EAG/Committee preferred using another set of transitions that were less favourable to BBE

Abbreviations: HS - health state, HST - highly specialised technology, PLS - patient level simulation

It is worth noting that by 3 years, the Markov trace estimated from the PLS-derived transitions has not reached equilibrium and that the proportion of people in HS1 continues rising which lack face validity. Table 3 shows that the transitions estimated from the PLS for BBE do not align with the ones derived from the EASE trial where the former lead to faster healing rates and significantly more patients achieving HS1 when treated with BBE. In their TE response, the company made this distinction between

the EASE trial and real-world settings where wounds treated in EASE may be easier to treat because “For example, clinicians often treat large and chronic wounds whereas in the EASE trial, wounds may have been smaller in size, making real-world observations more relevant”. This further supports that the PLS outputs lack face validity as worse (not better) outcomes would be expected if the wounds treated in clinical practice are larger and more likely to be chronic. Similarly, the PLS predicts very positive long-term outcomes for B-VEC, where after two years from the model start, all alive patients on B-VEC achieve HS1. While there could be several factors leading to such a discrepancy between the PLS and the trial setting (such as the simplifying nature of the PLS assumptions, the resistance of DEB wounds to heal in a real-life context, patient’s age, wound location), this comparison highlights the challenging nature of modelling complex wound dynamics and warns that simple assumptions and constant rates may not be applicable for modelling the condition.

2. Tube consumption for BBE

The EAG notes that the number of consumed BBE tubes predicted from the company’s Markov model, when the transitions are used from the PLS and the baseline distribution from EASE is used, is overestimated. A mean of 29.67 tubes per month was reported during the double-blinded phase of EASE, which lasted 90 days. This is equivalent to ~90 tubes per 13 weeks (which is the cycle length of the company’s Markov model). However, the Markov model predicts 145 tubes to be used within the first cycle based on the BBE consumption output from the TE PLS model. Based on this, the EAG believes that the PLS significantly overestimates BBE consumption considering that the PLS transitions are predicting patients to heal faster on BBE compared to the transitions from EASE. As a result, the EAG base case uses the mean of 90 tubes per 13 weeks and only consider the number of BBE tubes estimated from the TE PLS in a scenario analysis.

3. The assumption about non-responding chronic wounds

The EAG is concerned with the added assumption of non-responding chronic wounds and considers that this addition raises some face validity concerns. While the BSC efficacy is applied to the non-responding proportion, not all of the wound area classed as responding is immediately experiencing the efficacy of the active treatment due to the application constraints for B-VEC (the maximum weekly dose can cover 200 cm²). Instead, the responding portion not receiving active treatment at a given week would fare worse than the non-responding portion experiencing the efficacy of BSC because no closure rates are being applied to the responding portion whilst waiting for treatment in the next model cycle(s). The EAG thinks that the responding proportion of wounds waiting for B-VEC treatment should get at least some treatment benefit from BSC instead of zero closure rates. To illustrate the point, the EAG conducted a comparison between the company’s base case (where ■■■% of chronic wounds are responding) and a scenario where the responding portion is reduced to 80%. Table 4 shows the results

of health state occupancy at week 13 for both cases. Assuming a 10% increase in the non-responding proportion (from 10% to 20%) would be expected to hamper the efficacy of B-VEC. However, similar occupancies are seen with surprisingly a slightly higher proportion of patients in HS1 with the more pessimistic scenario for response rates. The EAG considers that this demonstrates a lack of face validity which is arising from the company allocating BSC closure rates to non-responding wounds and zero closure rates to wounds that are classed as responding but are not treated initially due to the restriction on the area that can be treated.

Table 4: Health state occupancy of alive adult patients who are on B-VEC using different values for the responding proportion of the chronic wounds

Time point	Responding % of chronic wounds	HS1	HS2	HS3	HS4	HS5	HS6
Baseline*	-	20.8%	27.8%	13.8%	15.8%	8.8%	12.8%
Week 13	10% (company's base case)	62.4%	8.9%	7.7%	8.7%	5.7%	6.7%
Week 13	80% (EAG scenario)	62.8%	5.3%	9.9%	9.0%	6.2%	6.8%

*The EASE baseline distribution is assumed

Abbreviations: HS - health state

4. Adapting inputs from the 4-state PLS to the TE PLS

The company had to modify inputs to fit in the six-state structure of the TE PLS model. One of these inputs was the number of wounds simulated for a patient. As discussed in the EAG report Section 4.2.5.1.1, the company used the average number of wounds reported per patient in Eng *et al.*¹⁰ where it used the mean, 25th, and 75th percentiles to inform the lower boundaries of the moderate, mild, and severe health states of the CS four-state model structure. With the change in structure from four to six states, the company changed the number of wounds simulated for each state, however the estimation of these values is not explained and is only reported as a table in an appendix to the company's TE response. Table 5 presents the average number of recurrent and chronic wounds simulated for each state in the original versus the updated model structure. The EAG notes that the number of simulated wounds in HS1 of the updated six-state model is significantly lower than that simulated for the very mild and mild state of the original model. The EAG also notes that number of wounds is simulated in the PLS to decide on which wounds will reopen, and the less wounds a patient has, the less likelihood they can have a reopened wound.

Table 5: Average number of recurrent and chronic wounds simulated in the TE PLS model versus the original CS PLS model

Initial model (4 health states)	Company	Average number of wounds simulated in original CS PLS model	New company base case (6 health states; based on HST28)	Average number of wounds simulated in the TE PLS model
Very Mild (BSAP $\leq 2.1\%$)		2 recurrent 0 chronic	HS1 (BSAP $< 5\%$)	0.5 recurrent 0.5 chronic
Mild (BSAP 2.1-5%)		7.5 recurrent 1.5 chronic		
Moderate (BSAP 5-25%)		14 recurrent 3.5 chronic	HS2 (BSAP 5 - $< 8\%$)	4 recurrent 2 chronic
			HS3 (BSAP 8 - $< 11\%$)	8.5 recurrent 3 chronic
			HS4 (BSAP 11 - $< 19\%$)	13 recurrent 3 chronic
			HS5 (BSAP 19 - $< 25\%$)	18 recurrent 4 chronic
Severe (BSAP $> 25\%$)		31.5 recurrent 7 chronic	HS6 (BSAP $\geq 25\%$)	33 recurrent 7 chronic

3.2. Description and critique of the structured expert elicitation submitted by the company (Key issues 2 & 4)

Due to the paucity of clinical evidence to inform how the healing rates might differ between recurrent and chronic wounds in the TE PLS model, and the need for additional parameters for the inclusion of the BBE arm in the TE PLS model (Section 3.1), the company conducted a structured expert elicitation (SEE) using the Sheffield elicitation framework (SHELF).^{14, 15} Three dermatologists, who had experience with B-VEC and BBE in Germany and Italy, were recruited for the SEE process.

The company's SEE was a three-stage process:

1. Training and preparation, where a training slide-deck on concepts of subjective probabilities and the elicitation process was developed using resources available from the SHELF website and training was delivered to ensure experts can express their uncertainty and beliefs in probabilistic terms. An evidence dossier of the pivotal trials for B-VEC and BBE (i.e., the GEM and EASE trials respectively) was also shared before Stage 2.

2. Individual elicitation, where each of the three experts was asked to provide independent judgements without interacting with each other. Experts first defined the plausible limits (i.e., the interval with a 0.98 probability the true value of the quantity in question falls), and then estimated the median, the 25th, and the 75th percentiles for this value. Based on this, appropriate distributions were fitted for each quantity per expert.
3. An elicitation workshop, where the three experts were engaged in a facilitated group discussion to reach a consensus on the elicited quantities. Only the quantities for which the estimated distributions differed substantially among the experts were discussed in this stage.

For quantities that were similar among the experts after the individual elicitation, mathematical aggregation was used. Otherwise, behaviour aggregation was conducted in the workshop.

Four quantities were included in the SEE. Table 2 summarises the elicited quantities with the SEE results and how these were used in the TE PLS model.

Table 6: Summary of the SEE results and the derived parameters

Elicited quantile	Expert 1	Expert 2	Expert 3	Consensus	Parameters used in the TE PLS model
Quantity 1: Among chronic wounds (open >8 weeks) treated with B-VEC, what proportion show any measurable improvement (i.e., any reduction in wound area from baseline) over time?					
Lower bound	0.50	0.20	0.75	0.75	The fitted distribution to the consensus quantiles has a mean of █████. Therefore █████% of the BSA covered by chronic wounds and treated by B-VEC was assumed to be responding as explained in Section 3.1.
25 th percentile	0.70	0.50	0.92	0.85	
Median	0.80	0.60	0.96	0.90	
75 th percentile	0.85	0.75	0.98	0.92	
Upper bound	0.95	1.00	1.00	0.95	
Quantity 2: Consider a wound area that has been open for more than 8 weeks, located on the back, with baseline area 1,200 cm ² (≈50% of an RDEB adult back) that has shown any measurable improvement after starting treatment with B-VEC. Assuming B-VEC can be applied to a maximum of 200 cm ² per week, how many weeks from the first B-VEC application does it typically take for the wound area to reach complete closure?					
Lower bound	20	10	24	Not needed as the elicitation outputs were strongly aligned. Instead, the elicited individual quantiles were mathematically aggregated into a pooled distribution	The pooled distribution had a mean 31.3 weeks. Assuming the stringent definition of wound closure as per GEM-1 (≥95% reduction in wound surface area), a rate of 9.13%* can then be calculated as the weekly closing proportion of responding chronic wounds.
25 th percentile	30	25	26		
Median	32	30	30		
75 th percentile	35	36	35		
Upper bound	45	45	50		

Quantity 3: Consider a wound area that has been open for more than 8 weeks located on the elbow, with baseline area 50 cm ² (≈8% of an RDEB adult arm) that has shown any measurable improvement after starting treatment with B-VEC. Assuming B-VEC can be applied to a maximum of 200 cm ² per week, how many weeks from the first B-VEC application does it typically take for the wound area to reach complete closure?					
Lower bound	2	2	4	2	The fitted distribution to the consensus quantiles has a mean of [REDACTED] weeks. Assuming the stringent definition of wound closure as per GEM-1 (≥95% reduction in wound surface area), a rate of [REDACTED]* can then be calculated as the weekly closing proportion of responding chronic wounds.
25 th percentile	5	4	8	5	
Median	7	7	12	7	
75 th percentile	7	8	18	9	
Upper bound	8	10	30	12	
Quantity 4: Once a recurrent or chronic wound treated with BBE has fully closed (100% epithelialization with no drainage), for how many days does it typically remain closed?					
Lower bound	2	7	2	2	The fitted distribution to the consensus quantiles has a mean of [REDACTED] days. This translates to a weekly reopening probability of [REDACTED]* as per the equation in the EAG report Section 4.2.5.1.1.
25 th percentile	2	10	7	10	
Median	3	15	15	15	
75 th percentile	5	20	20	18	
Upper bound	14	30	100	21	

**Based on the standard exponential decay equation: percent open at week x = initial percent open multiplied by $(1 - \text{the weekly closing rate})^{\text{time in weeks}}$*

Abbreviations: BSA - body surface area, TE - technical engagement, PLS - patient-level simulation

Three other questions were asked of the experts regarding the validation of some modelling assumptions. These included i) whether a wound closing under BBE would be expected to have the same reopening dynamics (in terms of speed and size of reopening) to a wound treated by BSC, ii) discontinuation rates on BBE, and iii) the plausibility of the weekly closing proportion of responding chronic wounds (3.17%) on BBE calculated from Davidovic *et al.*⁷ The panel agreed that “*consistent difference between BBE and BSC reopening dynamics is difficult to assert*”, and gave a wide range for discontinuation rates on BBE (25-50%). For the third question, they agreed that “*the approach can be treated as a pragmatic modelling workaround with some caveats*” such as healing rates are not truly exponential.

The EAG understands the need for the SEE, however it has the following concerns regarding the conduct of the SEE and how the SEE output was used to inform the TE PLS:

1. The EAG is concerned that the ambiguity of some of the questions may have an impact on the robustness of the SEE output. For example, the question about discontinuation rates for BBE does not specify a time period, and it is not obvious on what basis experts agreed on the aforementioned rate. The EAG also notes that some experts struggled with the wording and answering of the questions. For example, when answering quantity 1 (see Table 2) two experts gave an upper bound of 1.00 in their respective individual elicitation indicating that all chronic wounds respond to B-VEC. However, they agreed in the workshop that “some wounds can be non-responders”. Also, one expert gave a score of 1 of 5 in their feedback about the clarity of the wording of the elicited quantities compared to 4 out of 5 for another expert whereas feedback of one expert was not available.
2. The EAG notes that one of the elicited parameters may lack face validity. For the duration of closure of wounds treated by BBE (Quantity 4 in Table 2), The distribution fitted to the elicited values gives a mean of [REDACTED] days. This value is lower than the 16.5 days estimated for BSC based on the GEM-1 trial although BBE is given as an add-on to BSC.
3. In answering Quantity 4 from Table 2, the experts noted that assuming a fixed closure rate through the healing journey of a wound is not accurate. This resonates with the EAG’s opinion about the PLS model which relies heavily on the assumption that wound dynamics follow an exponential distribution, as discussed in Section 4.3.3.4 of the EAG report.
4. The EAG could not replicate how the weekly closure rate of 36.7% for chronic wounds on B-VEC was calculated. Based on the mean values estimated for quantities 2 and 3 (Table 2), the EAG can calculate rates of 9.13% for large wounds and 33.92% for small ones. Moreover, this difference in closure rates agrees with the EAG’s expert view mentioned in Section 3.1 that the responsiveness and closure speed of DEB wounds can vary considerably and that assuming one rate for all types of recurrent or chronic wounds is a strong assumption.

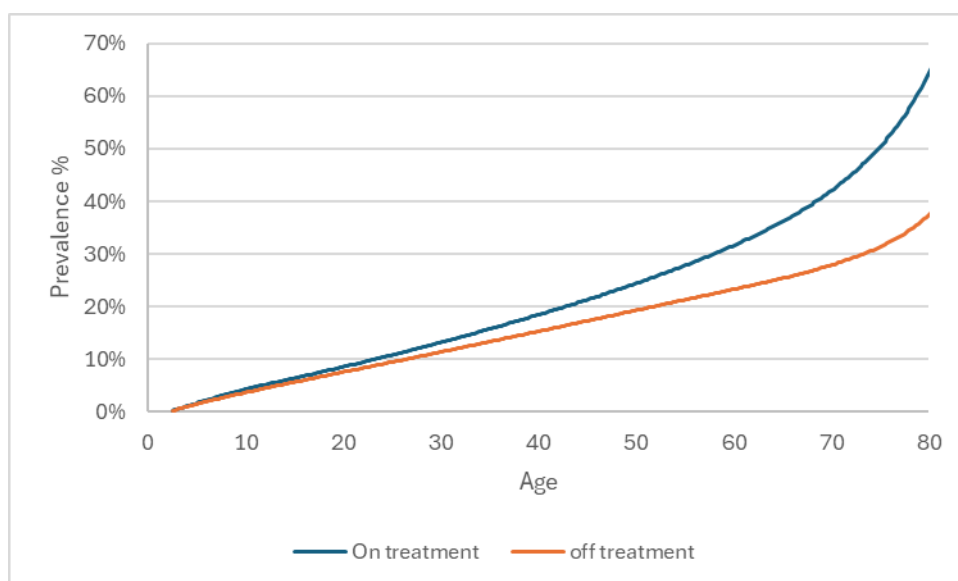
3.3. Description and critique of the updated calculations for irreversible clinical manifestations (Key issue 7)

For irreversible clinical manifestations (squamous cell carcinoma [SCC], complete or partial mitten deformity of foot, and complete mitten deformity of hand), the TE model estimates the prevalence at a given cycle (t_x) for a given HS as follows:

$$\text{Total number of cases with this manifestation at } t_x = \text{Number of cases with this manifestation } t_{x-1} + (\text{number of patients at } t_x \text{ multiplied by the incidence rate of the manifestation for this HS})$$

The EAG highlights that the model separates patients who discontinue treatment from patients still on treatment across the model cycles. Therefore, patients who will die or discontinue treatment in cycle t_x should be discarded from the total number of cases in the cohort still on treatment, however this is not the case. This leads to implausible prevalence results as shown in the next example. Estimated number of children on BBE who develop SCC was divided by total number of children still on BBE. The same was done for the population of children who discontinued BBE treatment. Figure 2 shows that the resulting proportions developing SCC are higher for the population on treatment compared to patients who discontinue treatment. The EAG does not believe that remaining on BBE would increase the likelihood of developing SCC given BBE superiority over BSC in transitioning patients to less severe states. In addition, the EAG previously critiqued the assumption that prevalence starts from 0% for all age groups at model start in the CS original model. This remains the case in the updated TE model.

Figure 2: Prevalence of SCC in the modelled children group in the BBE arm



4. Summary of the changes in the updated economic analysis presented by the company

Table 7 summarises the company's original base case model in the CS, the EAG's preferred analysis in the EAG report, and the company's updated base case model as presented in the company's TE response. It also indicates whether there is now agreement between the company's TE model and the EAG's preferences or whether the EAG considers a particular issue to remain unresolved.

Table 7 Summary of company's original base case (CS), EAG-preferred analysis (EAG report) and company's updated TE base case

Aspect of model/ issue identified in the EAG report Section 4.3.3	Company's original base case	EAG-preferred analysis	Company's updated TE base case	Agreement between EAG-preferred and company's TE base case
Correcting implementation errors in the company's PLS and Markov economic model	No	Yes	Yes	✓
Choice of utility date source: The EAG preferred the Generalised Linear Model based on EuroQol 5-Dimension (EQ-5D) estimates from EASE	No	Yes	Yes	✓
The PLS relies on GEM-1 in estimating wound healing rates on B-VEC and BSC (EAG report, Section 4.3.3.4). The EAG does not prefer to estimate transitions based on this, and prefers to use the transitions from HST28 based on EASE and apply the ITC estimate to calculate the transitions for B-VEC	No	Yes	No, this still uses the outputs from the PLS	✗
Validity of mapping algorithm between the different state structures: The EAG preferred the six-state structure to avoid the issues with mapping from six to four states.	No	Yes	Yes	✓
B-VEC impact on clinical manifestations: The EAG preferred not to include these based on lack of evidence and model implementation issues	No	Yes	No	✗
Mortality assumptions for RDEB patients: The EAG prefers the Gompertz distribution for both survival curve fits of RDEB (non-severe) which is applied to HS1-4, and RDEB-Severe which is applied to HS5-6.	No, different assumptions were applied to the four-state structure. The exponential fit was used.	Yes	HS1 follows GP mortality, HS2-5 RDEB non-severe, and HS6 RDEB-Severe. The Gompertz fit is used.	✓ The EAG notes that the Committee papers for HST28 do not explicitly mention which mortality was attributed to which health state. Therefore, the EAG adopts the company's updated base case
Concomitant medications: The EAG prefers to exclude these for the reasons mentioned in EAG report, Section 4.3.3.11	No	Yes	No	✗

Aspect of model/ issue identified in the EAG report Section 4.3.3	Company's original base case	EAG-preferred analysis	Company's updated TE base case	Agreement between EAG-preferred and company's TE base case
After discontinuation of B-VEC or BBE, The EAG prefers patients to distribute patients in accordance with the BSC steady state distribution as happened in HST28 and accepted by the company and the committee	No	Yes	Yes	✓
The appropriate baseline distribution of the cohort across the health states: The EAG prefers to use the baseline distribution as per the EASE trial	No	Yes	No	✗
Additional issues raised in the TE stage				
The EAG prefers to use the transitions for BBE from HST28	Yes	Yes	No, this is estimated from the PLS	✗
The EAG prefers to use the mean number of BBE tubes reported in the double-blinded phase of EASE	Yes	Yes	No, this is estimated from the PLS	✗

Abbreviations: BSC - best supportive care; EA - exploratory analysis; GP - general population; HS - health state; HST - Highly Specialised Technology; ITC - indirect treatment comparison; PLS - patient-level simulation; RDEB – recessive dystrophic epidermolysis bullosa; TE - technical engagement

5. Methods of the EAG's TE exploratory analyses

5.1. Company changes adopted by the EAG

The EAG base case uses the TE six-state Markov model structure submitted by the company in their TE response.

5.2. Exploratory analyses (EA) 1 to 6

5.2.1. EA1: correcting programming errors in the company's TE economic model

The EAG corrected the company's formulae used for extracting mortality probabilities for HS1. This was erroneously extracting probabilities from HS2, which are different. The EAG amended that to enable extraction from the right column in the 'Mortality' sheet, which is column B instead of C.

5.2.2. EA2: Transition probabilities used in the EAG TE base case

The EAG TE base case still uses the transition probabilities for BBE and BSC from HST28, as explained in the EAG report Section 4.4.2 under EA3 in the EAG report. For any given matrix, the EAG applied a continuity correction factor to allow transitions to all health states where the probability is zero. This was applied by adding a $1/36^{\text{th}}$ of a patient to all transitions of the matrix. These were re-adjusted so that the sum of all probabilities in any row of the matrix equals to 1.

This approach allows patients to transition to HS 5 and 6 from any other state and thereby addresses the company's concern that without these adjustments, the model did not have the potential to capture any benefit from B-VEC in reducing the likelihood of returning back to these severe states.

The ITC estimate was then applied to the continuity-corrected re-adjusted transitions of BBE to estimate the transitions for B-VEC as described in EAG report, Section 4.4.2, EA3.

5.2.3. EA3: B-VEC vial consumption

The PLS is still underestimating B-VEC vial consumption in the mildest health state (HS1). As explained in Section 4.3.3.5, results reported in the open label extension of the GEM trial suggest an average of 0.72 doses per week. Considering a dose to mean at least one syringe, this equates to 9.36 syringes at least within a 13-week time frame (which is the Markov model cycle length). However, the PLS predicts that less than ■ vials (less than ■) would be needed from year 3 onwards for a patient in HS1 (by year 3, all patients on B-VEC in the company's Markov base case model are in HS1).

Therefore, the EAG adjusted the vial consumption in HS1 to be at least 9.36 syringes (equivalent to 2.34 vials) in its base case. Other states were not adjusted as the consumption predicted by the PLS was already higher than 2.34 vials.

5.2.4. EA4: BBE tube consumption

As explained in Section 3.1, the PLS overestimates BBE consumption, therefore the EAG base case assumes 29.67 tubes would be used monthly for all patients on treatment in line with usage of BBE reported for the EASE trial in HST28.

5.2.5. EA5: Baseline distribution across health states

As explained in Section 4.3.3.14 of the EAG report, the EAG preferred not to include the baseline distribution at the model start from Bruckner *et al.* and used the starting distribution from the EASE trial instead. The company's TE response did not provide any evidence why Bruckner *et al.* should be favoured, hence the EAG preference remains unchanged, and uses the distribution from EASE.

5.2.6. EA6: Exclusion of clinical manifestation and concomitant medications

In the absence of new evidence to support the inclusion of clinical manifestation and concomitant medications in the Markov economic model, the EAG preferred to exclude them in its base case for the reasons discussed previously in EAG report Sections 4.3.3.8 and 4.3.3.11.

5.3. EAG TE scenario analyses

The EAG undertook the same additional scenario analysis (ASA) as listed under EAG report Section 4.4.2, using the EAG's base case as the starting point. These were as follows:

- ASA1: Applying the RR value for complete wound closure only to the transitions to HS1
- ASA2: Assuming a vial optimisation of 50%
- ASA3: Assuming a vial optimisation of 0%
- ASA4: Assuming a minimum consumption of B-VEC equivalent to one syringe per week

In addition, the EAG ran the following additional scenario analysis following the recent changes in the company's base case. These were:

- ASA5: Using the BBE tube consumption estimated from the PLS
- ASA6 and 7: Given the uncertainty associated with the ITC estimate of relative treatment effect (see EAG report Section 3.9), the EAG wished to explore how the impact of changing this parameter, therefore the EAG ran two scenarios using a relative risk value of 2 (ASA6) and 10 (ASA7).

6. Results of the EAG's TE exploratory analyses

The six changes explored in EA1 to EA6 are combined to produce the EAG's TE base case. Each of the scenarios listed in Section 5.3 are then applied using the EAG base case as the starting point. Results are shown in Table 8.

Results show that the key driver of the difference in the ICER between the EAG's TE base case and the company's TE base case is the source of transition probabilities applied. Using the HST28 transitions for BBE and BSC and applying the ITC estimate to BBE transitions for estimating B-VEC transitions shifts the cost-effectiveness comparison from B-VEC dominance over BBE to an ICER of £[REDACTED] per QALY gained and increases the ICER versus BSC from £[REDACTED] to £[REDACTED]. Assuming a minimum of 2.34 B-VEC vials every 13 weeks has the second most significant impact where discounted costs associated with B-VEC increase from £[REDACTED] to £[REDACTED] resulting in ICERs of £[REDACTED] and £[REDACTED] versus BBE and BSC respectively. Using the average tube consumption from EASE to estimate BBE treatment costs decreases the discounted costs associated with BBE from £3,800,000 to £2,800,000.

When including all the changes preferred by the EAG, the deterministic ICERs were £[REDACTED] and £[REDACTED] versus BBE and BSC respectively (probabilistic ICERs are £[REDACTED] and £[REDACTED] respectively). The EAG's scenario analyses show that the results are sensitive to the ITC estimate and how it's applied in addition to the minimum weekly number of B-VEC vials assumed.

Table 8: Results of the EAG's exploratory analyses

Option	Absolute outcomes by treatment arm			Incremental			ICER of B-VEC versus comparator (£/QALY)
	Costs (£)	QALYs (patients)	QALYs (carers)	Costs (£)	QALYs (patients)	QALYs (carers)	
Company's TE base case (Deterministic)							
B-VEC	████████	13.03	36.19	████████			
BBE	3,790,795	9.45	34.35	████████ 1	3.57	1.84	Dominant
BSC	1,349,644	5.71	31.14	████████	7.32	5.05	████████
EAG EA1: Correction of model errors in the company's TE economic model							
B-VEC	████████	13.11	36.24	████████			
BBE	3,793,382	9.48	34.37	████████ 1	3.62	1.87	Dominant

Option	Absolute outcomes by treatment arm			Incremental			ICER of B-VEC versus comparator (£/QALY)
	Costs (£)	QALYs (patients)	QALYs (carers)	Costs (£)	QALYs (patients)	QALYs (carers)	
BSC	1,349,916	5.72	31.15	██████	7.39	5.09	██████
EAG EA2: Transition probabilities used in the EAG TE base case from HST28 for BBE and BSC (after continuity correction) and applying the ITC estimate to BBE transitions for B-VEC							
B-VEC	██████	12.51	36.61				
BBE	3,252,499	10.45	35.91	██████	2.06	0.70	██████
BSC	1,202,610	7.97	34.35	██████	4.54	2.27	██████
EAG EA3: Apply a minimum of 2.34 vials of B-VEC each 13 weeks							
B-VEC	██████	13.03	36.19				
BBE	3,790,795	9.45	34.35	██████	3.57	1.84	██████
BSC	1,349,644	5.71	31.14	██████	7.32	5.05	██████
EAG EA4: Use the mean BBE tube consumption from EASE for all states							
B-VEC	██████	13.03	36.19				
BBE	2,808,013	9.45	34.35	██████	3.57	1.84	Dominant
BSC	1,349,644	5.71	31.14	██████	7.32	5.05	██████
EAG EA5: Assuming the same baseline distribution from EASE							
B-VEC	██████	13.71	36.87				
BBE	2,483,759	11.86	36.04	██████	1.85	0.83	Dominant
BSC	1,036,399	9.23	34.44	██████	4.48	2.43	██████
EAG EA6: Exclusion of clinical manifestations and concomitant medications							
B-VEC	██████	13.03	36.19				
BBE	3,385,844	9.45	34.35	██████	3.57	1.84	Dominant
BSC	900,389	5.71	31.14	██████	7.32	5.05	██████
EAG base case applying EAs 1+2+3+4+5+6 (Deterministic)							
B-VEC	██████	13.12	36.92				
BBE	2,235,990	11.26	36.51	██████	1.86	0.41	██████
BSC	572,399	9.17	35.08	██████	3.95	1.84	██████
EAG base case applying EAs 1+2+3+4+5+6 (Probabilistic)*							
B-VEC	██████	49.61					
BBE	2,267,138	47.21		██████	2.40		██████
BSC	647,155	43.14		██████	6.47		██████
EAG ASA1: EAG base case + estimating the transitions for B-VEC by applying the RR value for complete wound closure only to the transitions to HS1							
B-VEC	██████	12.75	36.74				

Option	Absolute outcomes by treatment arm			Incremental			ICER of B-VEC versus comparator (£/QALY)
	Costs (£)	QALYs (patients)	QALYs (carers)	Costs (£)	QALYs (patients)	QALYs (carers)	
BBE	2,235,990	11.26	36.51	████████	1.48	0.23	████████
BSC	572,399	9.17	35.08	████████	3.58	1.66	████████
EAG ASA2: EAG base case + assuming vial optimisation for B-VEC of 50%							
B-VEC	████████	13.12	36.92	████████	████████	████████	████████
BBE	2,235,990	11.26	36.51	████████	1.86	0.41	████████
BSC	572,399	9.17	35.08	████████	3.95	1.84	████████
EAG ASA3: EAG base case + assuming vial optimisation for B-VEC of 0%							
B-VEC	████████	13.12	36.92	████████	████████	████████	████████
BBE	2,235,990	11.26	36.51	████████	1.86	0.41	████████
BSC	572,399	9.17	35.08	████████	3.95	1.84	████████
EAG ASA4: EAG base case + assuming a minimum of one vial per cycle							
B-VEC	████████	13.12	36.92	████████	████████	████████	████████
BBE	2,235,990	11.26	36.51	████████	1.86	0.41	████████
BSC	572,399	9.17	35.08	████████	3.95	1.84	████████
EAG ASA5: EAG base case + using the BBE tube consumption estimated from the PLS							
B-VEC	████████	13.12	36.92	████████	████████	████████	████████
BBE	2,464,137	11.26	36.51	████████	1.86	0.41	████████
BSC	572,399	9.17	35.08	████████	3.95	1.84	████████
EAG ASA6: EAG base case + using an ITC estimate of 2							
B-VEC	████████	12.77	36.85	████████	████████	████████	████████
BBE	2,235,990	11.26	36.51	████████	1.51	0.34	████████
BSC	572,399	9.17	35.08	████████	3.60	1.77	████████
EAG ASA7: EAG base case + using an ITC estimate of 10							
B-VEC	████████	13.54	37.00	████████	████████	████████	████████
BBE	2,235,990	11.26	36.51	████████	2.28	0.48	████████
BSC	572,399	9.17	35.08	████████	4.37	1.92	████████

*QALYs are only reported as totals in the PSA in the economic model

Abbreviations: ASA - additional sensitivity analysis; B-VEC - beremagene geperpavec; BBE - birch bark extract; BSC - best supportive care; EA - exploratory analysis; ICER - incremental cost-effectiveness ratio; ITC - indirect treatment comparison; QALY - quality-adjusted life year

7. Discussion

The EAG considers that there remains significant uncertainty regarding the PLS structure and its assumptions. Whilst the company has tried to update the PLS to include BBE, the generated transitions deviated considerably from the ones directly estimated from EASE which lacked face validity. In addition, the changes in assumptions (such as the assuming a portion of chronic wounds will not respond to B-VEC or BBE) and in parameters (such as assigning a lower healing rate for chronic wounds on B-VEC) intended to make the simulation more realistic, however the EAG's concerns, which were mentioned in the EAG main report, remain. This may highlight the challenges in micro simulating such a chronic condition, where simplifying wound dynamics such as assuming an exponential rate of healing could be considered a strong assumption.

Considering the issues with the PLS and in absence of other data sources, the EAG decided to continue using the transition probabilities from HST28 for BBE and BSC. For B-VEC, the ITC estimate calculated by the EAG in its main report was applied to the transitions of BBE to generate those of B-VEC. The EAG would have preferred to use the transitions preferred by the EAG/Committee of the HST, however these were redacted. Hence, the EAG used the unredacted transitions, acknowledging that the currently used BBE transitions are favourable for BBE versus BSC. However, because the ITC estimate is applied to the BBE transitions, it can be inferred that the B-VEC transitions are also favourable for B-VEC versus BSC.

The EAG finds the TE Markov model, which is based on the six-state structure, satisfactory and adopts it to build its base case and scenario analyses. The EAG base case preferences led to deterministic ICERs in the range of [REDACTED] and [REDACTED] for B-VEC when compared to BBE and BSC respectively. The EAG's scenario analyses demonstrate that these ICERs could increase further if applying the RR from the ITC to fewer transitions or if less favourable assumptions were made regarding vial sharing or minimum vial usage per week. In addition, the results are expectedly sensitive to the ITC estimate.

8. References

1. National Institute for Health & Care Excellence. Single Technology Appraisal - Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]. Technical engagement response form. (Company response). 2026.
2. National Institute for Health and Care Excellence (NICE). Beremagene geperpavec for treating wounds associated with epidermolysis bullosa: EAG report.; 2025.
3. Krystal Biotech. Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]: Company evidence submission. London, UK: National Institute for Health and Care Excellence.; 2025.
4. Has C, Nyström A, Saeidian AH, Bruckner-Tuderman L, Uitto J. Epidermolysis bullosa: Molecular pathology of connective tissue components in the cutaneous basement membrane zone. *Matrix Biol* 2018;71-72:313-29.
5. Toyonaga E, Nishie W, Komine M, Murata S, Shinkuma S, Natsuga K, *et al.* Skipped exon in COL7A1 determines the clinical phenotypes of dystrophic epidermolysis bullosa. *Br J Dermatol* 2015;172:1141-4.
6. FDA Center for Drug Evaluation and Research. Multi-discipline review of Filsuvez.; 2023.
7. Davidovic M, Gewert S, Has C. Real-World Experience With Oleogel-S10 for Wounds in Epidermolysis Bullosa. *JEADV Clinical Practice*;n/a.
8. Fulchand S, Nazarov J, Harris N, So JY, Villanueva Gaona R, Alvarez E, *et al.* Natural history study of recessive dystrophic epidermolysis bullosa wounds and patient reported outcomes using mobile application home photography. *Sci Rep* 2025;15:28767.
9. Gurevich I, Agarwal P, Zhang P, Dolorito JA, Oliver S, Liu H, *et al.* In vivo topical gene therapy for recessive dystrophic epidermolysis bullosa: a phase 1 and 2 trial. *Nat Med* 2022;28:780-8.
10. Eng VA, Solis DC, Gorell ES, Choi S, Nazarov J, Li S, *et al.* Patient-reported outcomes and quality of life in recessive dystrophic epidermolysis bullosa: A global cross-sectional survey. *J Am Acad Dermatol* 2021;85:1161-7.
11. Suzuki S, Gilbar P, Yu B, Matsuyama C, Yamaguchi M. Current status of drug vial optimization use to prevent waste associated with injectable anticancer agents. *J Oncol Pharm Pract* 2019;25:244-6.
12. Gilbar PJ, Chambers CR, Musicco F. Preventing drug vial wastage and reducing expenditure associated with injectable cancer drugs: International oncology pharmacy survey. *J Oncol Pharm Pract* 2022;28:1332-9.
13. National Institute for Health and Care Excellence (NICE). Birch bark extract for treating epidermolysis bullosa: final draft guidance. In; 2023.
14. Oakley, J.E. and O.H. Tony. The Sheffield Elicitation Framework (SHELF). 2026. <https://shelf.sites.sheffield.ac.uk/> (Accessed
15. University of Sheffield. Technical support document 26: Expert elicitation for long-term survival outcomes.; 2025.

Committee Briefing

Explanation

This page details the Managed Access Team's overall assessment on whether a medicine could be suitable for Managed Access and if data collection is feasible. The feasibility assessment does not provide any guidance on whether a medicine is a cost-effective, or plausibly cost-effective, use of NHS resources. This document should be read alongside other key documents, particularly the company's evidence submission and External Assessment Group (EAG) Report. Further detail for each consideration is available within the separate tabs.

The feasibility assessment indicates whether the Managed Access Team have scheduled to update this document, primarily based on whether it is undertaking actions to explore outstanding issues. There may be other circumstance when an update is required, for example when the expected key uncertainties change or a managed access proposal is substantially amended. In these cases an updated feasibility assessment should be requested from the Managed Access Team.

Topic name:

Topic ID:

Managed Access Lead:

Date of assessment(s):

Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa

ID3959

Sarika Paul

16/07/2025

Feasibility of successful managed access	Comments / Rationale	
No managed access proposal	Rationale for rating	There is no managed access proposal and no ongoing studies. The uncertainties identified by the EAG may benefit from further real world evidence data collection, but a proposal would need to be submitted to enable this.
	Previous ratings and rationale for change	

Managed Access Proposal	No	
Managed Access Team input at Committee meeting	Low	Limited input expected at committee meeting.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	This technology is eligible for managed access through the IMF, though no proposal has been made to enable this.
Are there outstanding uncertainties that could be resolved with further data collection?	Low	Many of the uncertainties identified by the EAG could be resolved with the addition of good real world evidence, however no managed access proposal has been made to enable this.
Can data collection from ongoing clinical trials and RWE sources resolve relevant uncertainties?	No	There are no ongoing trials listed by the company in their submission, and no registries proposed for further data collection.
Are there any other points to note that suggest RWE data collection may be beneficial or challenging in resolving uncertainties?	Low	No managed access proposal has been made, so no RWE data collection has been proposed.
Are there any other substantive issues (excluding price) that are a barrier to a MAA?	Not applicable	As there is no proposal, this has not been investigated in detail

Key questions for committee if Managed Access is considered	
1	
2	
3	

4	
5	
6	

Highlighted uncertainties, other issues or ongoing Managed Access Team actions	
1	
2	
3	
4	
5	
6	