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

For projector – contains no confidential information

Highly specialised technology appraisal committee [21 May 2026]

Chair: Paul Arundel

Lead team: Iolo Doull, Ed Wilson, Tina Garvey

External assessment group: Sheffield Centre for Health and Related Research (SCHARR)

Technical team: Emma Douch, Alan Moore, Christian Griffiths

Company: Krystal Biotech

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

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Background on dystrophic epidermolysis bullosa (DEB)

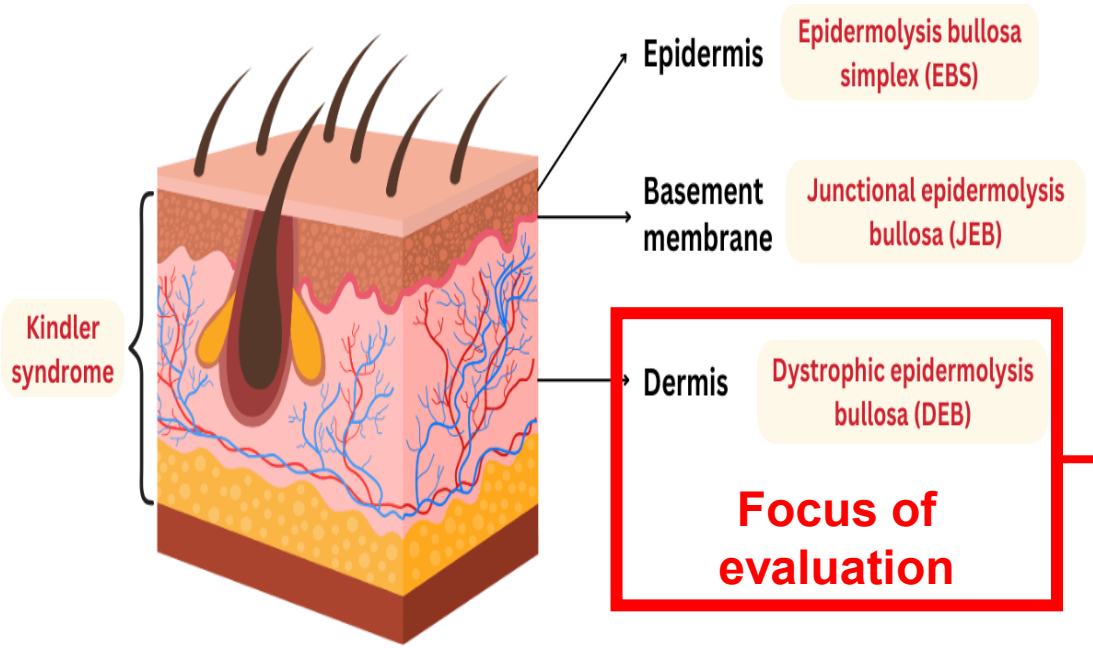
Rare genetic condition causing skin fragility & painful, slow-healing wounds; large QoL impact.

Epidermolysis bullosa (EB): general term for group of lifelong rare inherited skin disorders

- Caused by disrupted skin anchoring proteins

Classification: according to where on body blistering occurs and layer of skin affected

Different types of EB



Dystrophic epidermolysis bullosa (DEB): Blistering in inner layer of skin (dermis) caused by human COL7A1 gene mutations

Epidemiology: ~25% of EB cases. ~625 to 1,150 people in UK*.

Symptoms: Usually presents at birth/early childhood. Large QoL impact from:

- Skin tearing after minor trauma, reduced healing, digit fusion
- Internal manifestations (eye, mouth, oesophagus and stomach with damage, scarring and pain)

Severity: Influenced by location of mutation, environmental and familial factors

❖ Dominant (DDEB): mildest form, blistering may be limited to hands, feet, knees, and elbows; near-normal life expectancy

❖ Recessive (RDEB): more severe, blistering may be widespread; increased risk of skin cancers with associated mortality risk of up to ~80% by age 55 (severe cases)†

COL7A1, Collagen Type VII Alpha 1 Chain; QoL, quality of life

Source: *Petrof et al 2022 (1 in 90,000) and Horn et al 1998 (1.02 per 50,000).
† Robertson et al. 2021

Natural history of dystrophic epidermolysis bullosa (DEB)

Dynamic cycle of wound healing and reopening, with new wounds frequently occurring

1. Wound opens with daily actions such as rubbing, scratching, or light bumps
- Blistering at the dermal-epidermal junction (DEJ)

2a. Recurrent wounds
- Tend to be small-to-medium in size Tend to heal spontaneously, most within 3 weeks
- Blister easily

2b. Chronic wounds
- Tend to be larger and more painful
- Tend to remain open for >4 weeks (defintion varies throughout literature)
- Sometimes never heal

3. Wound reopens especially in areas of frequent friction, resulting in a continuous cycle of opening and closing

New wounds open elsewhere on body, restarting the cycle of healing and re-opening

3. Potential tumour formation and early onset SCC caused by immune exhaustion and dysregulation from persistent inflammation & bacterial colonisation

B-VEC, Beremagene geperpavec; DDEB, dominant dystrophic epidermolysis bullosa: EB, epidermolysis bullosa; RDEB, recessive dystrophic epidermolysis bullosa; SCC, squamous cell cancer

- Does this diagram capture the natural history of EB? For DDEB and RDEB?
- Are larger wounds harder to close than smaller ones?
- Are new wounds that open normally limited to specific body areas? Would these be expected to respond differently to B-VEC than re-opened wounds?

Patient perspectives (1)

Submissions from CureEB, DEBRA and patient experts at TE

DEB is a devastating, multi-organ condition causing constant pain, chronic wounds and emotional distress

- Wounds triggered by minimal friction (even sleep); may persist for years or lifelong
- Progressive disability: repeated damage causes scarring and mitten deformities, limiting hand use and mobility
- High psychological burden from life-long relentless pain, exhausting daily wound care, lack of independence and stigma associated with physical appearance of wounds
- Financial & educational impact: disrupted education/work; many carers leave work to provide full-time care

Huge unmet need for targeted treatments → current treatments only manage symptoms with limited benefit

- Daily wound care: may take hours, exhausting, painful (sometimes requiring morphine), with heavy physical, emotional, and financial strain on families and patients
- Only 1 approved wound healing cream (birch bark extract) with strict usage criteria and varied reported benefit

B-VEC offers first targeted gene therapy with potential for improved wound healing and QoL

- High impact even if modest benefit: longer closure = less infections, better mental health, independence, family wellbeing, lower care burden. Potential reduced cancer risk and NHS costs (dressings, pain relief, clinical time)
- Home administration essential to reduce travel burden and ensure equitable access
- Easy to apply within existing wound-care routines but restricted by surface-area limits and EB subtype eligibility.
- Reductions in dressing time and dressing use unlikely to be captured in QALY estimates.
- Reduced opioid use during dressing changes → fewer long-term risks & acute side effects (sedation, nausea)
- Some people may develop antibodies to B-VEC

B-VEC, Beremagene geperpavec; DEBRA, Dystrophic Epidermolysis Bullosa Research Association; EB, epidermolysis bullosa; QoL, quality of life; QALY, quality adjusted life years; TE, technical engagement

Background to DEB symptoms

DEBRA EB Insight study shows widespread symptoms; B-VEC localised treatment for skin

Eye symptoms including corneal abrasions (63%)

Scarring alopecia on scalp

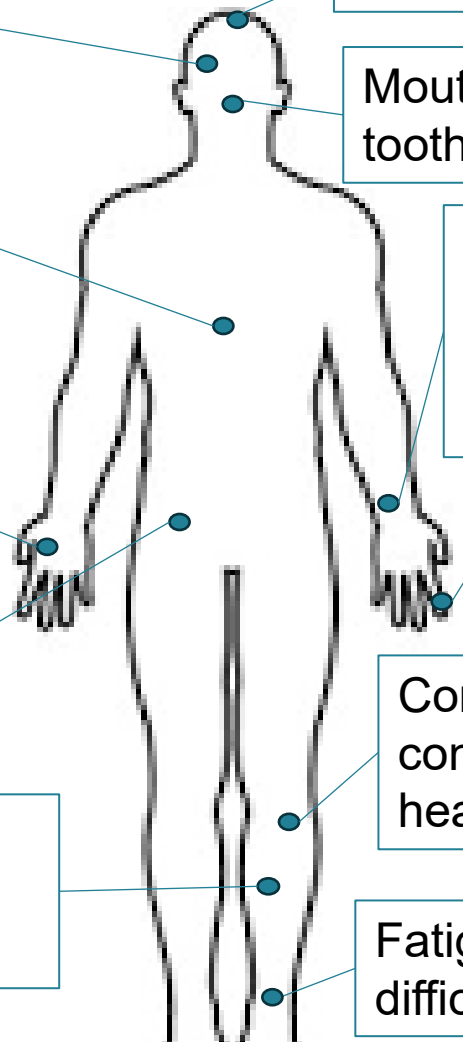
Mouth/dental symptoms (85%) including tooth decay, shortened tongue, small mouth

GI symptoms (84%): Painful swallowing (dysphagia), anaemia and malnutrition from blisters inside mouth, throat, and GI tract

Fragile (88%) and painful (79%) skin that blisters easily from mild friction, especially on the palms and feet → causes scarring and milia (small white bumps, 73%)

Fusion of fingers and toes (28%) and restricted joint movement from scarring

Thickened, discoloured, misshapen, or completely absent fingernails & toenails (75%)



Renal complications due to mucosal lesions or glomerular disease

Constant itch from continuous wound healing (90%)

High risk of SCC (especially recessive DEB) and constant itch from continuous inflammation and wound healing

Fatigue (65%) and difficulty sleeping (61%)

Underlying cause directly treated by beremagene geperpavec (B-VEC): localised, re-dosable treatment applied to skin

Psychological impact: 70% report EB has negative impact on self-confidence, with 50% experiencing bullying or abuse due to their EB

B-VEC, Beremagene geperpavec; DEB, dystrophic epidermolysis bullosa; GI, gastrointestinal; SCC, squamous cell cancer

Patient perspectives (2)

Living with EB

"Living with this condition is horrific, it's very painful, hours and hours of wound care and dressings changes. …The itching... is nearly as bad as the pain"

"My son…was born with no skin on his feet, knees, and hands and even where there was intact skin, it blistered"

"The impact to their mental health cannot be underestimated"

"The wounds look like raw meat, blisters are sometimes as big as a golf ball."

"…seams in my clothes rub holes in my skin…"

Current treatments

…there is one 'treatment' available on the NHS… We have found that it is only beneficial on superficial wounds"

"From birth, management of the condition requires lengthy dressing changes that can take between two and five hours daily."

"We had to use morphine because dressing changes were so painful."

Perspectives on B-VEC

"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"

"If B-VEC improves wound healing, the impact would be incredible. Hopefully less pain, reduced dressing change time, more robust skin and reduced itch."

"It doesn't cure the disease, but it has been a complete game changer…"

"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."

Clinical perspectives

Submissions from British Association of Dermatologists (BAD) and clinical experts at TE

Major unmet need in DEB:

- EB causes constant and debilitating pain from birth and can be fatal in severe cases
- Large QoL impact, including on families, who must be trained on wound care
- Pathway of care well defined with little geographical variation
    - ❖ Current care: birch bark extract (BBE): benefit in only ~50% and no impact on recurrence; used with supportive care (complex wound care, pain management, nutritional & psychological support)
- Treatment aim: faster healing, longer closure, fewer infections/complications (SCC, anaemia, osteoporosis)
- Clinically significant response = durable complete closure of >50% treated wounds

Beremagene geperpavec is a "potential game changer" for EB

- First topical gene therapy for DEB, restores type VII collagen; good safety, re-dosable but not curative
- Benefits from wound closure: less pain/itch, fewer infections, reduced wound care and may reduced SCC risk
- Weekly administration in 4 specialised centres by 2 healthcare professionals and 2-4 hours per patient
    - Challenges: trained staff, aseptic prep, pharmacy/nursing/day-care capacity
    - Option for home use after training; issues with stability, delivery, vial sharing
    - No extra monitoring needed
- Potential for development of anti-type VII collagen antibodies but clinical impact unclear

B-VEC, Beremagene geperpavec; DEB, dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; QoL, quality of life; SCC, squamous cell cancer; TE, technical engagement;

Equality considerations

Stakeholders raised inequalities related to socioeconomic status and B-VEC access by location

Company: Many people with DEB meet the Equality Act 2010 disability criteria due to progressive scarring that leads to hand/foot abnormalities

- Families face high costs associated with raising children with disability, difficulties accessing health and social care, and financial strain when supporting family members with disability — often more pronounced in minority ethnic communities

Patient organisation: DEBRA, BAD, patient expert at TE

- Outpatient treatment for B-VEC could create additional burden → travel time and costs potentially worsening inequalities for those living far from specialist centres or lacking financial resources
- Treatment available only at specialist centres → inequalities in access disproportionally effect those on low income or with language barriers → may increase time required to interact with health services
- Only available for dystrophic EB → patients with acute and chronic wounds likely benefit most due to long-term healing effects

- Are there any inequality issues that need to be considered in decision-making?

BAD, British Association of Dermatologists; B-VEC, Beremagene geperpavec; DEB, dystrophic epidermolysis bullosa; DEBRA, Dystrophic Epidermolysis Bullosa Research Association; EB, epidermolysis bullosa; TE, technical engagement

Treatment pathway

Link to supplementary appendix: decision problem and population having BBE

Clinical expert: consensus over UK pathway but patient & carer preference influence regimen
→ manage wounds on case-by-case basis
- Multi-disciplinary management at 1 of 4 specialist centres in UK

Best supportive care measures

Intervention	Aim
Lancing & draining blisters	Prevent expansion
Dressings & regular bathing	Minimise infection risk
Antibiotics	Treat infection
Analgesics, antipruritics, nonadherent wound dressings	Treat pain and itch
Dental care	Improve dental hygiene & nutrition
Long-term enteral feeding	Meet nutritional needs (severe EB)
Psychiatric medication	Manage itch
Topical MediHoney	Promote healing, reduce infection
Laxatives	Relieve associated constipation

Pharmaceutical treatment options

Birch bark extract (BBE)
- Partial thickness wounds only
- DEB and JEB
- Use from 6 months or older

AND

OR

Beremagene geperpavec (B-VEC)
- Any wound
- DEB with mutation in COL7A1 gene
- Use from birth

B-VEC, Beremagene geperpavec; EB, epidermolysis bullosa

- Is there a defined pathway of care for EB?
- How is BBE currently used? Are there any restrictions on use? Does this align with expected use of B-VEC?
- Where is EB currently managed? Would B-VEC be given at specialist centres?
- What are the most appropriate comparators for the population having B-VEC in clinical practice?

Beremagene geperpavec (B-VEC) (Vyjuvek, Krystal Biotech)

Re-dosable gene therapy with dose based on age and wound size

Marketing authorisation

- 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."
- EMA licence granted April 2025. MHRA licence granted May 2026

Mechanism of action

Topical, re-dosable gene therapy that delivers functional *COL7A1* gene to restore COL7 production and normalise anchoring fibril formation

Administration

- Applied cutaneously to wounds once a week with dose based on age and wound size:

Age	Dose (PFU)	Volume (mL)
≤3 years	Max 2×10^9	Max 1ml
>3 years	Max 4×10^9	Max 2ml
Wound area (cm^2)	**Dose (PFU)**	**Volume (mL)**
< 20	< 4×10^8	< 0.2
20 to < 40	4×10^8 to < 8×10^8	0.2 to < 0.4
40 to 60	8×10^8 to < 1.2×10^9	0.4 to < 0.6
60 to < 200	1.2×10^9 to < 4×10^9	0.6 to < 2

- Wounds should be treated until closed before selecting new wound(s) to treat
- If wounds re-open they should be prioritised for weekly treatment

Price

- List price: £21,500 per 1 ml vial of B-VEC (4 extractable 0.5ml doses when prepared)
- List price 12 months of treatment (pre-TE): Year 1: [redacted] reducing to [redacted] by Year 5*
- A patient access scheme has been approved

*Source: Company budget impact analysis submission, April 2025

cm, centimetres; mL, millilitres; PFU, Plaque-Forming Unit, TE, technical engagement

Key issues

Key issue	ICER impact	Resolved?
Limited clinical evidence in people with dominant DEB (DDEB)	Uncertain	No – for discussion
Lack of ITC between B-VEC (GEM-3 study) and BBE (EASE study)	Large	No – for discussion
Appropriate health state utility estimates	Large	Yes – see supplementary appendix
Validity of the company's patient level simulation as a source of clinical effectiveness and drug usage	Large	No – for discussion
Algorithm to map 6-state to 4-state model structure lacks face validity	Large	Yes – see supplementary appendix
Uncertain association between reduced clinical manifestations and mortality in patients with reduced wound burden	Large	No – for discussion
People who stop treatment stay in health state they occupy when discontinuing	Small	Yes – see supplementary appendix
Company assumes vial sharing in 80% of people	Small	No – for discussion
No modelling of B-VEC and BBE used concurrently	Uncertain	No – for discussion
Administration costs and resource use may be underestimated	Medium	No – for discussion

BBE, birch bark extract; B-VEC, Beremagene geperpavec; ICER, Incremental Cost-Effectiveness Ratio
Small impact: <5% increase on ICER; Medium impact: 5-20% ICER change; Large impact: >20% ICER change

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

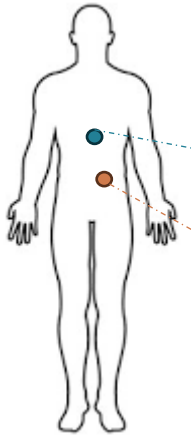
- ❑ Background and key issues
- ✓ **Clinical effectiveness**
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Key clinical trial, GEM-3

Phase III, intra-patient, double-blinded, RCT

GEM-3 trial design



Random treatment allocation (N=31)

6-month treatment period or until wound closure*

30 days after last B-VEC dose

Wound 1: weekly treatment with B-VEC

Wound 2: weekly treatment with placebo

Safety follow up period

GEM-3 OLE Open label extension study (N=24)

GEM-3 trial aspects

Population	≥6 months with genetically confirmed clinical diagnosis of DEB including *COL7A1* mutations. 2 cutaneous wounds: similar size, appearance, region on body
1° outcome	% 1° wounds with complete closure at 6 months
Key 2° outcomes	Key endpoint: % wounds with complete closure at 3 months • Δ in pain severity during changes in wound dressing. **Exploratory endpoints:** Δ in general HRQoL(EQ-5D-5L) and skin-specific HRQoL (Skindex-29)

Response defined as: 100% wound closure from exact wound area selected at baseline (investigator determined skin reepithelialisation without drainage) for at least 2 consecutive weeks

Dosing of B-VEC in GEM-3 trial

Age	Dose (PFU)
≥6 months to <3 years	Max 1.6×10^9
≥3 to < 6 years	Max 2.4×10^9
≥6 years	Max 3.2×10^9
Wound area (cm^2)	**Dose (PFU)**
< 20	4×10^8
20 to <40	$< 8\times10^8$
40 to 60	1.2×10^9
- Remaining B-VEC used on ≥4 2° wounds up to max weekly dose - Wounds that reopen treated at next visit + some open wounds next to closed 1° wound	

cm, centimetre; B-VEC, Beremagene geperpavec; DEB, dystrophic epidermolysis bullosa: HRQoL, health related quality of life; N, number; OLE, open label extension; PFU, Plaque-Forming Unit; RCT, randomised controlled trial

Baseline characteristics in B-VEC trials

Characteristic	GEM-3 (n=31)*	GEM-1 (n=11)
Age		
Median (range), years	16.1 (1–44)	21.0 (13–35)
≤12 years, n (%)	10 (32)	NR
>12 to ≤18 years, n (%)	9 (29)	NR
>18 years, n (%)	12 (39)	NR
N male (%)	20 (65)	8 (73)
Size of target wound		
Median (range), cm2	BVEC: 10.6 (2.3–57.3), Placebo: 10.4 (2.3–51.5)	NR
<20 cm^2, n (%)	B-VEC: 23 (74), Placebo: 22 (71)	NR
20 to <40 cm^2, n (%)	B-VEC: 6 (19), Placebo: 8 (26)	NR
40 to 60 cm^2, n (%)	B-VEC: 2 (6), Placebo: 1 (3)	NR

Technical team:

- B-VEC licence includes wound size up to 200 cm^2 → no data in wound sizes over 60cm^2

- Are baseline characteristics from clinical trials reflective of people who would have B-VEC in clinical practice?
- What proportion of EB wounds are >60 cm^2? Would these wounds be treated with B-VEC?

NICE

cm, centimetre; B-VEC, Beremagene geperpavec; n, number

Key clinical trial results

More wounds closed with B-VEC than placebo at 3 and 6 months in GEM-3

GEM-3: Key endpoint analyses

Endpoint (ITT population)	B-VEC (n=31)	Placebo (n=31)	Absolute difference, % (95% CI)
1° endpoint: complete wound closure at 6 months,* n (%)	20.9 (67)	6.7 (22)	46 (24–68) p = 0.002
Key 2° endpoint: complete wound closure at 3 months,† n (%)	**21.9 (71)**	**6.1 (20)**	51 (29–73) p = <0.001
Durability of response,‡ n (%)	15.4 (50)	2.2 (7)	42.6 (23–63)

Complete wound closure = investigator determined 100% wound closure (skin reepithelialisation without drainage) from exact area selected at baseline. Multiple imputation methods to account for missing data leading to fractional counts . Primary wounds assessed at *Weeks 22+24 or 24+26 or †Weeks 8+10 or 10+12. ‡ Supplemental analysis defined as meeting the 1° and key 2° endpoint simultaneously at both at 3 & 6 months

Other key results

GEM-3 (results B-VEC vs. placebo):

- No statistically significant reduction in pain severity
- *General and skin-specific HRQoL (≥12 years):* improvements in EQ-5D, similar Skindex-29 results

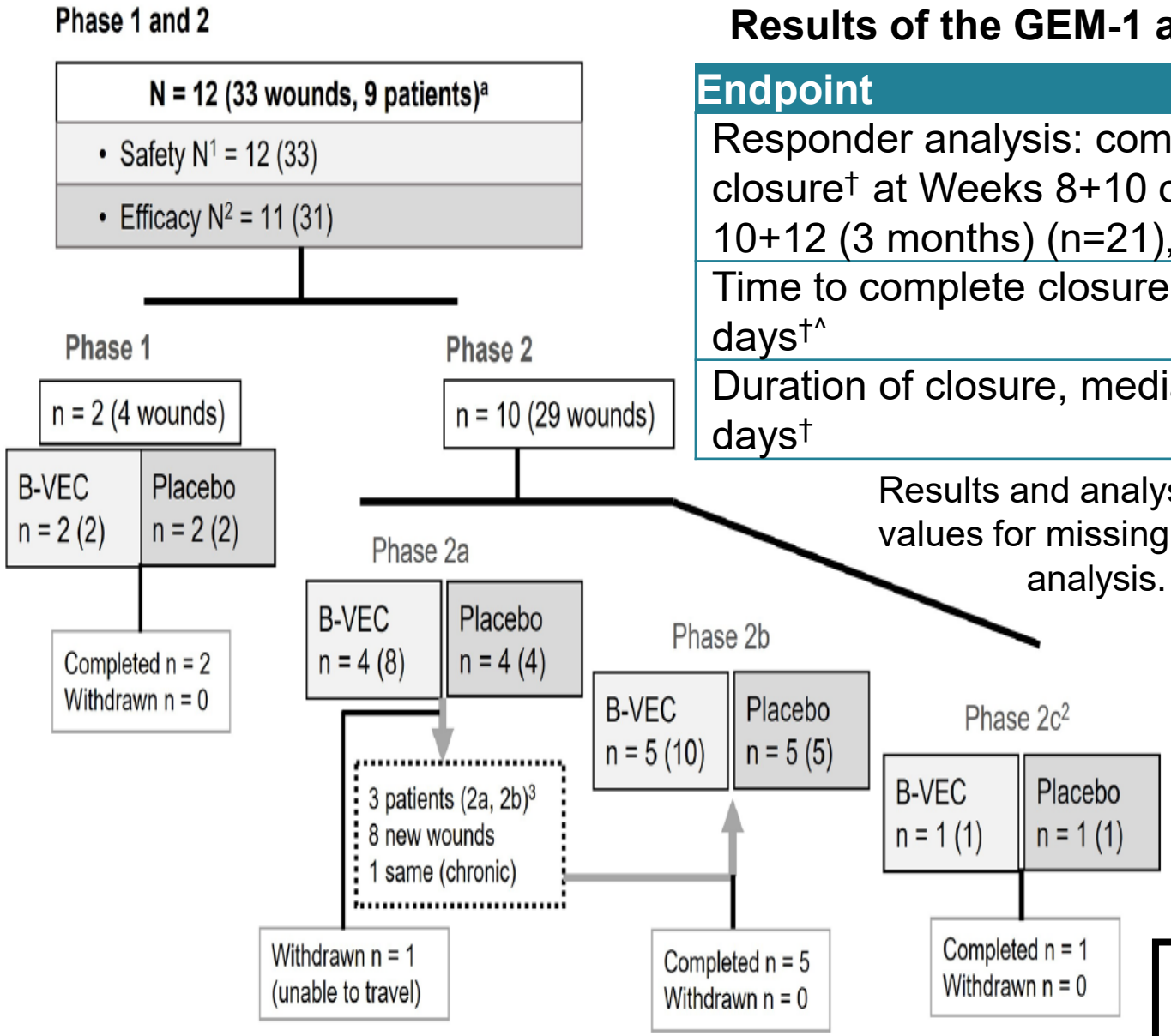
GEM-3 OLE: 10/16 (63%) GEM-3 rollover subjects had ongoing response at 12 months

EAG comments: varying 1° outcome imputation method varies absolute difference by ≤8%

- ~20% placebo-treated wounds fully closed → suggests recurrent wounds that may heal in 21 days and unclear if distribution even across arms
- Cannot attribute HRQoL change to specific treatment arm in GEM-3 given intra-patient design

B-VEC, beremagene geperpavec; CI, confidence interval; HRQoL, health related quality of life; OLE, open label extension; ITT, intent-to-treat, n, number;. **Purple**: used in EAG base case.

Key clinical trial, GEM-1 and 2



B-VEC, beremagene geperpavec; CI, confidence interval; n, number

Results of the GEM-1 and 2 studies

Endpoint	B-VEC	Placebo*	P value
Responder analysis: complete wound closure† at Weeks 8+10 or Weeks 10+12 (3 months) (n=21), n (%)	11/14 (79)	0/7 (0)	-
	Difference: 79%		0.0026‡
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 (94–118)	16.5 (0–66)	0.0009

Results and analysis reported based upon observed data without imputed values for missing data. *N=1 not imaged and excluded from responder analysis. †Complete closure = ≥90% reduction in wound surface area from baseline.‡ Significant at p<0.025. Phase 1 protocol collected wound closure data at weeks 6 & 12 (no Week 8 or 10 datapoints), so phase 1 patients excluded from the responder analysis. ^Time to wound closure = time from 1st treatment to complete wound closure (for 2 consecutive weeks)
Green: used in company base case

EAG : Less stringent definition of wound closure vs. GEM-3 (>90% vs 100% reduction in wound area)

Key Issue: Limited data in dominant DEB (DDEB)

Almost all clinical evidence from RDEB (more severe) subtype

Background: Clinical effectiveness data comes predominantly for people with RDEB (more severe genotype):

- only N=1 in GEM-1 and GEM-3 trials with an extra N=1 treatment naïve patient in GEM-3 OLE

Company: Acknowledge limited data specific to DDEB → consequence of condition rarity

Consider in context of substantial disease burden with unmet need → no curative treatments:

- BBE recommended for RDEB and DDEB despite lack of difference in 1° endpoint vs placebo in the DDEB subgroup of pivotal trial (EASE) and early access authorisation report shows only modest benefit
- Mechanism of action expected to be effective in RDEB and DDEB
  - ❖ Biology (loss of functional COL7, compromised dermal-epidermal adhesion) shared between subtypes
  - ❖ DDEB included in global regulatory decisions for B-VEC
  - ❖ Response in DDEB supported by:
    - US evidence: DDEB responded to B-VEC (29% of people treated in US have DDEB)
    - GEM-3 OLE: complete closure of B-VEC treated wounds with durable response in N=2 with DDEB
    - Collecting more data in DDEB through post-authorisation study

EAG: cannot determine if treatment effect consistent across DEB subtypes given that clinical evidence from GEM-1 and 3 predominantly in RDEB patients:

- Clinical expert: biological rationale for varying effect by subtype as DDEB has one functional COL7A1 allele (vs none in RDEB) → may be less severe collagen abnormalities and different biological response
- No subgroup analysis or pre-planned subgroups in GEM-1 or 3 by subtype

B-VEC, Beremagene geperpavec; COL7, Type VII Collagen; DDEB, dominant dystrophic epidermolysis bullosa: N, number; OLE, open label extension; RDEB, recessive dystrophic epidermolysis bullosa

Key Issue: Limited data in dominant DEB

EAG (cont.): Lack of subtype differences in EASE may not generalise to B-VEC, as BBE does not replace COL7 → unaffected by presence of non-mutated COL7A1 gene

- US data limited, subject to bias & not presented by company

Scenario: 100% modelled population have RDEB (better aligns with GEM-3 population)

NICE technical team: EAG HST28: potential difference in BBE efficacy by subtype unresolvable issue → recommended in full licenced population. Model assumes differences in mortality by subgroup so % RDEB vs DDEB may impact severity calculations.

Distributions of subgroups in key clinical trials and company's model

Numbers in:	Dominant (D) DEB	Recessive (R) DEB
GEM-1 (B-VEC)	0 (0%)	12 (100%)
GEM-3 (B-VEC)	1 (3%)	30 (97%)
EASE (BBE)	20 (9%)	175 (79%)
Company base case model (Bruckner et al.)	37%	63%

Stakeholders: BAD: Mechanistic rationale supports benefit in DDEB but most have low wound burden → only small numbers (likely <10%) would meet any wound-surface-area threshold for treatment eligibility

Clinical expert (at TE): Greatest benefit in severe RDEB, with potential benefit for all DEB patients

Patient expert (at TE): benefit in DDEB as wounds usually in zones → can target with B-VEC:

- Likely lower costs in DDEB as smaller BSA to treat

- How does the presentation and outcomes of DDEB differ vs. RDEB in clinical practice?
- Would B-VEC be used in people with DDEB in the NHS in England. If yes, how would treatment eligibility be determined? Would DDEB be expected to respond differently to treatment with B-VEC than RDEB?
- What % have RDEB and DDEB in clinical practice and what % of each subtype would have B-VEC?
- How should this issue be considered in any recommendation?

BAD, British Association of Dermatologists; BBE, birch bark extract; B-VEC, Beremagene geperpavec; BSA, body surface area; COL7, Type VII Collagen; DDEB, dominant dystrophic epidermolysis bullosa: HST, highly specialised technology; N, number; RDEB, recessive dystrophic epidermolysis bullosa; TE, technical engagement

Key issue: Comparative effectiveness

Issue 1a: Company's lack of ITC for B-VEC vs BBE

Background: company state ITC not feasible → base relative effectiveness on a patient level simulation (PLS) for all treatments (see key issue slides)

Company: ITC using GEM trials and EASE data not feasible because:

1. Differences in study designs: frequency of placebo use, permitted concomitant treatments, trial design
2. Heterogenous patient population: median age, wound size and EB subtype proportions differ
3. Differences in endpoint definitions for complete wound closure and time to wound closure (GEM trials had stricter closure thresholds and required confirmation at consecutive visits vs immediate confirmation in EASE). Statistical summaries differed (e.g., mean vs median) for change in target wound size

EAG: Acknowledge challenge in conducting ITC but absence limits ability to inform decision making

- Company approach relies on PLS of wound outcome for B-VEC & BSC which EAG considers highly uncertain

Stakeholders: **BAD**: B-VEC and BBE promote wound healing through different mechanisms (only B-VEC via collagen VII expression) → GEM-3 vs EASE trial differences make ITC impossible
Chiesi (BBE manufacturer): key differences between trials mean ITC between BBE and B-VEC not feasible with current evidence
Patient expert (at TE): endpoint of trials very different and different mechanism of action for B-VEC and BBE

BAD, British Association of Dermatologists; BBE, birch bark extract; B-VEC, Beremagene geperpavec; EB, epidermolysis bullosa: ITC, indirect treatment comparison; TE, technical engagement

Definitions of response across trials

Natural course of EB has the following stages:

- Wound closure
- Old wounds re-opening

Defintion	GEM-3 (B-VEC)	GEM-1 (B-VEC)	EASE (BBE)
Inclusion criteria for wound size	2 target wounds similar in size	• Phase 1: 2 wounds ≤10 cm^2; • Phase 2a & b: ≥3 wounds ≤20 cm^2 • Phase 2c: ≥2 wounds ≤50 cm^2	10–50 cm^2 aged ≥ 21 days to 9 months outside of anogenital region
Complete wound closure	100% healing (skin re-epithelialization without drainage)	≥90% reduction in wound surface vs. baseline	Skin re-epithelialisation without drainage
Criteria for meeting wound closure	Wounds fully closed at 3 or 6 months, confirmed at 2 consecutive visits 2 weeks apart		Any wound closed ≥ once by 45 or 90 days without further confirmation
Time to wound closure	Time from the first treatment to complete wound closure confirmed at 2 consecutive visits 2 weeks apart		Counted even if wound later re-opened
Duration of wound closure	Not collected	Time from complete closure to the first reopening of the same wound	Not collected but change in BSAP over time reported

New wounds opening in different locations on body: not collected in trials

- Are wound closure outcomes comparable across trials?
- Is BBE used in people with wound sizes outside of the trial range?

BBE, birch bark extract; B-VEC, Beremagene geperpavec; BSAP, body surface area percentage; cm, centimetre; EB, epidermolysis bullosa

Key issue: comparative effectiveness

Company derive clinical effectiveness using patient level simulation; EAG using ITC

Approaches considered in company and EAG base cases and scenarios

	Base case	Scenario
EAG	Own Bucher ITC using % with wound closure at 3 months in GEM-3 (B-VEC) and EASE (BBE) using placebo arm as common comparator (see supplementary appendix): • Complete wound closure (**RR: 3.12**, 95% CI 0.66, 14.82) vs. BBE → applied to HST28 transitions to derive B-VEC relative effectiveness • Does not rely on the multiple assumptions and inputs included in the company's approach	Assume ITC RR = 2 or 10
Company	Patient level simulation (see supplementary appendix). • EAG's ITC estimate only used for weekly % of recurrent wounds closed for BBE (wounds in EASE and GEM-3 small so likely recurrent).	Bucher ITC based on the relative change in % in each health state in replicated HST28 6-state model over 2 consecutive cycles (see supplementary appendix)

NICE Technical Team: source of clinical effectiveness is one of the biggest model drivers

- Note median wound size larger in EASE (19.20 (SD 9.398)) vs GEM-3 (BVEC: 10.6 cm^2 (range 2.3–57.3cm^2), Placebo: 10.4 cm^2 (range 2.3–51.5 cm^2)) → introduces uncertainty to EAG's ITC?

BBE, birch bark extract; B-VEC, Beremagene geperpavec; CI, confidence interval; cm, centimetre; EB, epidermolysis bullosa; HST, highly specialised technology; ITC, indirect treatment comparison; RR, relative risk; SD, standard deviation

Key issue: comparative effectiveness

Issue 1b: Appropriateness of company and EAG approaches

EAG's ITC	Company (after TE)	EAG (after TE)
Uses EASE data for BBE	Only part of open BSA treated in EASE (735 cm² vs ~1,450 cm² BSA affected) and HST28 vial use suggests only ~366 cm² treated. Disconnect with PLS where all open wounds treated	- 735 cm² is median → mean "affected wound surface area of 1100 cm² at baseline" (12% BSA) (FDA multi-discipline review) - PLS outcomes highly uncertain → prefer direct data from EASE
Uses 'approximation method' for HST28 transitions. Direct EASE transitions preferred by committee are confidential	EAG bases clinical effectiveness on transitions not used for decision making	Direct transitions from EASE less favourable to BBE vs placebo than approximated transitions → B-VEC transitions would be worse if applied ITC RR to redacted values
HST28 transitions force all severe-state patients (HS5/HS6) to improve immediately and never return	Removes ability to show benefits of B-VEC in these states	Added continuity correction factor to allow transitions to all health states where probability is 0→ allows patients to transition to HS5 and 6 from any other state
Only captures rate of wound closure → time to closure & change in target wound size not assessed in GEM-3	BBE does not affect the skin structure or quality or address underlying disease mechanism → comparing time to wound closure vs. B-VEC not clinically realistic	Duration of closure for B-VEC extremely uncertain

How should relative effectiveness of B-VEC vs BBE and BSC be approached? Is the EAG's ITC appropriate for decision making? Are baseline characteristics across trials (including wound size) comparable?

BBE, birch bark extract; B-VEC, Beremagene geperpavec; BSA, body surface area; cm, centimetre; EB, epidermolysis bullosa; FDA, Food and Drug Administration; HS, health state; HST, highly specialised technology; ITC, indirect treatment comparison; PLS, patient level simulation; RR, relative risk; TE, technical engagement

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

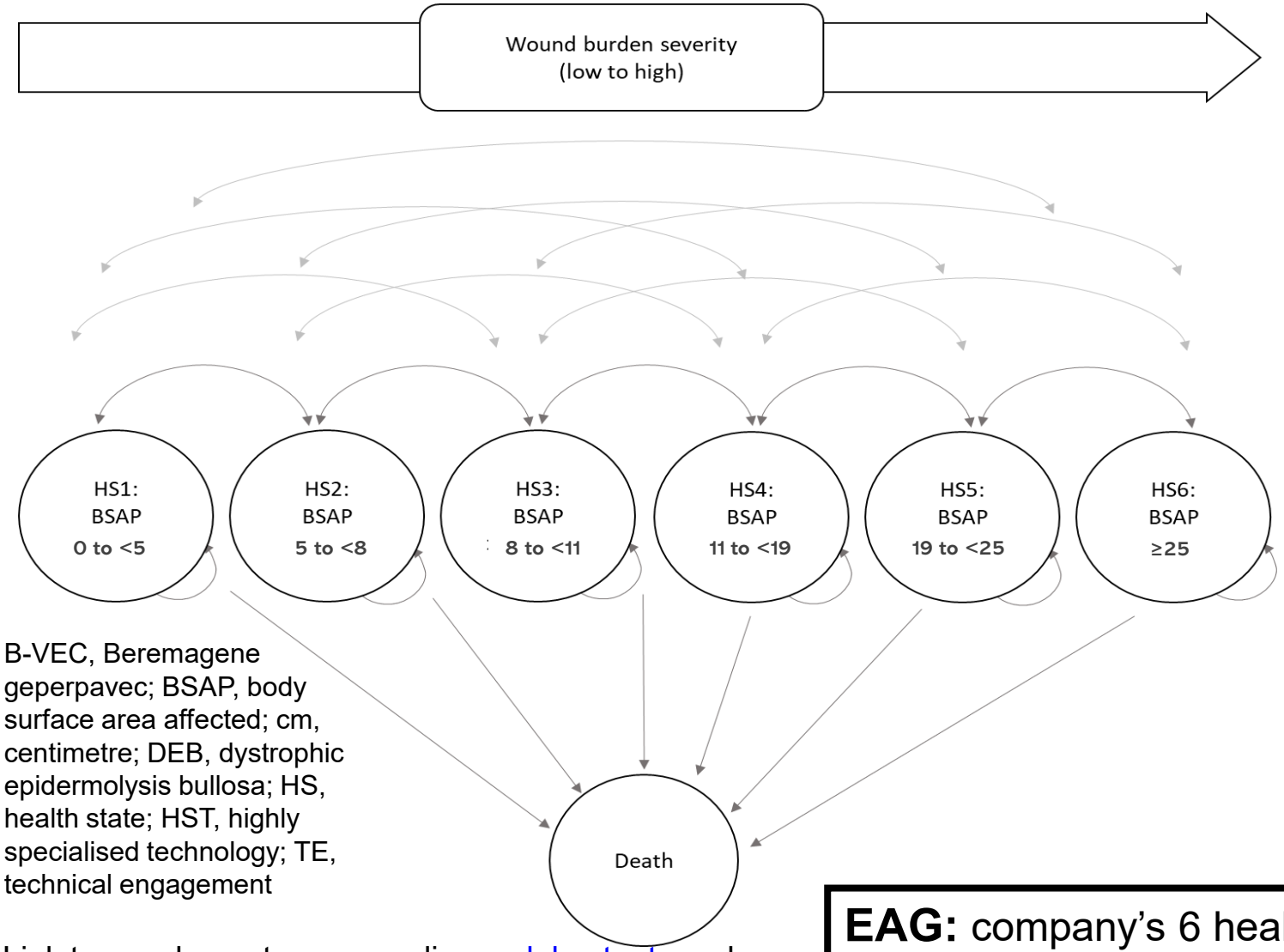
- ❑ Background and key issues
- ❑ Clinical effectiveness
- ✓ **Modelling and cost effectiveness**
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

Company's model after technical engagement: overview

Company uses 6 health state Markov model based on structure used for BBE in HST28

Company's Markov model structure



B-VEC, Beremagene geperpavec; BSAP, body surface area affected; cm, centimetre; DEB, dystrophic epidermolysis bullosa; HS, health state; HST, highly specialised technology; TE, technical engagement

Link to supplementary appendix: model outputs and key issue (pre-TE): model structure

- Markov cohort-level, state transition
- Updated from 4 to 6 health states at TE to align with model structure in HST28
- Lifelong time horizon with 13-week cycle
- People move through health states according to transition probabilities
- Can move from any given health state to another or to death
- Probabilities based on patient level simulation for 10 years, after which steady state applies
- No stopping rule, B-VEC used for life with yearly 1% annual discontinuation
- Separate transition probabilities, mortality risk and drug usage according to age (0-6, 6-18, >18 years) → aggregated for whole cohort
- Mortality also varied by DEB subtype
- Opening of new wounds not specifically modelled

EAG: company's 6 health state model provided at TE appropriate for decision making

How company incorporated evidence into model (after TE)

Company rely on efficacy data from the PLS; utilities from HST28

Input	Assumption and evidence source
Baseline	• % in 3 age groups (0-6, 6-18, >18 years, aggregated in model) & % male: GEM-3 • % with RDEB and DDEB and baseline distribution by BSAP score: Bruckner et al. • Average weight and height per subtype: Reimer et al. for RDEB and general population for DDEB
Efficacy	Transitions estimated using PLS: Clinical evidence from GEM-1 and GEM-3 and OLE (B-VEC and BSC) and SEE (all comparators)
Utilities	• Generalised Linear Model based on EuroQol 5-Dimension (EQ-5D) from EASE • Carer utilities by health state from HST28
Costs & resource use	• Vial consumption estimated by PLS for all treatments (BBE and B-VEC add on to BSC) • Admin costs: YHEC literature review (B-VEC); no extra costs BSC or BBE (self-administered) • Clinical manifestations (costs only): National Schedule of NHS costs 2023/24 • No costs or utilities for AEs; % using concomitant BSC medications: Eng et al. • Wound dressing: Pillay *et al.* (costs) and Jones *et al* (carer hours changing dressing), mapped to health states using distribution from SEE in HST28.
Stopping	• 1% annual discontinuation for B-VEC and BBE; 8.3% having BBE discontinue at 13 weeks. • People who stop B-VEC or BBE redistributed across health states in line BSC arm distribution
Mortality	DDEB: General population, RDEB: Kaplan-Meier data from Petrof *et al.,* extrapolated with Gompertz

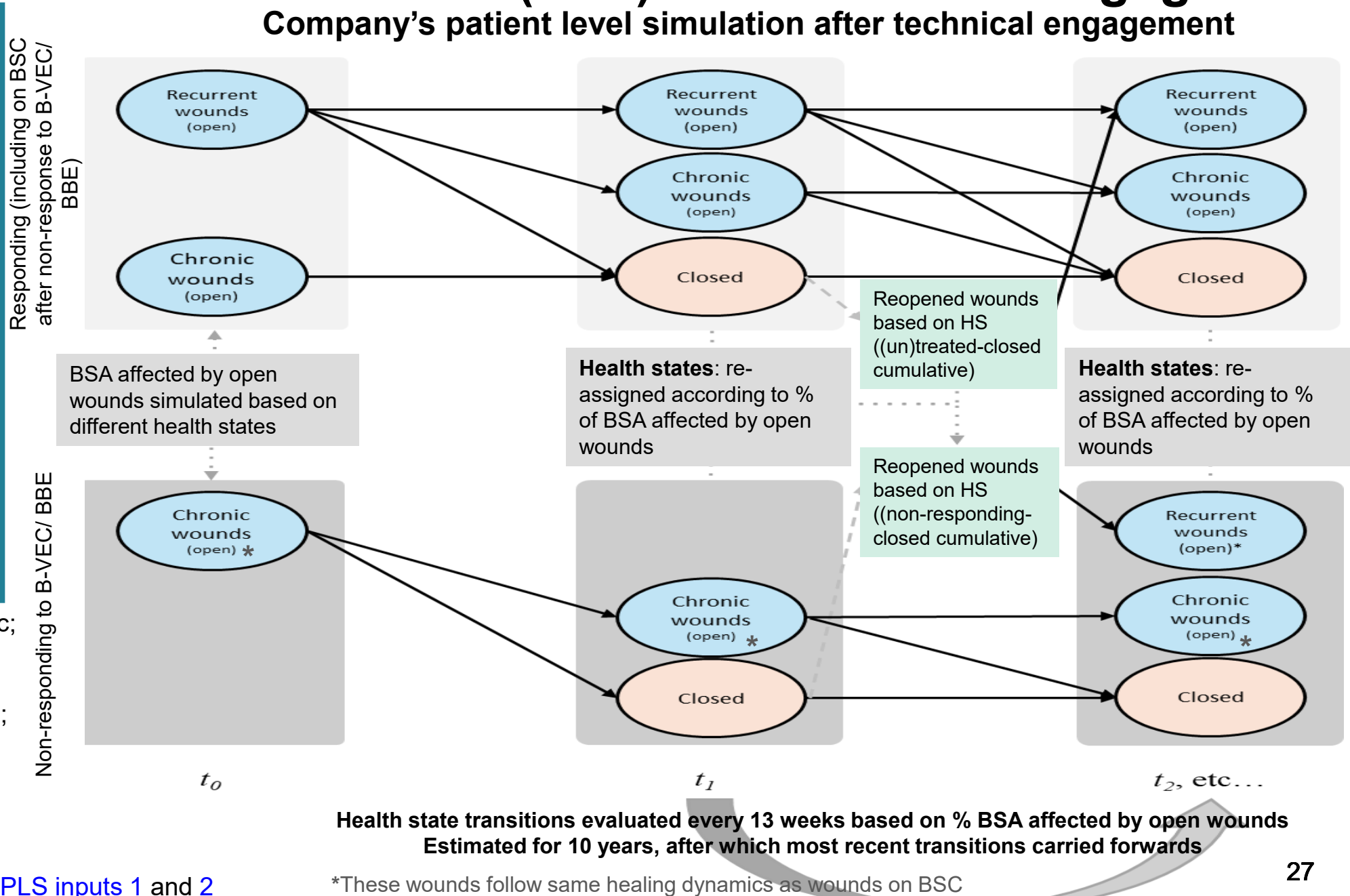
AE, adverse event; B-VEC, Beremagene geperpavec; BSAP, body surface area percentage; BSC, best supportive care; DDEB, dominant dystrophic epidermolysis bullosa: HST, highly specialised technology; OLE, open label extension; PLS, patient level simulation; RDEB, recessive dystrophic epidermolysis bullosa; SEE, structured elicitation exercise; TE, technical engagement; YHEC, York Health Economics Consortium

Company's patient level simulation (PLS) after technical engagement

Background:

- Intra-patient design of GEM-1 & GEM-3 → no data on wound outcomes where all wounds treated
- Company base case determines clinical effectiveness from PLS for B-VEC, BSC and, after TE, BBE
- Populated with data from GEM-3, GEM-1, OLE, a SEE & literature

B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSA, body surface area; BSC, best supportive care; HS, health state; OLE, open label extension; PLS, patient level simulation; SEE, structured expert elicitation; t, time; TE, technical engagement



*These wounds follow same healing dynamics as wounds on BSC

Link to supplementary appendix: PLS inputs 1 and 2

Modelling the disease course of EB

EB wound dynamics:	Company modelled?	EAG modelled?
Wounds close with treatment	**Yes, in PLS:** weekly closure rate:	**Yes:** Complete closure at 3 months from GEM-3 and EASE used in ITC
Old wounds re-open	**Yes, in PLS:** uses duration of closure in trials extrapolated using exponential curve	**Indirectly**: duration of closure not collected in GEM-3 or EASE
Recurrent wounds become chronic	**Yes, in PLS:** wounds failing to close for 8 consecutive weeks (1 – reponing rate)[8]	**Indirectly**: conversion rate not collected in GEM-3
New wounds open in new area	**No:** People cannot have increase in BSAP vs baseline → new wounds opening not differentiated from old wounds reopening.	**Potentially**: people may move to HS with higher BSAP vs. baseline

Weekly closure rate	B-VEC	BSC	BBE (after TE)
Recurrent wounds	42.54% (GEM-1)	14.17% (GEM-1)	16.27% (EAG's ITC)
Chronic wounds	36.7% (SEE)	0.57% (Fulchand et al.)	3.17% (Davidovic et al.)

Weekly % reopening	B-VEC	BSC	BBE (after TE)
	[redacted] (median [redacted] days in GEM-3 & OLE)	[redacted] (median [redacted] days in GEM-1)	[redacted] (median [redacted] days from SEE)

Recurrent → chronic per week	B-VEC	BSC	BBE (after TE)
	1.19%	29.45%	24.16%

B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSAP, body surface area percentage; BSC, best supportive care; EB, epidermolysis bullosa; OLE, open label extension; ITC, indirect treatment comparison; PLS, patient level simulation; SEE, structured expert elicitation

NICE Technical Team: Important model captures characteristics of EB, including new and re-opening wounds

- Does the company and EAG's modelling reflect wound dynamics of EB seen in clinical practice?

Key issue: Company's PLS: clinical effectiveness (1)

EAG: company's modelling of chronic wounds remains problematic after TE

EAG: *Issue 1: modelling chronic wounds*

Company after TE	EAG
Base case: different closure rates for chronic & recurrent wounds after TE, assuming [redacted]% chronic wounds respond to B-VEC (SEE) and 73% to BBE (Davidovic *et al.:* 2/11 BBE treated wounds fully & 6/11 partially closed)	Model applies BSC closure rates to non-responders but 0% rates to "responding" wounds delayed by B-VEC dosing constraints ***Scenario***: 80% chronic wounds respond to B-VEC. Leads to higher % in HS1 vs company base case → lacks face validity

Modelling chronic and recurrent wound closure rates in the company's PLS model after TE

Tx	Chronic wounds		Recurrent wounds	
	Source	Base case	Source	Base case
B-VEC	SEE	36.7%	GEM-1	42.54%
BSC	Fulchand et al.: new 6-month cohort study (29 x chance of chronic vs recurrent wounds closing)	0.57%		14.17%
BBE	Davidovic et al.: 73% response rate. No data on closure extent → assume 50%	3.17%	EAG's ITC (after TE)	16.27%

Stakeholders: Patient expert (at TE): B-VEC closes chronic wounds but some report these re-open within a few weeks

B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSC, best supportive care: HS, health state; ITC, indirect treatment comparison; PLS, patient level simulation; SEE, structured expert elicitation; TE, technical engagement

Key issue: Company's PLS: clinical effectiveness (2)

EAG: company's PLS derived transitions lack face validity

EAG: *Issue 2: modelling transitions*

Tx	Background	Company after TE	EAG
B-VEC	100% in B-VEC arm in very mild state by ~2 years → suggests "near cure"	- Chronic wound closure involves a) induction (open wounds), b) maintenance (only new wounds treated). - Very mild (HS1) not "cured" → may still have minimal open wounds (low BSAP).	Implausible and contradicts: • GEM-3 OLE: complete wound closure in rollover subjects = 61% to 90% (never 100%) • GEM-3 response rate at month 3 (68%) & 6 (74%)
BBE	Company updated PLS to include BBE after TE	Transitions may differ from those in HST28 → large and chronic wounds more likely in clinical practice vs EASE	• PLS shows faster healing rates & more people in HS1 vs EASE data (hard to directly compare as different cycle length) • Expect worse outcomes if larger and more chronic wounds in clinical practice vs trial

Health state occupancy (%) in Markov model of alive patients on BBE using 2 sets of transition probabilities

Time point	Source of transitions applied	HS1	HS2	HS3	HS4	HS5	HS6
Baseline (EASE)	-	21	28	14	16	9	13
Day 90	HST28 EASE approximated transitions (optimistic)*	22	32	15	31	0	0
Week 13	The PLS	46	17	11	13	8	5
Year 3	HST28 EASE approximated transitions (optimistic)*	20	44	21	16	0	0
Year 3	The PLS	75	9	6	9	0	1

*The EAG/Committee preferred using another set of transitions that were less favourable to BBE. B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSAP, body surface area percentage; HS, health state; HST, highly specialised technology; OLE, open label extension; PLS, patient level simulation; TE, technical engagement

Key issue: Company's PLS: clinical effectiveness (3)

EAG raises additional issues with the PLS about inputs and health state wound counts

EAG: *Other issues*

Issue 3. GEM-1 informs wound closure assumptions for improved granularity vs GEM-3: granularity not used in model → median duration of closure (weekly % wound reopening) uses constant hazards (conflicts GEM-1 KM data) and increase in size of reopened wound applied as one-off

- Dosing regimen inconsistent with GEM-1 and B-VEC SmPC
- PLS fails to incorporate available 3- and 6-month GEM-3 data

Issue 4. Inconsistent mapping of wound count in new 6HS model: fewer wounds in HS1 vs. original 4-HS model → may artificially reduce likelihood of wound reopening

Issue 5. SEE informs several PLS inputs: Ambiguous question wording in the SEE may weaken robustness.

- Mean time to closure with BBE shorter than BSC alone yet BBE is add-on → lacks face validity
- SEE does not support constant (exponential) wound-healing rates as seen in PLS
- EAG could not replicate chronic-wound closure-rate calculation, and despite SEE evidence of variation by wound size, single rate for all wound sizes applied in the model

EAG base case: PLS not appropriate for decision making → HST28 transitions for BBE and BSC with RR from ITC applied to BBE transitions for B-VEC

Stakeholders: Chiesi (BBE manufacturer): PLS highly uncertain, relying on a small phase 1/2 study (GEM-1)

- assumptions about EB wound dynamics, chronic wound response, and sustained very mild states on B-VEC not well supported by evidence → more robust GEM-3 data should be used to inform economic model.

Is the company's PLS appropriate for decision making?

B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSC, best supportive care; EB, epidermolysis bullosa; HS, health state; ITC, indirect treatment comparison; KM, Kaplan-Meier OLE, open label extension; PLS, patient level simulation; RR, relative risk; SEE, structured expert elicitation; SmPC, summary of product characteristics

Link to supplementary appendix: number of wounds by health state in 4- and 6- state model

Health state distributions after technical engagement

Company's model includes:

- More people in HS6 (most severe) at baseline vs EAG's model (which uses EASE transitions)
- Rapid accumulation in HS1 (least severe) health state
  - ~100% of people modelled to be in HS1 by month 24 vs <40% in EAG's model

B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSC, best supportive care; HS, health state; TE, technical engagement

Link to supplementary appendix: health state occupancy graphs for BBE and BSC

Key issue: Company's PLS: drug usage

EAG: drug usage from company's PLS lacks face validity

Link to supplementary appendix: vial usage outputs from the PLS

Background: company base case after TE uses vial usage over time predicted by PLS for all comparators

Company (after TE): Cannot use trial data as no people had B-VEC for all open wounds. PLS tracks use over time in dynamic wounds → reflects induction and maintenance phase (real-world B-VEC vial usage)

- GEM-3 & OLE: sustained wound closure (median [redacted] days) with B-VEC

EAG: *B-VEC use underestimated*: Biological mechanism (2-month cutaneous half-life of COL7 and a 4-8 week epidermis turnover rate) suggests duration of wound closure ~3 months → need for repeat B-VEC dosing

- Aligns with GEM-1 (wound closure of ~103 days) but not PLS (predicts <[redacted] vials (<[redacted] syringe) yr 3+ in HS1)
- PLS outputs in very mild state (HS1) also lack face validity as:
  - Lower use in 6HS (BSAP <4%) vs. 4HS (BSAP <2.1%) and lower use vs OLE (9.36 vials / 13 wks)
- Duration of wound closure highly uncertain → trial data shows wide range (103 - 345 days)

***BBE use overestimated*:** EASE: mean 29.67 tubes /month (~90 tubes / 13 wks)

- Markov model predicts 145 tubes used within the 1st cycle → patients heal faster on BBE vs EASE

Base case: B-VEC: company's PLS with minimum min 9.36 syringes (2.34 vials) / cycle to align with OLE data

***BBE*:** 90 tubes per cycle to align with EASE data

Stakeholders: **NHS England**: Real world use may be longer and across higher baseline BSAP with higher B-VEC usage vs model

Chiesi (BBE manufacturer): PLS usage likely unrealistically low vs OLE. High % in HS1 with low vial use implausible → doesn't reflect dynamic wound healing

How should drug usage be modelled?
Are the company's or EAG's assumptions more appropriate?

B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSAP, body surface area percentage COL7, Type VII Collagen; HS, health state; OLE, open label extension; PLS, patient level simulation; TE, technical engagement; wks, weeks

Baseline wound area and age in the company's PLS

Background: company calculates drug usage by health state for 3 age cohorts based on BSAP affected

Age

Baseline characteristics: 3 age cohorts (0-6, 6-18 and 18+ years) → 33% in each
Max dosage per week: company made simplifying assumption to apply max 2ml regardless of age, given that people enter the Markov model at 2.2 in 0-to-6-year cohort → may overestimate costs in youngest patients.

Wound area

Baseline characteristics:
- Total BSAP: based on weight and height in Reimer et al. (RDEB) and general population (DDEB) → uniformly distributed by severity
- Baseline BSAP affected: uniformly distributed in each health state

Max treated area per week: 200cm^2 → aligns with max age in licence but no further cap on smaller BSA categories

Licenced dose of B-VEC by age and wound size

Age	Dose (PFU)	Volume (mL)
≤3 years	Max 2×10^9	Max 1
>3 years	Max 4×10^9	Max 2

Wound area (cm^2)	Dose (PFU)	Volume (mL)
< 20	< 4×10^8	< 0.2
20 to < 40	4×10^8 to < 8×10^8	0.2 to < 0.4
40 to 60	8×10^8 to < 1.2×10^9	0.4 to < 0.6
60 to < 200	1.2×10^9 to < 4×10^9	0.6 to < 2

B-VEC, Beremagene geperpavec; BSA, body surface area; BSAP, body surface area percentage; cm, centimetre; DDEB, dominant dystrophic epidermolysis bullosa; ml, millilitre; PFU, Plaque-Forming Unit; PLS, patient level simulation; RDEB, recessive dystrophic epidermolysis bullosa

Is the company's modelling of wound size and age appropriately aligned with the licence?

Vial usage for B-VEC from the company's PLS

Background: company calculates drug usage by health state for 3 age cohorts

- When people transition to next age bracket, drug use for that cohort reflects total time in the model
- After 10 years, drug usage is constant/ cycle unless moving up an age bracket

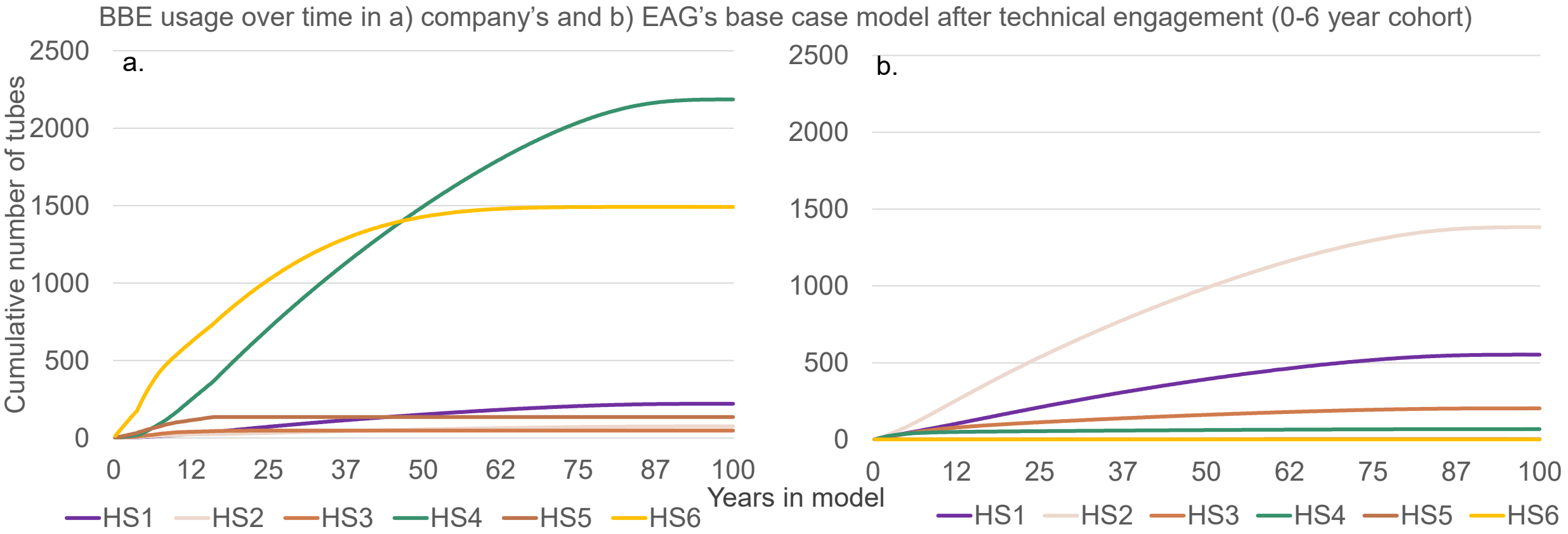
B-VEC, Beremagene geperpavec; HS, health state; PLS, patient level simulation

[redacted]

NICE technical team: Company model estimates much lower B-VEC vial use vs EAG's model after 1st year

- Raymakers et al. (2024) estimated:
  - lifetime B-VEC cost / patient of $15 million (range $10 - $20 million) for RDEB and $17 million (range $11 - $22 million) for DDEB → considerably higher than total discounted drug costs for B-VEC (with PAS) in company's (£[redacted]) & EAG's (£[redacted]) models
  - annual cost of B-VEC~$300 000 / patient / year → considerably lower annual cost vs PAS price

Vial usage for BBE from the company's PLS



BBE, birch bark extract; HS, health state; PLS, patient level simulation

Average number of tubes consumed (full population)	Company	EAG (uses EASE data instead of PLS)
Year 1	926.9	356.0
Year 2	723.9	356.0
Year 3	647.4	356.0
Year 10	515.9	356.0

Key issue: B-VEC in combination with BBE

No scenarios available using BBE when max treatable area for B-VEC exceeded

Background: B-VEC SmPC: max treated dose 200 cm² yet average 1,450 cm² BSA affected in EASE

- Company assumes B-VEC or BBE used to treat wounds up to max BSA; BSC used for other wounds

NICE Technical Team: TE call with clinical experts suggested possibility of BBE used in combination with B-VEC to cover wounds that fall outside of the B-VEC maximum treatable area

Company: Acknowledge request to model additional arm using B-VEC with BBE but not feasible given time constraints → major model restructure required, including changes to clinical, economic, utility, transition probabilities, PLS & sensitivity analyses.

- Lack of data on combination use → modelling combination would introduce substantial additional uncertainty
- B-VEC and BBE combination use not seen in the markets where commercially available.

EAG comments: impact on ICERs of combination treatment approach highly uncertain as:

- No robust trial evidence for B-VEC/BBE combination; would have to use PLS to estimate clinical effectiveness from concurrent treatment of different BSAP proportions with different treatments → EAG consider PLS flawed and biased

Stakeholders: **DEBRA**: B-VEC alternative therapy if BBE does not work on targeted wound

- Would BBE be used concurrently with B-VEC for wounds falling outside of the max BSA for B-VEC?
- If yes, how should this be considered in the modelling?

B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSA, body surface area; BSC, best supportive care; DEBRA, Dystrophic Epidermolysis Bullosa Research Association; ICER, incremental cost-effectiveness ratio; PLS, patient level simulation; SmPC, summary of product characteristics

Key issue: Vial sharing of B-VEC

Company states vial sharing plausible and used for most people in model

Background: B-VEC vial includes 5 x 0.5ml doses (5 syringes), but company assumes:

- Last 0.5ml not fully collected due to air pockets so each vial produces 4 doses only
- A single patient uses a max 4 syringes, so vial sharing possible between multiple patients

Company: acknowledge lack of real-world data to support vial sharing but consider vial sharing:

- Appropriate: based on healthcare provider feedback and published literature in other medications → providers agree vial optimisation in best interest for NHS.
- Practiced: ~83% countries practice vial sharing (Suzuki et al.) and UK study suggests cost savings in 74% cases
  - ❖ France real-world data (n=22): vial sharing reduced B-VEC use by 35%; further efficiencies expected as services matures and patient health improves.
- Possible: 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

Vial sharing assumptions in the company and EAG base cases

Assumption	Base case (company & EAG)	Scenarios
Vial sharing (1 vial shared between ≥2 patients)	80%	**Company**: 0%, 50%, 70% and 90% people have vial optimisation **EAG**: 50%, 25% and 0% vial sharing
Vial wastage (0.5ml per dose)	20% (0.5ml wastage per vial)	**Company:** 2 vials fill 9 syringes (0.25ml wastage per vial)

B-VEC, Beremagene geperpavec; n, number; C, centigrade

Key issue: Vial sharing of B-VEC

EAG: vial sharing in clinical practice uncertain; company's vial sharing rate arbitrary

EAG comments: Company's assumption that 80% share vials is key model driver unsupported by evidence

- unclear whether vial sharing feasible for B-VEC as:
  - ❖ Need to use within 7 days if mixed under aseptic conditions, and within 24 hours otherwise
  - ❖ Mixed syringes must be stored and transported under refrigeration
- PLS predicts most people having B-VEC in HS1 (very mild state) with low vial usage → need 4 patients / vial
  - ❖ Vial sharing only feasible in specialist centres; home or local use logistically complex due to refrigerated transport and coordination
- Suzuki et al. and "UK study" in oncology drugs → easier to optimise (larger N and multi-use indications)

***Base case*:** unclear if vial sharing possible in clinical practice but in absence of evidence to inform, aligns base case with company (80%)

Stakeholders: BAD: Vial sharing:

- May be possible for young children, especially <3 years old whose max treatable BSA only half a vial (1.6 ml)
- May be unnecessary if additional stability data allow unused vials to be stored for later use

Chiesi (BBE manufacturer): unclear if company's vial sharing assumptions plausible → no guidance in SmPC

NHS England: Little scope for vial sharing initially; a) requires complex coordination across reconstitution methods → limited hospital or commercial aseptic service capacity, b) expect most patients on max dose B-VEC

NICE technical team: company and EAG may overestimate vial sharing as % assumed not based on evidence

- Would B-VEC vial sharing be possible in clinical practice?
- If yes, what % of vial sharing should be modelled?
- What % of a B-VEC vial will be wasted in clinical practice?

B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSA, body surface area; HS, health state; ml, millitre; N, number; SmPC, summary of product characteristics

Key issue: Home administration of B-VEC (1)

Company assumes B-VEC self-administered at home after nurse training at initial visit

Background: Company model only includes administration costs for B-VEC; BBE and BSC self-administered

- 30 minutes nursing time associated with B-VEC administration for 1st B-VEC dose only, none for doses 2+

Company: healthcare provider uses time at 1st administration to train patients and carers to self administer subsequent doses at home

Stakeholders: **BAD:** Currently administered by 2 healthcare professionals in specialist hospital setting, taking 2-4 hours / week / patient → Unless drug stability changes, extra pharmacies, nurses & day care beds needed

- Currently unclear if people can deliver and dispose of B-VEC at home

Clinical expert: plan for home delivery in place with 4 specialist centres; shared with NHS England

Patient expert: patient testimony from France suggests administration at local clinics

NHS England:

Issue	Company's model	NHS England response to TE
Admin time for nurses	0.5 hours Band 6 nursing time for 1st dose only	Significant underestimation based on experience with B-VEC
Costs for homecare	Home delivery: £70.98 Preparation: £48.46 per weekly administration (~£6,227 per year)	Uncertainty re homecare set up → cant provide costings estimates. Based on standard NHSE homecare delivery charges, initial estimates considerably above company's modelled costs ([redacted]/ patient / year for aseptic preparation and delivery only) → likely higher with compounding for gene therapies

BAD, British Association of Dermatologists; B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSC, best supportive care

Key issue: Home administration of B-VEC (2)

Stakeholders: NHS England (cont.):

Issue	Company's original model	NHS England response to TE
Admin training	Carer's trained to self-administer at 1st visit	Costs likely higher → extra training and clinical time for newly initiated patients. Uncertainty of delivery means unable to provide estimates.
Admin costs	£32.29 for 1st administration, £3.29 if self-administered	HRG code for B-VEC admin unclear → suggest "combined day case/ ordinary elective spell" for Intermediate Skin Procedures at each administration and cost for ≥2 nurses (≥19 years, code JC42C, £1,111; ≥≤18 years, code JC42D, £1,186).
Reconstitution costs	£48.46 per weekly administration; NHS pharmacy	Hospital aseptic pharmacies report no long-term capacity to reconstitute B-VEC. Reconstitution costs (hospital or commercial) remain unknown but must be considered.

EAG: Agree home delivery and associated costs are area of uncertainty
Scenarios: 50% and 100% of B-VEC administrations take place in specialist care, applying NHS England's suggested using HRG code for admin costs

- Where would B-VEC be administrated in clinical practice?
- What % have at home and what costs associated?
- Are the company's administration costs appropriate for decision making?

B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSC, best supportive care; HRG, Healthcare Resource Group

Key issue: Clinical manifestations

Link to supplementary appendix: clinical manifestations and mortality 1 and 2

Background: EB associated with cutaneous and non-cutaneous symptoms (see background slide)

- Company models cost for clinical manifestations from EB using health state specific prevalence rates (lowering BSAP = lower rate of clinical manifestations) based on rates in RDEB reported in Eng et al. 2021

Company: Larger BSAP (disease severity) and higher % clinical manifestations supported by literature and clinical experts → B-VEC maintains people in less severe HS with lower % clinical manifestations

Base case after TE: presence of irreversible clinical manifestations tracked for full cohort not by health state

EAG: Uncertain if reduced wound burden = reduced non-cutaneous clinical manifestations as:

- EAG's and 2/3 company's clinical experts note localised treatment may not affect non-skin related symptoms
- Improvements in clinical manifestations not in HST28 despite BBE being localised treatment
- Eng at al. did not classify wounds using BSAP or link decreased disease severity to wound healing

Irreversible cases (SCC, mitten deformity) / cycle includes people who die or stop treatment → lacks face validity:

- Children on BBE have higher risk of SCC vs off BBE → unlikely as more transition to mild HS with BBE vs. BSC
- SCC prevalence starts at 0% across all age groups but likely already present in older populations.

Company assumes reduced mortality risk by lowering BSAP affected → highly uncertain & not backed by evidence

Base case: exclude costs for clinical manifestations

Stakeholders: **BAD, clinical & patient expert (at TE):** Chronic wounds cause infection & inflammation, leading to anaemia, osteoporosis & SCC → reduced with prolonged healing on B-VEC.

- Reduced GI wounds may also improve nutrition & allow weight gain.
- B-VEC likely disease modifying as reduces wound burden & sequelae

- Would clinical manifestations, including SCC risk, improve with reduced BSAP after treatment?

BAD, British Association of Dermatologists; B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSAP, body surface area percentage; EB, epidermolysis bullosa; GI, gastrointestinal; HS, heath state; HST, highly specialised technology; RDEB, recessive dystrophic epidermolysis bullosa; TE, technical engagement; SCC, squamous cell cancer

Other issues raised by EAG

EAG base case excludes concomitant medications and uses baseline distribution from EASE

Issue	Company's original model	EAG response
Concomitant medications	Data from Eng et al. used to estimate concomitant medication usage by severity.	Statistically significant difference between mild and severe cases observed only for opiates, gabapentin, and MediHoney; all other medications showed no significant association with severity. ***Base case:*** exclude costs for concomitant medications
Baseline distribution by health state	Derived by severity based on Bruckner *et al.*	Definitions in Bruckner *et al.* do not fully align with modelled health states ***Base case:*** baseline distribution by health state from EASE

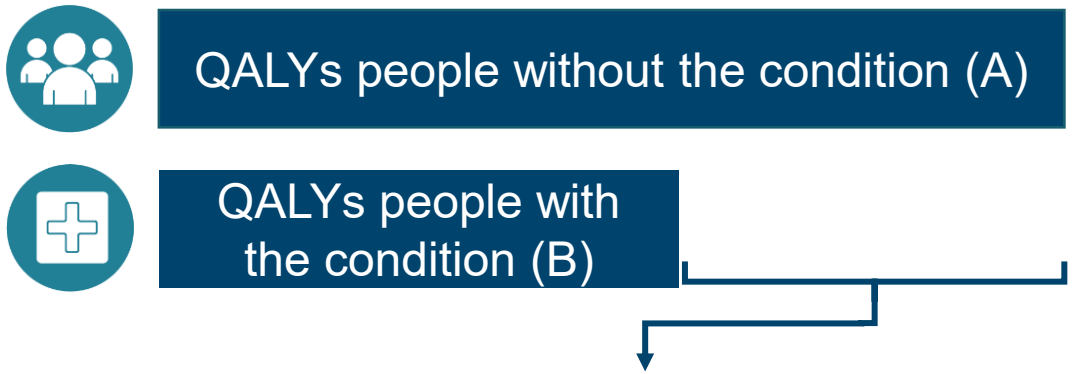
HS in company's model	Definition according to Bruckner et al.
HS1 (BSAP <5%)	—
HS2 (BSAP 5 - <8%)	Mild: BSAP <10.0%
HS3 (BSAP 8 - <11%)	Moderate: BSAP 10.0-30.0%
HS4 (BSAP 11 - <19%)	
HS5 (BSAP 19 - <25%)	
HS6 (BSAP ≥25%)	Severe: BSAP >30%

Should costs for concomitant medications be included in the model?
Which source should be used to determine the starting distribution by health state?

BSAP, body surface area percentage; HS, heath state; HST, highly specialised technology;

QALY weightings for severity (1/2)

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

Abbreviations: QALY, quality-adjusted life year

QALY weightings for severity (2/2)

Background: Both company and EAG base case after TE meet threshold for x1.2 modifier. All EAG scenarios meet the criteria for x1.2 QALY weighting.

EAG: company does not provide info on how lifetime QALYs calculated or provide average age for full modelled cohort → severity weighting calculated based on weighted average age for subgroups.

Baseline characteristics in the company's model

	Average age (weighted), years	% female
Company & EAG base case	17	36

	QALYs of people without condition (based on trial population characteristics)	QALYs with the condition on current treatment (BSC)	**Absolute QALY shortfall (has to be >12)**	**Proportional QALY shortfall (has to be >0.85)**	**QALY weight**
Company base case	23.15	5.71	17.44	75.33%	**X1.2**
EAG base case	23.15	9.17	13.98	60.39%	**X1.2**

Does the committee agree it is appropriate to apply a QALY weighting for severity?

NICE

BSC, best supportive care; QALY, Quality-Adjusted Life Year; TE, technical engagement

Summary of company and EAG base case assumptions

Key EAG assumptions differ for clinical effectiveness, vial usage and clinical manifestations

Assumption	Company base case	EAG base case
Clinical effectiveness	PLS for B-VEC, BSC and BBE	EASE transitions for BBE and BSC with continuity correction applied, ITC GEM-3 vs EASE for B-VEC (RR 3.12 applied to transition probabilities from HST28)
Vial usage per health state	PLS for B-VEC, BSC and BBE	PLS for B-VEC and BSC with: • min 9.36 syringes B-VEC (2.34 vials) / cycle (GEM-3 OLE) • 90 tubes BBE / cycle (EASE)
Clinical manifestations	Reduced risk with lower wound burden	Risk does not change with treatment
Concomitant medications	Included	Excluded
Baseline distribution	Bruckner et al.	EASE trial
Common assumptions after TE (see supplementary appendix 1 and 2)		
Utility values	EASE trial (HST28) using generalised linear model	
Number of health states	6	
Health state after discontinuation	Redistributed according to BSC distribution	
Mortality extrapolation for RDEB	Gompertz (EAG corrected) for both severe and non-severe health states	

B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSC, best supportive care; HST, highly specialised technology; ITC, indirect treatment comparison; OLE, open label extension study; PLS, patient level simulation; RDEB, recessive dystrophic epidermolysis bullosa; RR, relative risk

Link to supplementary appendix: carer QoL

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

Patient Access Scheme discounts

- There are confidential discounts in place for B-VEC and other medicines used in the model
- B-VEC is dominant in the company's base case vs. BBE. The ICER is under £25,000 per QALY gained for B-VEC vs BSC.
- The EAG's base case is above the range NICE normally considers acceptable for B-VEC vs both comparators

NICE

B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSC, best supportive care; ICER, Incremental cost-effectiveness ratio; QALY, Quality-Adjusted Life Year

Company base case and changes to EAG base case

Key cost effectiveness drivers are choice of clinical effectiveness and B-VEC vial usage

Impact of varying assumptions in EAG base case, applied to company base case after TE

No.	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) vs BBE	ICER (£/QALY) vs BSC
1	**Company base case**	See part 2	See part 2	B-VEC dominant	Under £25,000
2	HST28 transition probabilities for BBE and BSC (after continuity correction), ITC RR for B-VEC	Increase	Decrease	Over £35,000	Over £35,000
3	Apply a minimum of 2.34 vials of B-VEC each 13 weeks	Increase	No change	Over £35,000	Over £35,000
4	Mean BBE tube consumption from EASE for all states	Increase (vs BBE only)	No change	Under £25,000	Under £25,000
5	Assuming the baseline distribution from EASE	Increase	Decrease	Over £35,000	Under £25,000
6	Exclusion of clinical manifestations and concomitant medications	Increase	No change	B-VEC dominant	Under £25,000
EAG base case (1 + 2 + 3 + 4 + 5 + 6)		Increase	Decrease	Over £35,000	Over £35,000

B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSC, best supportive care; HST, highly specialised technology; ITC, indirect treatment comparison; ICER, Incremental cost-effectiveness ratio; QALY, Quality-Adjusted Life Year; RR, relative risk

Company base case and changes to EAG base case

ICER remains over threshold for cost effectiveness when varying assumptions applied to EAG base case

No.	Scenario	ICER B-VEC vs BBE and BSC
EAG base case		
1	Transitions for B-VEC applying RR for complete wound closure only to HS1	Over £35,000
2 + 3	Vial optimisation for B-VEC of a) 50% and b) 0%	Over £35,000
4	Minimum of one vial per cycle	Over £35,000
5	BBE tube consumption from PLS	Over £35,000
6 + 7	ITC estimate of a) 2 and b) 10	Over £35,000
8 + 9	a) 100% and b) 50% have B-VEC in specialist centres	Over £35,000
10	Vial optimisation for B-VEC of 25%	Over £35,000
11	9.68% discontinuation rate Year 1 for B-VEC and 1% annually Year 2+	Over £35,000
12 + 13	a) 25% and b) 50% discontinuation rate at 90 days for BBE	Over £35,000
14	100% have RDEB	Over £35,000

B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSC, best supportive care; HS, health state; ITC, indirect treatment comparison; ICER, Incremental cost-effectiveness ratio; PLS, patient level simulation; QALY, Quality-Adjusted Life Year; RR, relative risk

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Other considerations**
- ❑ Summary

NICE National Institute for Health and Care Excellence

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

NICE managed access team: company has not submitted a managed access proposal at this stage but consider that the uncertainties identified by the EAG may benefit from further real world evidence data collection.

NICE technical team: There is an ongoing post-authorisation study in B-VEC. A managed access proposal may address some of the high uncertainty around B-VEC vial usage, and use of BBE with B-VEC

B-VEC, Beremagene geperpavec; BBE, birch bark extract

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

Key issues

Key issue	ICER impact	Resolved?
Limited clinical evidence in people with dominant DEB (DDEB)	Uncertain	No – for discussion
Lack of ITC between B-VEC (GEM-3 study) and BBE (EASE study)	Large	No – for discussion
Appropriate health state utility estimates	Large	Yes – see supplementary appendix
Validity of the company's patient level simulation as a source of clinical effectiveness and drug usage	Large	No – for discussion
Algorithm to map 6-state to 4-state model structure lacks face validity	Large	Yes – see supplementary appendix
Uncertain association between reduced clinical manifestations and mortality in patients with reduced wound burden	Large	No – for discussion
People who stop treatment stay in health state they occupy when discontinuing	Small	Yes – see supplementary appendix
Company assumes vial sharing in 80% of people	Small	No – for discussion
No modelling of B-VEC and BBE used concurrently	Uncertain	No – for discussion
Administration costs and resource use may be underestimated	Medium	No – for discussion

BBE, birch bark extract; B-VEC, Beremagene geperpavec; ICER, Incremental Cost-Effectiveness Ratio
Small impact: <5% increase on ICER; Medium impact: 5-20% ICER change; Large impact: >20% ICER change

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

Supplementary appendix

NICE National Institute for Health and Care Excellence

Decision problem

Link to main slides: treatment pathway

	Final scope	Company	EAG comments
Population	People with dystrophic epidermolysis bullosa (DEB)	Limited population to align with BBE→ >6 months old with partial thickness wounds	Clinical expert advice suggests all DEB-related wounds partial thickness as close to dermal-epidermal junction
Comparators	Established clinical management without B-VEC including, but not limited to: • treatments that help ease and control infections, pain, and other aspects of DEB • Birch bark extract (BBE)	Aligned with scope	Company models BBE and B-VEC as add-on to BSC. Relevant comparators: • BBE with BSC • BSC alone in those ineligible for BBE
Outcomes	% complete wound closure; time to and duration of wound closure; % BSA with wounds; pain; Δ in itching; incidence of SCC; mortality; AEs of treatment; HRQoL	Separate % BSA with wounds: • % BSA of wound healed • Δ in total body wound burden Δ in wound size over time less relevant→ B-VEC promotes durable wound closure.	Following outcomes not pre-specified in GEM-3: • % BSA of wound healed • Δ in total body wound burden • Time to & duration of wound closure (GEM-1) • % BSA with wounds

- Would all DEB-related wounds be partial thickness?
- How should any optimisation of the B-VEC population be considered in a recommendation?

AE, adverse event; BBE, birch bark extract; B-VEC, Beremagene geperpavec; BSA, body surface area; BSC, best supportive care; DEB, dystrophic epidermolysis bullosa; HRQoL, health related quality of life; MA, marketing authorisation; SCC, squamous cell carcinoma

BBE population in SmPC and NICE recommendation

HST28:

1.1 Birch bark extract is recommended, within its marketing authorisation, as an option for treating partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa in people aged 6 months and over.

SmPC:

Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.

HST, highly specialised technology; SmPC, summary of product characteristics

Key clinical trials in the company's submission: B-VEC

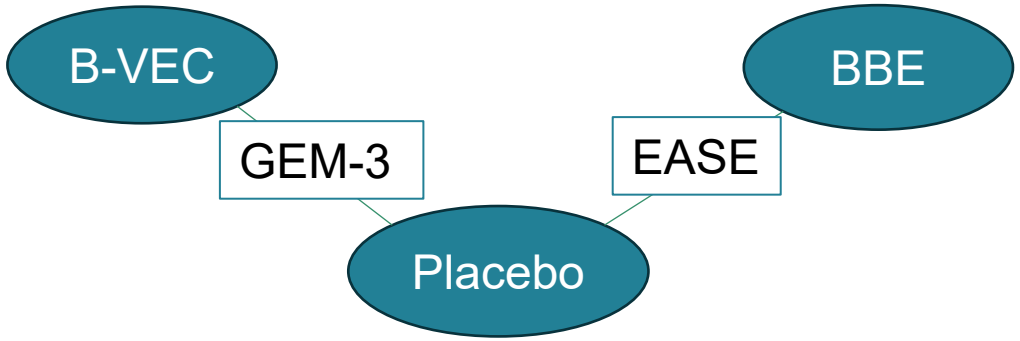
Link to main slides: GEM-3 trial

Name	GEM-1	GEM-3	GEM-3 OLE	EASE
Intervention	B-VEC	B-VEC	B-VEC	BBE
Comparator	Placebo gel	Placebo gel	None	Placebo gel
N	12	31	47 (24 from GEM-3, 23 B-VEC naïve)	223 (175 with RDEB, 20 with DDEB)
Tx duration	Max 2 months	6 months or until closure	Until closure	90 days
Design	Open-label, intra-patient-controlled phase I/II RCT	Double-blind, intra-patient-controlled phase III RCT	Single arm, open label extension	Double-blind, phase III RCT
Population	• Aged ≥18 (phase 1), ≥5 (phase 2a), or ≥2 (phase 2b and c) • Genetically confirmed clinical DEB diagnosis	• ≥6 months with genetically confirmed clinical DEB diagnosis. • 2 cutaneous wounds similar in size, anatomical region, and appearance	1. Completed GEM-3 study or 2. B-VEC naïve patients with DEB	• ≥ 4 years old with DEB, JEB, or KEB • Target wound 10–50 cm2, aged ≥ 21 days and < 9 months
Key outcome	• % wounds with complete closure at weeks 8, 10, 12 • Time to & duration of wound closure	% 1° wounds with complete wound closure at 6 months	• Safety and tolerability • HRQoL • Durability of wound closure	% with 1st complete target wound closure w/i 45 days (clinical assessment)
In model	Yes: company clinical effectiveness inputs for patient level simulation			Yes: comparator data

B-VEC, Beremagene geperpavec; DDEB, dominant dystrophic epidermolysis bullosa: DEB, dystrophic epidermolysis bullosa: HRQoL, health related quality of life; N, number; OLE, open label extension; RCT, randomised controlled trial; JEB, junctional epidermolysis bullosa; KEB, kindler epidermolysis bullosa; N, number; OLE, open label extension; RDEB, recessive dystrophic epidermolysis bullosa; RCT, randomised controlled trial; Tx, treatment

Background: EAG's ITC

EAG's ITC network diagram and key aspects



Arm	B-VEC	BBE
Outcome	% wounds with complete closure at 3 months confirmed at 2 consecutive visits 2 weeks apart	% with 1st complete closure of wound within 90±7 days
Intervention	B-VEC: 21.9% (n=31)	BBE: 50.5% (n=109)
Placebo	6.1% (n=31)	43.9% (n=114)
ITC results, B-VEC vs BBE (95% CI)	**RR: 3.12 (0.66, 14.82)** Clinical effectiveness for B-VEC modelled by applying RR to BBE transitions from HST28	

Company approximation approach used to generate transition probabilities in HST28

EAG uses transitions from EASE based on company's approximation method in HST28 (direct transitions from EASE preferred by committee but confidential)

BBE

Day 0-30	HS1	HS2	HS3	HS4	HS5	HS6
HS1	1	0	0	0	0	0
HS2	0.109	0.891	0	0	0	0
HS3	0	0.382	0.618	0	0	0
HS4	0	0	0.368	0.632	0	0
HS5	0	0	0	1	0	0
HS6	0	0	0	0	1	0

Starting health state / *Ending health state*

CCM

Day 0-30	HS1	HS2	HS3	HS4	HS5	HS6
HS1	1	0	0	0	0	0
HS2	0.022	0.978	0	0	0	0
HS3	0	0.358	0.642	0	0	0
HS4	0	0	0.284	0.716	0	0
HS5	0	0	0	0.999	0.001	0
HS6	0	0	0	0	1	0

B-VEC, Beremagene geperpavec; BBE, birch bark extract; CCM, current clinical management; HS, health state; HST, highly specialised technology; ITC, indirect treatment comparison; n, number; RR, risk ratio

Link to main slides: key issue: comparative effectiveness

Company's Bucher ITC

- Company conducted ITC based on difference in relative change in % of patients in each health state over 2 consecutive model cycles at months a) 3 vs Baseline; b) 6 vs 3, d) 9 vs 6, e) 12 vs 9 in replicated HST28 model
- Data for B-VEC and BSC (placebo) from PLS based on wound dynamics observed in GEM-1, GEM-3 and OLE.
- Data for BBE and CCM (placebo) from HST28 model, based on change in BSA with open wounds in EASE.

Scenarios: 1. BBE = ITC rate applied to B-VEC transitions; B-VEC/BSC = PLS; 2. BBE/BSC = HST28 transitions, B-VEC = ITC rate applied to BBE transitions, 3 & 4. As per #1 (scenario #3) and #2 (scenario #4) using original HST28 baseline instead of Bruckner et al.

Health state	Days	Transitions from PLS, B-VEC vs placebo, mean, SE (95%CI)	Transitions from EASE, BBE vs placebo, mean, SE (95%CI)	Bucher ITC BBE vs B-VEC, mean, SE (95%C), p-value
Very mild	Baseline to 90	[redacted]	0.49, 0.05 (0.4, 0.59)	[redacted]
	90 to 180	[redacted]	0.07, 0.01 (0.06, 0.08)	[redacted]
	180 to 270	[redacted]	0.08, 0.01 (0.06, 0.09)	[redacted]
	270 to 360	[redacted]	0.06, 0.01 (0.05, 0.07)	[redacted]
Mild	Baseline to 90	[redacted]	0.49, 0.05 (0.39, 0.59)	[redacted]
	90 to 180	[redacted]	0.09, 0.01 (0.07, 0.11)	[redacted]
	180 to 270	[redacted]	0.07, 0.01 (0.06, 0.08)	[redacted]
	270 to 360	[redacted]	0.06, 0.01 (0.05, 0.07)	[redacted]
Moderate	Baseline to 90	[redacted]	-0.33, 0.03 (-0.4, -0.27)	[redacted]
	90 to 180	[redacted]	-0.06, 0.01 (-0.07, -0.05)	[redacted]
	180 to 270	[redacted]	-0.06, 0.01 (-0.07, -0.04)	[redacted]
	270 to 360	[redacted]	-0.05, 0.01 (-0.06, -0.04)	[redacted]
Severe	Baseline to 90	[redacted]	0, 0 (0, 0)	[redacted]
	90 to 180	[redacted]	0, 0 (0, 0)	[redacted]
	180 to 270	[redacted]	0, 0 (0, 0)	[redacted]
	270 to 360	[redacted]	0, 0 (0, 0)	[redacted]

B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSA, body surface area; BSC, best supportive care; CCM, current clinical management; HST, highly specialised technology; ITC, indirect treatment comparison; PLS, patient level simulation; OLE, open label extension; SE, standard error

Company's model after technical engagement: overview

Technology affects **costs** by:

- Drug costs: higher vs BSC but less vs BBE
- Additional administration costs
- Reduced cost of bandages, monitoring and management of clinical manifestations

Technology affects **QALYs** by:

- Moving patients to lower BSAP scores associated with reduced risk of death and increased QoL for patients and carers

Assumptions with greatest **ICER** effect:

- Assuming lowering wound burden with treatment reduces
  - mortality risk (most severe forms of DEB = higher wound burden and mortality risk)
  - risk of clinical manifestations, including non-cutaneous manifestations of DEB
- Varying the amount of assumed vial sharing for B-VEC
- Applying a minimum B-VEC vial usage

B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSAP, body surface area percentage; BSC, best supportive care; DEB, dystrophic epidermolysis bullosa; ICER, incremental cost effectiveness ratio; QALY, Quality-Adjusted Life Year; QoL, quality of life

Key issue: Model structure

Link to main slides: company's model after TE

Company updates model from 4 to 6 health states at TE

Background: Company's original submission included 4 health states with mapped inputs from the 6-health state model used in HST28 → company updated at TE to align with EAG's preferred 6 health state structure

Company: original health states aligned with categories reported in Eng et al. + extra "Very Mild" state for improved health with B-VEC when most or all wounds have closed

- 6HS structure has less granularity in milder disease range → designed for a treatment with limited efficacy and no disease-modifying effect
- B-VEC aims to maintain no open wounds & treat only reopened ones → requires more granularity in milder states

Base case: 6 health state model → inputs from 4-health state model mapped to 5

Scenario: 7 health state model→ extra health state captures full value of B-VEC in milder health states.

EAG comments: 6-health-state structure provides greater granularity in disease severity, resulting in a more accurate representation of the patient trajectory as does not include:

- mapping algorithm from 6 states to 4 states associated with structural uncertainty
  - Company calibrated mapping manually until the ICERs of BBE vs. BSC from the 6- and 4- HS model aligned with an estimated PAS for BBE (total costs of BBE arm of replicated model = published costs for HST28 model) → mapping only chosen as happens to produce matching QALYs and costs.
  - Lacks face validity: 100% of HS2 patients (BSAP 4-7%) assumed to belong to mild health state (2.1-5%)
  - Lacks granularity in 5-25% BSAP range (HS2 to 5 in HST28), all of which are considered moderate
  - Constrains BBE patients to mild and moderate and BSC patients mainly to moderate
- reversible and irreversible clinical manifestations which the EAG prefer to exclude.

B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSAP, body surface area percentage; BSC, best supportive care; HS, health state; HST, highly specialised technology; TE, technical engagement; ICER, incremental cost effectiveness ratio; PAS, patient access scheme; QALY, Quality-Adjusted Life Year; TE, technical engagement

Comparison between HST28 and company's modelling

Factor	HST28	Company base case
Time horizon	50 years	Lifetime (up to 100 years)
Cycle length	30 days	3 months
Model start age	16.7 years	Varies by age subgroup: 0-6 years : mean 2.2 years (13%) 6-18 years: mean 12.6 years (48%) ≥ 18 years: mean 28.0 years (39%)
Transition probabilities	EASE observed TPs, with steady state assumption after 810 days	Simulated using data from GEM-1, GEM-3 and EASE trials, steady state assumed after 10 years
Source of resource use estimates	Literature/ SEE estimates	HST28 committee papers, British National Formulary, SEE estimates
Source of utilities	EASE (EQ-5D-3L & EQ-5D-Y)	EASE EQ-5D
Mortality	Estimates based on Petrof et al. (2022) for each EB subtype	
Stopping rate	8.3% to 90 days, 1% yearly after	1% per annum for B-VEC, HST28 rates for BBE
Vial usage	Mean tube usage per month from EASE and OLP (CON)	PLS for all treatments with 80% B-VEC vial optimisation
Carer utility	Time-trade-off study results with a 'subsequent carer' modifier	HST28 values

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; HST, highly specialised technology; SEE, structured expert elicitation

Assumptions and inputs in the company's PLS (1)

Modelling wound closure

- Weekly closure occurs via treated closure (B-VEC/BBE) or spontaneous closure (BSC)
- Recurrent closure rates estimated by aggregating wound-level data from GEM-1 with censoring at first closure
- Wounds ≤2 cm² assumed to close completely once treated in a given week

Recurrent and chromic wound closure rates

Model Input	B-VEC	BSC	BBE (after TE)
Weekly closing rate: recurrent wounds	[redacted] (if treated, GEM-1)	[redacted] (GEM-1) (0% pre-TE)	[redacted] (EAG's ITC)
Weekly closing rate: chronic wounds	[redacted] (SEE)	[redacted] (Fulchand et al)	[redacted] (Davidovic et al. 2025)
% chronic wounds respond to treatment	[redacted] (SEE)	-	73% (Davidovic et al. 2025)

Modelling wound reopening

1. Calculate % reopening: based on median duration of closure in trials, extrapolated using exponential distribution
2. Define N wounds/patient in mild–severe health states by applying normal distribution to average in Eng et al.
3. Calculate expected reopened wounds = total wounds x % reopening: fractions implemented probabilistically
4. Translate to wound area by sampling sizes from normal distribution based on GEM-1 data: mean [redacted] cm², SD [redacted]
5. Calculate wound growth (BSC and BBE only); Based on GEM-1 data, one-off adjustment of x 4.45 initial size applied to re-opened wounds
6. Total reopened area capped at cumulative area previously closed

Median duration of wound closure (reopening probability)

B-VEC	BSC	BBE (after TE)
median [redacted] days in GEM-3 & OLE → weekly reopening probability [redacted]%.	median [redacted] days (GEM-1)→ weekly reopening probability [redacted]%.	median [redacted] days (SEE)→ weekly reopening probability [redacted]

B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSC, best supportive care; cm, centimetre; N, number; OLE, open label extension; SEE, structed expert elicitation; TE, technical engagement

Assumptions and inputs in the company's PLS (2)

Modelling recurrent to chronic wounds

- Conversion defined as failing to close for 8 consecutive weeks (Eng et al.).
- Calculated by (1 – reopening rate)[8]

Converted chronic wounds:

- BSC: never heal.
- B-VEC: heal at same weekly rate as recurrent wounds.

Recurrent → Chronic /week

B-VEC	BSC	BBE (after TE)
[redacted]	[redacted]	[redacted]

Treated area and vial use:

- Weekly treated area = chronic + recurrent open area
- Only applied if patient is compliant (90% assumed based on [redacted] compliance in GEM-3; company scenario: [redacted]).
- B-VEC: Capped at 200 cm^2 as per SmPC, 250 cm^2 treated for BBE (3 applications a week)
- Chronic wounds prioritised when allocating treated area.
- Vials calculated from treated area using assumptions on:
  - Syringes per vial: base case = 4, scenario = 4.5
  - Vial sharing: base case: [redacted], scenarios: [redacted]%

B-VEC, Beremagene geperpavec, BBE, birch bark extract; BSC, best supportive care; cm, centimetre; SmPC, summary of product characteristics; TE, technical engagement

Number of wounds in company's model pre- and post-TE

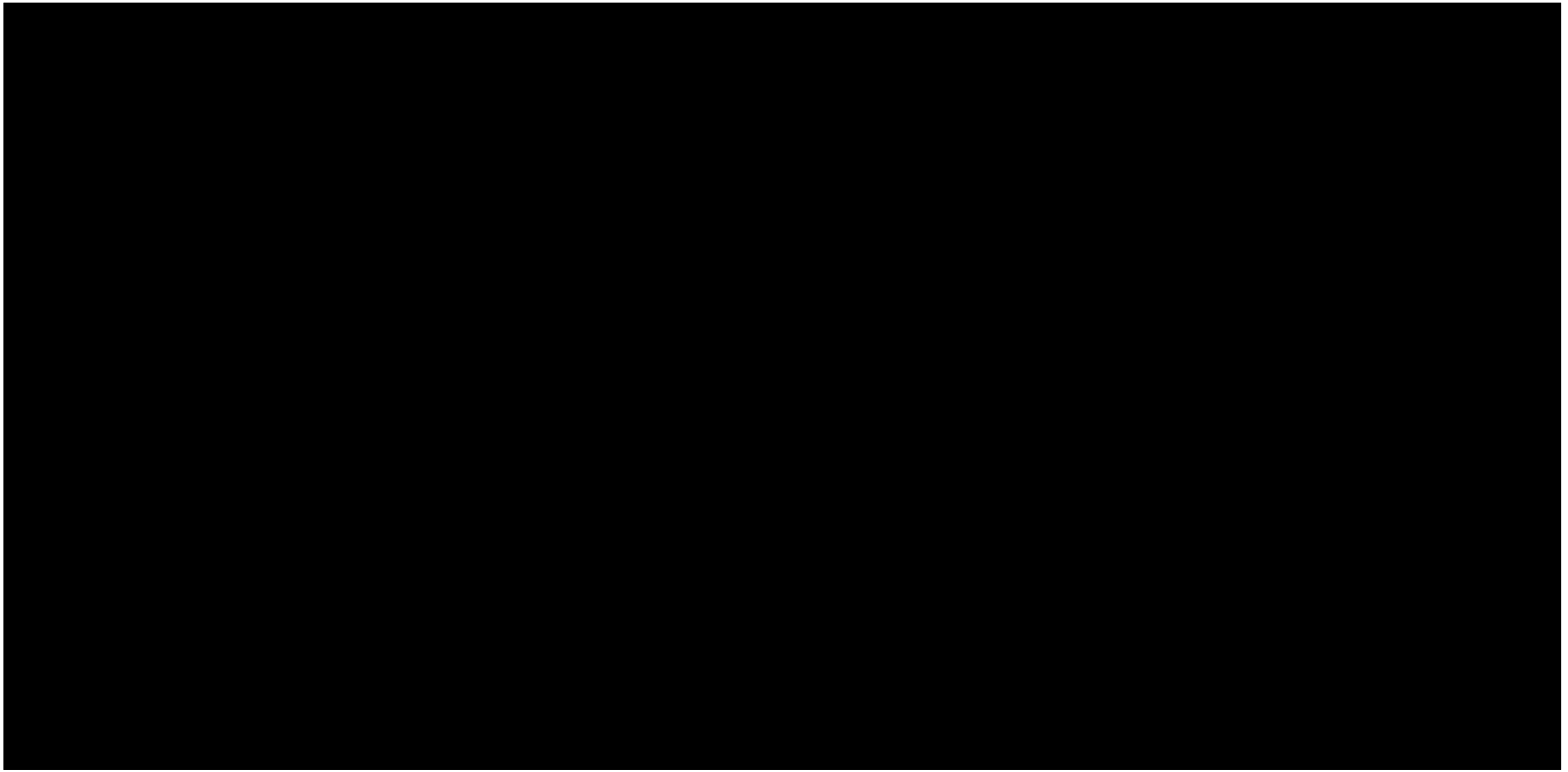
- Company used average number of wounds per patient in Eng et al. → mean, 25th, and 75th percentiles inform the lower boundaries of the moderate, mild, and severe health states in 4HS model.
- Changed N wounds simulated for each state when updated to 6HS model but estimation of values not explained

Initial Company model (4 health states)	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 ≤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 ≥25%)	33 recurrent 7 chronic

BSAP, body surface area percentage; CS, company submission; HS, health state; HST28, highly specialised technology; PLS, patient level simulation; TE, technical engagement

Link to main slides: key issue: company's PLS after TE

Health state distributions in the company's base case



Link to main slides: key issue: company's PLS after TE

BBE, birch bark extract; BSC, best supportive care; HS, health state; TE, technical engagement

Vial usage for BBE and B-VEC from the company's PLS

Link to main slides: key issue: vial usage from the PLS

Transitions through the company and EAG model

Subgroup in Markov model	Starting age in Markov model	Years in PLS drug usage cohorts from entering model		
		0 to 6 years	6 to 18 years	18+
0 to 6 years	2.2	0-5	5 - 16	16+
6 to 18 years	12.62	-	0 to 5	6+
18+ years	27.99	-	-	0+

B-VEC, Beremagene geperpavec
BBE, birch bark extract; HS, health state; PLS, patient level simulation

Number of B-VEC vials and BBE tubes / cycle by health state, by year and by age subgroup in PLS

		Mean number of vials per cycle, B-VEC						Mean number of tubes per cycle, BBE					
Subgroup	Year	HS1	HS2	HS3	HS4	HS5	HS6	HS1	HS2	HS3	HS4	HS5	HS6
0-6	1	[redacted]											
	5	[redacted]											
	10	[redacted]											
6-18	1	[redacted]											
	5	[redacted]											
	10	[redacted]											
18+	1	[redacted]											
	5	[redacted]											
	10	[redacted]											

Key issue: Clinical manifestations and mortality

Link to main slides: key issue: clinical manifestations

Background: Lack of natural history and trial data to inform mortality estimates:

- Company assumes general population mortality for DDEB and extrapolates mortality from Petrof et al. (2022) Kaplan-Meier for severe and non-severe RDEB subtypes using exponential curve to extrapolate (pre-TE)
  - ❖ Exponential chosen as constant hazard of death needed when some people enter model at older age.
  - ❖ Higher risk of death in severe RDEB, which decreases with lower wound burden through treatment.

EAG: excess mortality related to severe RDEB from non-cutaneous manifestations (anaemia, poor nutrition from mucosal wounds and GI strictures) unlikely affected by reducing wound burden by B-VEC or BBE

- Company's mortality rates arbitrary→ no data that vary by BSAP and unclear if lower mortality in severe RDEB linked to wound burden
- High prevalence and biological aggressiveness of SCC in RDEB → unlikely just from scar tissue presence
- Exponential curve inappropriate: survival can be modelled with other curves regardless of entry age, and Gompertz fits better; prefer Gompertz for both severe and non-severe RDEB.

Company (TE): health state specific mortality appropriate as link between disease severity and clinical manifestations in literature → B-VEC maintains people in less severe health states with lower % clinical manifestations

Base case (post TE): Gompertz for severe & non-severe RDEB

Stakeholders: **Clinical expert (TE):** Reduced chronic wounds may = less SCC risk & improve mortality in severe RDEB.

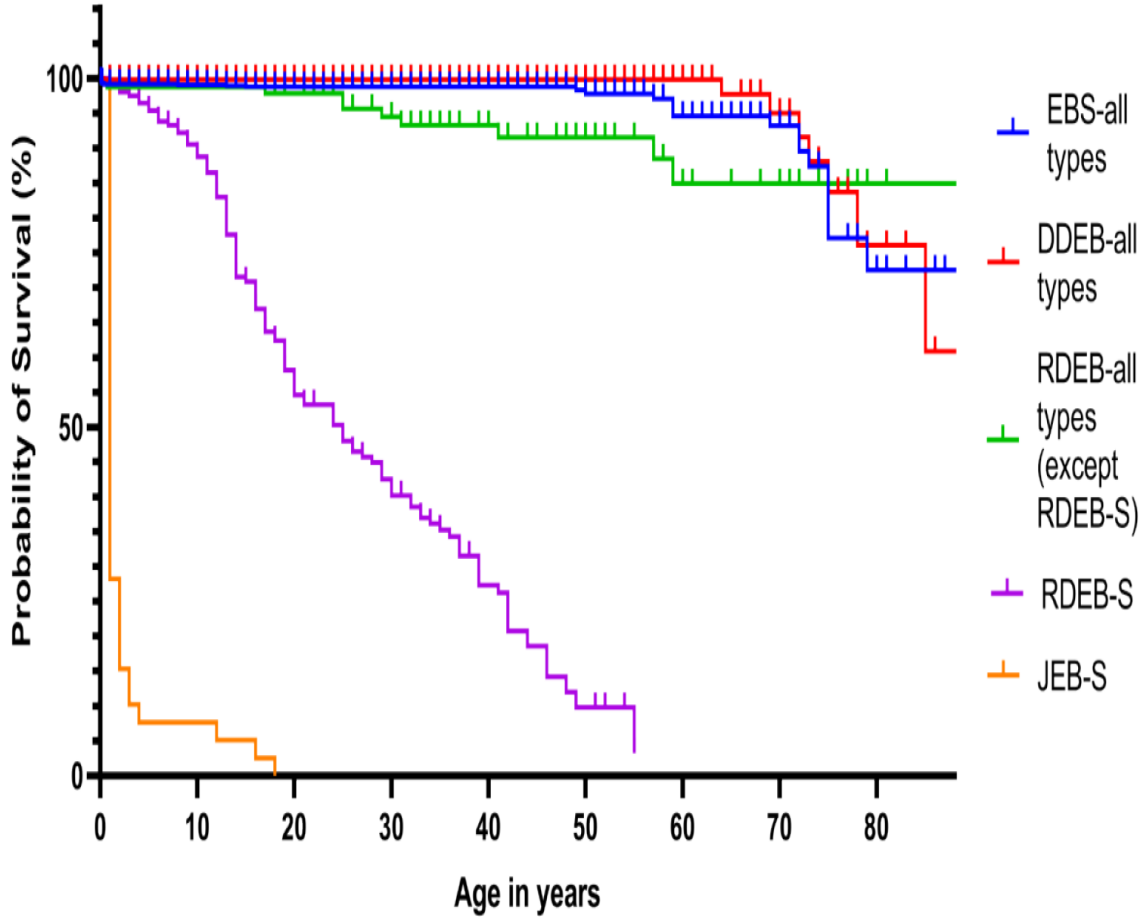
Mortality curves in company's base case (mapped to 6HS model post-TE)

	Mortality curve (age entered model)
DDEB	All severities, all ages: general population
RDEB	HS1: average of general population and RDEB non-severe RDEB HS2-5: RDEB non-severe RDEB HS6: RDEB severe

B-VEC, Beremagene geperpavec; BBE, birch bark extract; BSAP, body surface area percentage; DDEB, dominant dystrophic epidermolysis bullosa; GI, gastrointestinal; HS, health state; SCC, squamous cell cancer; RDEB, recessive dystrophic epidermolysis bullosa; TE, technical engagement

Key issue: Plausibility of reduced clinical manifestations

Probability of survival among patients with EB according to age and EB type in Petrof et al. (2022).



Link to main slides: key issue: clinical manifestations

DDEB, dominant dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; RDEB, recessive dystrophic epidermolysis bullosa; JEB, junctional epidermolysis bullosa; S, severe

Carer QoL

Link to main slides: summary of company and EAG base case assumptions

Carer QoL in the company's model

Health state	HST 28 company's base case	Number of carers	% of utility loss for additional carers	Carer QALYs accrued per year in health state
HST28 data*				
HST 28 HS 1 (BSAP ≤ 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 ≥ 25%)	0.64	1.78	77%	1.18
* The 77% for 2nd caregivers only applied in the post technical engagement model in HST28 and therefore the company did not apply this in their replication of the HST28				

QALY accrual in company and EAG base case

	Company base case			EAG base case		
	QALYs patients	QALYs carers	Inc. QALYS carers	QALYs patients	QALYs carers	Inc. QALYS carers
B-VEC	13.03	36.19		13.12	36.92	
BBE	9.45	34.35	1.84	11.26	36.51	0.41
BSC	5.71	31.14	5.05	9.17	35.08	1.82

NICE technical team: Extremely large carer QALYs accrue in company and EAG base case → plausible?

EAG: absolute QALYS high as multiple carers permitted but only incremental QALYs decision-relevant.

- Approach aligns with HST28

BSAP, body surface area percentage; HS, health state; HST, highly specialised technology; Inc., incremental; QALY, Quality-Adjusted Life Year; QoL, quality of life

Issues resolved at technical engagement (1)

Company updates model structure and distribution on stopping treatment with BBE and B-VEC

Issue	Company's original model	Company response to TE	Stakeholder response to TE	EAG response
Model structure	4-HS structure to align with Eng et al. + extra "Very Mild" state for improved health with B-VEC → mapped inputs from the 6-HS model used in HST28 categories	6-HS structure as per HST28. ***Scenario:*** 7-HS structure to capture full value of B-VEC in milder health states.	**Chiesi (BBE manufacturer):** mapping from 6 to 4HS oversimplifies progression in highly heterogeneous condition • BSAP not relevant outcome → not collected in GEM-1 or -3 and BSA use capped by licence → should model wound healing not BSAP • Could impact bandage costs & overall QALY gains	Company's 6HS model appropriate. Understand rationale for 7-HS model but: • No transitions available except from unreliable PLS. • Claim extra HS captures impact of B-VEC lacks face validity → lower B-VEC incremental QALYs in HS1 using 7HS vs. 6HS
Health state on stopping B-VEC/ BBE	People remain in HS occupied on treatment	People redistributed across health states in line with the HS distribution observed in BSC arm	**BAD:** expect return to former HS over months once stop treatment **Chiesi (BBE manufacturer):** dynamic cycle of wound healing and reopening, reverting to baseline. **NHS England**: RWE useful.	Issue resolved.

B-VEC, Beremagene geperpavec; BAD, British Association of Dermatologists; BBE, birch bark extract; BSA, body surface area; BSAP, body surface area percentage; BSC, best supportive care; HS, health state; PLS, patient level simulation; QALY, Quality-Adjusted Life Year; RWE, real world evidence; TE, technical engagement. Link to main slides: summary of company and EAG base case assumptions

Issues resolved at technical engagement (2)

Company updated base case uses EAG's preferred utility values and survival extrapolation

Issue	Company's original model	Company response to TE	Stakeholder response to TE	EAG response
Utility values	Utility values from vignette study, despite relevant health state utilities from EASE being available.	Updated base case uses Generalised Linear Model (GLM) based on EQ-5D from EASE trial. Issue with age-adjustment of carer utility corrected.	**Chiesi (BBE manufacturer):** agree that EASE EQ-5D appropriate and so vignette unwarranted. Vignette values overestimate QALY gain for B-VEC vs BBE	Issue resolved
Survival curve for each health state	Exponential curve (to represent constant hazard of death)	• Gompertz curve for both severe and non-severe RDEB • Severe RDEB curve only used for worst health state (HS6), all other health states use non-severe curve from Petrof et al.	-	Gompertz has better fit to observed mortality data for severe RDEB than exponential → issue resolved

Link to main slides: summary of company and EAG base case assumptions

B-VEC, Beremagene geperpavec; BBE, birch bark extract; HS, health state; TE, technical engagement; RDEB, recessive dystrophic epidermolysis bullosa