NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using beremagene geperpavec in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: June 2026

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using beremagene geperpavec in the NHS in England.

For further details, see NICE’s technology appraisal and highly specialised technologies guidance manual.

The key dates for this evaluation are:

- Closing date for comments: 17 July 2026
- Second evaluation committee meeting: 24 September 2026
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Beremagene geperpavec should not be used to treat skin wounds associated with dystrophic epidermolysis bullosa (DEB) in people of all ages who have mutations in the collagen type 7 alpha 1 chain (COL7A1) gene.

1.2 This recommendation is not intended to affect treatment with beremagene geperpavec that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For babies, children or young people, this decision should be made jointly by the healthcare professional, the child or young person if appropriate, and their parents or carers.

What this means in practice

These are NICE's draft recommendations. If these recommendations become final, beremagene geperpavec would not be required to be funded and should not be used routinely in the NHS in England for the condition and population in the recommendations.

This is because the available evidence does not suggest that beremagene geperpavec is value for money in this population.

Why the committee made these recommendations

Usual treatment for skin wounds associated with DEB is birch bark extract and best supportive care, which includes wound management, surgery and pain management.

Clinical trial evidence shows that beremagene geperpavec with best supportive care closes wounds more quickly than placebo with best supportive care.

Beremagene geperpavec has not been directly compared in a clinical trial with birch bark extract. An indirect comparison suggests that it is likely to be more effective, but the extent of this is uncertain because the studies used different ways to measure results.

There are also uncertainties in the economic model because of the assumptions about:

- who would have beremagene geperpavec in clinical practice
- how the wounds develop, close and progress
- whether people would have beremagene geperpavec at home, instead of in a specialist clinic, and how that would be delivered
- whether beremagene geperpavec reduces non-skin-related complications of DEB
- how much beremagene geperpavec a person needs over their lifetime.

Even when considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates are substantially above the range that NICE normally considers an acceptable use of NHS resources.

Collecting more evidence during a managed access period may resolve some uncertainty in the evidence but the company has not submitted a managed access proposal. So, beremagene geperpavec should not be used.

2 Information about beremagene geperpavec

Marketing authorisation indication

2.1 Beremagene geperpavec (Vyjuvek, Krystal Biotech) is indicated for 'the treatment of wounds in patients with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene, from birth'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for beremagene geperpavec.

Price

2.3 The list price is £21,500 per 1-ml vial of beremagene geperpavec, providing 4 extractable 0.5-ml doses when prepared (excluding VAT; company submission).

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes beremagene geperpavec available to the NHS with a discount and it would have also applied to this indication if beremagene geperpavec had been recommended. The size of the discount is commercial in confidence.

Sustainability

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Krystal Biotech will be included here when guidance is published.

3 Committee discussion

The evaluation committee considered evidence submitted by Krystal Biotech, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Epidermolysis bullosa (EB) is a rare condition caused by gene mutations that mean certain skin anchoring proteins are not expressed correctly or are disrupted. This results in very fragile skin that blisters and breaks frequently, particularly in response to minor trauma or friction. There are various types of EB, but beremagene geperpavec is only indicated for dystrophic EB (DEB). DEB affects a part of the skin called the sublamina

densa, below the lamina lucida. There are 2 types of DEB, defined by whether 1 or 2 copies of the collagen type 7 alpha 1 chain (COL7A1) gene are affected. In dominant DEB (DDEB), the mutation is only in 1 copy of the COL7A1 gene. Life expectancy is typically unaffected, and blistering is usually confined to areas exposed to friction. Recessive DEB (RDEB) is often more serious because both copies of the COL7A1 gene are affected. This form of the condition often leads to widespread blistering and more extensive skin damage, resulting in an increased risk of death from aggressive skin cancer. The clinical experts explained that wounds can also form internally, and can lead to widespread complications affecting body systems such as the eyes and gastrointestinal tract. Severe forms of DEB are likely to present from birth and so are often diagnosed in babies or children. The committee concluded that DEB can be a severe and life limiting condition, particularly in the more severe cases, that often affects young children.

Natural history of the condition

3.2 The clinical experts explained that, in people with DEB, blistering may be caused by daily actions such as rubbing, scratching, or light bumps. A patient expert at the meeting explained that blisters were not limited to any specific area and are not self limiting. That is, they blister or a subsequent wound may continue to increase in size if not managed carefully. The clinical experts explained that there are 2 different types of wounds:

- recurrent wounds, which:
  - are generally small to medium sized
  - usually heal spontaneously within a few weeks
- chronic wounds, which:
  - tend to be larger and more painful
  - may cover an entire body region, such as the back or a limb

- tend to remain open for at least 4 weeks, with some never fully healing.

The clinical experts explained that DEB is associated with a dynamic cycle of wound healing and reopening. It is a progressive disease and the ability to heal reduces over time. After the age of 10 years, wound healing becomes increasingly difficult because stem-cell reserves in the bone marrow deplete. This can cause recurrent wounds to become chronic. So, the number and size of chronic wounds increase over time. The clinical experts explained that people with both subtypes of DEB can experience a range of wound types, but those with RDEB are more likely to develop chronic wounds. Skin affected early in life becomes more fragile after series of closing and reopening, breaking down very easily. After infancy, many wounds are from the reopening of previously damaged skin rather than entirely new lesions. So, it can be difficult to distinguish between new and recurrent wounds. Wound reopening is most common in areas of high friction such as the hands, feet and elbows. This can cause increased scarring, which can lead to digit fusion (known as mitten deformities). The clinical experts explained that some people with DEB are born with damage to the skin. Known as birth wounds, these are harder to heal than new wounds. They often become chronic, associated with severe scarring that may limit the ability to ever walk. The committee concluded that wound patterns in DEB are complex, involving a combination of new wounds forming, existing wounds reopening, and some wounds becoming chronic over time.

Effects on quality of life

3.3 The patient experts emphasised that DEB can have a debilitating impact on all aspects of life, particularly in more severe forms such as RDEB. It can cause constant blistering and pain, and substantial segments of skin may fall off. A patient expert explained that blistering and wounds can be so severe that people may be unable to walk, hold or touch anything.

They explained that chronic wounds can consist of completely raw skin that can cover extremely large areas and are intensely painful. The patient experts also noted that with some wounds not healing for many months and increased risk of infection, this can lead to fatigue and sleep disruption, which are often exacerbated by persistent pain and itching. They also emphasised the large impact of non-skin-related symptoms. These include corneal abrasions, which can cause vision loss, and gastrointestinal and oral lesions that can lead to nutritional problems and may impair growth in children. A patient organisation emphasised the substantial psychological burden associated with the condition, driven by lifelong relentless pain, loss of independence, and stigma associated with the visible appearance of wounds. The patient expert also explained that wound management is highly burdensome, in their case taking them up to 7 hours per day. Some carers may need to leave work to provide full time care, which has financial implications. Education can also be disrupted by wound dressing and hospital visits. The clinical experts explained that high levels of inflammation from infection of chronic wounds can cause health conditions such as anaemia and osteoporosis. They emphasised that specialist care is delivered at 4 centres across the UK, so some people need to travel considerable distances to access treatment. The committee concluded that DEB has extensive and severe effects on the quality of life of people with the condition, their families and carers.

Clinical management

Treatment options

3.4 The clinical experts explained that there were no licensed disease-modifying treatments for DEB. Current care has 3 broad categories:

- wound management, which includes bathing to wash wounds, lancing and draining blisters and using non-adhesive dressings and bandages to manage open wounds. NICE's highly specialised technologies guidance on birch bark extract for treating epidermolysis bullosa (from

here referred to as HST28) recommends birch bark extract for partial thickness wounds (wounds that extend through multiple different layers of the skin surface) associated with DEB and junctional EB in people 6 months and over. The clinical experts explained that birch bark extract, if used, is always an add-on to standard wound management. Antibiotics are also used to treat infection

- surgery, which is used to manage complications of DEB such as fusion of fingers and squamous cell cancer
- pain management, which includes pharmacological and non-pharmacological interventions to manage the pain and itch from DEB and from surgical and wound management procedures.

Treatment for clinical manifestations also includes dental care for oral blisters and long-term nutritional support. Opioids such as morphine might also be needed for pain relief during dressing changes. The clinical experts at the meeting emphasised the unmet need for new treatments to address the underlying cause of DEB. They stressed that best supportive care is limited to symptom management. And birch bark extract, while licensed for the condition, is not disease modifying and may have limited effectiveness in closing wounds. The committee recalled the high burden of treating and dressing wounds (see section 3.3). It concluded that people with DEB would welcome a treatment that reduces treatment burden and addresses the underlying cause of the condition.

Comparators

3.5 The clinical experts explained that response rates to birch bark extract vary. They estimated that about 50% of people see a benefit in wound-closure rates. They emphasised that only about 10% of people with DDEB use birch bark extract in clinical practice. This is because they typically have smaller, fewer and less severe wounds compared with RDEB, many of which resolve spontaneously over time. The clinical expert also explained that birch bark extract usually only has a small benefit in severe RDEB. A patient expert emphasised that some people do not want to use

birch bark extract, especially on large chronic wounds, because its oily consistency can hinder wound drying and may increase the risk of infection. The thickness of the preparation can also limit its practicality for larger wounds, because applying dressings evenly can be difficult and may leave residual product on the wound. So, many people rely on best supportive care alone. The committee noted that the summary of product characteristics permits beremagene geperpavec to be used on wound areas of up to 200 cm² per week. It recalled that people with DEB may have wounds distributed across their body, including some large chronic wounds. So, it thought that some people may wish to treat wounds over the maximum permitted surface area. The clinical experts at the meeting confirmed that beremagene geperpavec would likely be the preferred treatment for large, chronic wounds, because it directly addresses the underlying cause by replacing the missing COL7A1 gene. But birch bark extract would likely be used at the same time, to treat small and superficial wounds. The committee concluded that the relevant comparators were birch bark extract with best supportive care and best supportive care alone. It agreed that further real-world evidence would be useful to resolve the uncertainty about who uses birch bark extract in clinical practice. It also concluded that beremagene geperpavec and birch bark extract (with best supportive care) may also be used in combination in clinical practice.

Clinical effectiveness

Data sources

3.6 Clinical-effectiveness data for beremagene geperpavec came from 2 clinical trials and an open-label extension study. Both trials used an intra-patient design in which different target wounds (a single wound used to assess outcomes such as wound closure and speed of wound healing) on the same person were treated. The trials were:

- GEM-1/-2 (from here, referred to as GEM-1), which was an open-label randomised controlled trial, consisting of 2 phases. Phase 1 enrolled 2 people aged 18 and over with 2 wounds of less than or equal to 10 cm^2. Phase 2 consisted of 3 parts and enrolled 10 people aged 2 years and over with at least 2 wounds of less than or equal to 50 cm^2. Wounds were treated with a range of doses between 8×10^8 and 1.2×10^9 plaque forming units (PFU) or placebo at a range of dosing frequencies. The primary outcome was the proportion of wounds with complete closure at weeks 8, 10 and 12. Time to, and duration of, wound closure was also collected
- GEM-3, which was a double-blind, randomised controlled trial in 31 people aged over 6 months. The key outcomes were the proportion of wounds with complete wound closure at 6 months (the primary outcome) and at 3 months (considered a key secondary outcome). 2 wounds of similar size were treated, 1 with beremagene geperpavec and another with placebo. People had beremagene geperpavec at a dose according to their age and wound area up to a maximum dose of 1.2×10^9 PFU for 6 months or until wound closure, after which they were followed up for 30 days
- an open-label extension study for GEM-3, which enrolled 23 people with DEB who had not previously had beremagene geperpavec and 24 people from GEM-3. People had weekly beremagene geperpavec up to the maximum weekly dose (1×10^9 PFU) until wound closure. The key outcomes were safety and tolerability, health-related quality of life and durability of wound closure.

The committee noted that, in GEM-1 and GEM-3, beremagene geperpavec and placebo were used as add-ons to best supportive care. The committee agreed that the relevant clinical-effectiveness data from beremagene geperpavec came from GEM-1, GEM-3 and the GEM-3 open-label extension study.

Results

3.7 The GEM-3 results suggested that more wounds closed when treated with beremagene geperpavec compared with placebo. Specifically:

- complete wound closure increased by 46% with beremagene geperpavec compared with placebo at 6 months (primary endpoint; beremagene geperpavec 67%, placebo 22%, 95% confidence interval [CI] 24 to 68; p=0.002)
- complete wound closure increased by 51% with beremagene geperpavec compared with placebo at 3 months (key secondary endpoint; beremagene geperpavec 71%, placebo 20%, 95% CI 29 to 73; p<0.001).

There was no statistically significant reduction in pain severity. Health-related quality-of-life improvements were seen in people aged over 12 years using the EQ-5D-5L but not the Skindex-29 instrument. In the open-label extension study, 63% of people had complete wound closure at 12 months for primary wounds previously treated with beremagene geperpavec during GEM-3. The GEM-1 results supported a benefit for beremagene geperpavec compared with placebo because:

- 79% more people met the criteria for a responder (defined as complete wound closure at weeks 8 and 10 or weeks 10 and 12) with beremagene geperpavec than placebo (79% compared with 0%, p=0.0026)
- there was a shorter median time to complete closure with beremagene geperpavec (13.5 days, 95% CI 8 to 21) than placebo (22.5 days, 95% CI 8 to 64)
- there was a longer median duration of closure with beremagene geperpavec (103 days, 95% CI 94 to 118) than placebo (16.5 days, 95% CI 0 to 66).

The committee agreed that the available clinical evidence supported a

benefit in wound-closure rates for beremagene geperpavec compared with placebo.

Generalisability

Wound dynamics

3.8 The committee acknowledged that DEB is characterised by dynamic wound patterns, with wounds continually opening and closing over time. It considered whether the clinical trials for beremagene geperpavec adequately captured the full natural history of the condition. The committee noted that:

- Complete wound closure had been captured as an outcome in both GEM-1 and GEM-3. The EAG noted that this was defined differently, with a less stringent definition in GEM-1 (90% or more reduction in wound surface compared with baseline) compared with GEM-3 (100% reduction in wound area from baseline).
- Target wounds that reopened had only been assessed in GEM-1, which captured the time to wound closure and duration of closure. The EAG emphasised that GEM-1 only included a small number of people and used different doses to that in the licence for beremagene geperpavec.
- The opening of new wounds or wounds that were closed at baseline had not been captured in the clinical evidence. This was because both trials used an interpatient design, which monitored changes in target wounds identified at baseline only.
- The GEM trials did not distinguish between chronic and recurrent wound types. The committee recalled that treatment and outcomes differed between wound types (see section 3.2). The company explained that data on wound types was not collected because beremagene geperpavec promotes wound closure by replacing the missing COL7A1 gene, regardless of wound type. It noted that the available evidence suggested consistent treatment effect across

different wound sizes and ages. But the EAG noted that 22% of wounds in the placebo arm closed within 6 months of entering the study, suggesting that some recurrent wounds close spontaneously. But it was uncertain whether wounds that closed spontaneously were evenly distributed in both trial arms. The committee acknowledged this introduced uncertainty into the results.

The company emphasised that because beremagene geperpavec addresses the underlying condition by replacing the defective COL7A1 gene, it is likely to keep wounds closed for longer than birch bark extract or best supportive care. But the committee agreed that the duration of wound closure with beremagene geperpavec was highly uncertain and supported by limited evidence. It was concerned that the company's clinical evidence did not fully capture the natural history of DEB, especially the opening of new wounds. It agreed that this introduced uncertainty into the results.

DEB subtypes

3.9 The marketing authorisation for beremagene geperpavec included all people with DEB with mutation in the COL7A1 gene. The committee recalled this included people with RDEB and DDEB. But the EAG advised that only 1 person GEM-1, 1 person in GEM-3 and 1 extra person in the open-label extension study had DDEB. The company considered that the lack of data in DDEB was a consequence of the rarity of the condition. But it expected beremagene geperpavec to be effective in both subtypes because it replaces the missing functional COL7A1 gene. The company provided evidence of response in the DDEB subtype from both the US and the open-label extension study to support this. The committee recalled the difference in severity and treatment outcomes for the different DEB subtypes (see section 3.1). The EAG was concerned that the treatment effect from the company's clinical trials may not be generalisable to people with DDEB. It noted biological rationale for differences in treatment effect by subtype, given that DDEB is associated

with less severe collagen abnormalities and retention of a functional COL7A1 gene. The clinical experts at the meeting supported this, stating that people with DDEB generally have a smaller wound burden, with mostly recurrent wounds that close within a few weeks with best supportive care. They explained that only a small proportion of people with DDEB were likely to have beremagene geperpavec in clinical practice, and this population would be determined by the specialist centres. This would mostly be adults with recurrent wounds that have become chronic, or wounds that are particularly painful or in areas affecting functionality and that may not heal without further treatment. But most people with RDEB were likely to have beremagene geperpavec in clinical practice. The committee noted that the company had not provided analyses considering the impact of beremagene geperpavec by subtype. It noted that the population with DDEB who would have beremagene geperpavec in clinical practice was uncertain because it had not been defined by the company. It agreed that the following should be submitted at consultation:

- the proportion of people having beremagene geperpavec for RDEB and DDEB in clinical practice
- the criteria for identifying people with DDEB for treatment, including any wound-burden thresholds for treatment
- clarification of which people with DDEB are represented by the RDEB data in the GEM studies.

The committee concluded that it was uncertain which people with DDEB would have beremagene geperpavec in clinical practice and how these people were represented in the clinical evidence. It agreed that the company should provide clarification at consultation.

Comparative effectiveness

Indirect treatment comparison

3.10 There were no clinical trials directly comparing beremagene geperpavec with birch bark extract. The committee noted that clinical-effectiveness data for birch bark extract was available from the EASE trial. This was a phase 3 randomised double-blind trial that included people with both subtypes of DEB as well as junctional EB (in which blistering occurs in the basement membrane of the skin). A single target wound of between 10 cm^2 and 50 cm^2 was randomised to have either birch bark extract gel or a control gel for 90 days. After this, people could have birch bark extract for up to 24 months. The company stated that an indirect treatment comparison (ITC) between GEM-3 and EASE was not feasible. This was because there were differences between trials in:

- the overall trial design, frequency of placebo use and permitted concomitant treatments
- the characteristics of the people included, such as:
  - median age
  - wound size
  - DEB subtype proportions
- trial endpoint definitions, including:
  - complete wound closure: GEM-1 and GEM-3 used stricter closure criteria and only counted wound closure at the end of the assessment period, but EASE counted closure at any time during the assessment period
  - time to wound closure.

The company also reiterated that birch bark extract was likely to be used on smaller, recurrent wounds. But beremagene geperpavec is likely to be used for treating larger wounds (see section 3.5). It stated that comparing the 2 treatments in an ITC was inappropriate. So, it used a patient-level simulation (PLS) to derive the relative treatment

effect in its base case, which did not use the wound-closure data from GEM-3 (see section 3.7). Clinical experts at the meeting also agreed that differences in trial design and outcomes made an ITC challenging to complete. The EAG acknowledged this, but noted that its absence limited the ability to inform decision making. It did a Bucher ITC comparing the GEM-3 and EASE wound-closure data, using the placebo arm as a common comparator and the following secondary outcomes from each study:

- the proportion of wounds with 100% closure at 3 months confirmed at 2 consecutive visits 2 weeks apart in GEM-3 for beremagene geperpavec (71%)
- the proportion of wounds that closed at least once within 90 days in EASE for birch bark extract (50.5%).

This resulted in a relative risk of 3.12 (95% CI 0.66 to 14.82), supporting a benefit in wound closure for beremagene geperpavec compared with birch bark extract. The committee agreed that the results of the EAG's ITC suggested that beremagene geperpavec is better than birch bark at closing wounds associated with DEB.

EAG's ITC

3.11 The company was concerned that the EAG's ITC only captured the rate of wound closure, because time to closure and duration of closure were not assessed in GEM-3 (see section 3.6). It reiterated that beremagene geperpavec was expected to keep wounds closed for longer than birch bark extract or best supportive care because it addresses the underlying condition (see section 3.5). So, by excluding benefits related to the duration of wound closure, the EAG's ITC was likely to substantially underestimate the overall treatment effect of beremagene geperpavec. The company was also concerned about the use of the EASE data, in which not all open wound area was treated. This introduced a disconnect with the PLS used to estimate vial usage, which assumed that the entire open wound area was treated (see section 3.14). The committee also

noted that the median wound size in EASE was considerably larger than in GEM-3, which may have introduced uncertainty into the results. It considered that EASE included wound sizes that may be different to those treated in clinical practice (see section 3.5). It noted this likely favoured beremagene geperpavec because GEM-3 had smaller wounds to close. But the committee noted that the company's approach did not use data from GEM-3, which it decided was the most robust source of clinical-effectiveness data. It agreed that excluding duration of wound closure was a limitation of the EAG's approach, meaning the ITC likely underestimated the full treatment effect of beremagene geperpavec. The committee noted the limited clinical evidence and that the ITC was an anchored comparison of available phase 3 data. It noted that the different methods of assessing wound closure between trials (with stricter closure thresholds requiring confirmation in the GEM trials) may also have resulted in an underestimate of the relative treatment effect of beremagene geperpavec with the EAG's approach. But it agreed that the EAG's ITC did provide a comparison of EASE and GEM-3. Despite the limitations, the committee concluded that it was a useful comparison of birch bark extract and beremagene geperpavec.

Economic model

Company's modelling approach

3.12 The company's model after technical engagement consisted of a state transition model with 7 health states to model the disease course of DEB. Beremagene geperpavec was compared with best supportive care and birch bark extract. Both beremagene geperpavec and birch bark extract were assumed to be used as add-ons to best supportive care. The company model after technical engagement aligned with that used in HST28. The model was based on the body-surface-area percentage (BSAP) score, which is a way of measuring DEB disease severity. Health states 1 to 6 were defined by taking the BSAP score range reported for EASE and dividing it up equally between 6 states. The higher BSAP score

health states represented more severe disease and a seventh health state represented death. The committee noted that BSAP only describes the amount of the skin surface covered in wounds. It does not capture the impact or location of wounds, and does not describe other aspects of the condition, such as damage to the gastrointestinal tract. In each of the 13-week cycles, people in the modelled cohort could move between any of the health states and to the absorbing death state. Movement between the health states was determined by transition probabilities (see section 3.14). Transition probabilities, risk of death and drug use were calculated according to age (0 to 6 years, 6 to 18 years and 18 years and over) and aggregated for the whole cohort. The model also included an increased risk of death for people with RDEB based on rates from Petrof et al. (2022). Beremagene geperpavec was assumed to be used for life but 1% of people were modelled to stop treatment every year (see section 3.17). The committee concluded that the company's model after technical engagement was appropriate for decision making.

Baseline distribution by health state

3.13 The company derived the baseline distribution in each health state from Bruckner et al. (2020) using the percentage of body surface area covered by wounds in the RDEB and DDEB population. Bruckner et al. defined 3 severities, based on the body surface area covered by open wounds: mild (BSAP less than 10%), moderate (BSAP 10% to 30%) and severe (BSAP over 30%). The EAG explained that these definitions did not fully align with those in the company's model. So, it preferred to use the baseline distribution by health state from EASE. The committee noted that this aligned with the EAG's preferred source of clinical-effectiveness evidence for birch bark extract in the ITC (see section 3.10). So, to best align with the available clinical evidence, it agreed that the EAG's approach using the EASE baseline distributions by health state was appropriate for decision making.

Modelling clinical effectiveness

Company's PLS

3.14 GEM-1 and GEM-3 did not track changes in BSAP of participants because of their intra-patient designs. So, the company designed a PLS model to estimate wound closure and reopening rates over time for beremagene geperpavec and comparators. In this, people in the 3 age cohorts were distributed across 3 mutually exclusive health states: recurrent wounds (open), chronic wounds (open), and closed wounds. Transitions between these states were estimated by the proportion of body surface area affected by open wounds. This was simulated within the model and used to reassign people to health states at each weekly cycle. Closed wounds could subsequently reopen, and a proportion of chronic wounds were assumed not to respond to beremagene geperpavec and birch bark extract. Health-state transitions were estimated every 13 weeks for 10 years based on the change in body surface area affected and applied in the company's Markov model. After 10 years, the most recent transitions were carried forward, that is, a steady state assumed from 10 years onwards. The committee decided this was associated with uncertainty in a progressive condition such as DEB. The committee thought that the structure of the company's PLS was acceptable for modelling wound closure and reopening. But it was concerned that people could not have an increase in BSAP from baseline. So, the model did not capture opening of new wounds, or reopening of old wounds that were closed at baseline. The committee acknowledged that wound burden generally increases with age because of greater skin fragility (see section 3.2). So, it found it implausible that the extent of skin affected by wounds would not increase over the modelled lifetime. This was particularly because some people entered the model as young as 2 years old. It also noted that incorporating transition probabilities from the PLS into the Markov model added unnecessary uncertainty. Instead, it would have preferred the company to use the PLS directly to generate the complete cost-effectiveness outcomes. The committee concluded that the

company's modelling approach introduced unnecessary complexity. It agreed that the PLS did not fully capture the progressive nature of DEB and any updates to the PLS at consultation should allow for increases in BSAP affected by wounds from baseline.

Clinical data in the PLS

3.15 The company populated the PLS using a range of sources:

- After technical engagement, to calculate the weekly closure rates separately for chronic and recurrent wounds, it:
  - based rates of recurrent wound closure for beremagene geperpavec and best supportive care on wound-level data from GEM-1 with censoring at first closure (42.54% and 14.17% respectively). For birch bark extract, it applied the relative risk from the EAG's ITC (3.12) to the rate for beremagene geperpavec, giving a weekly closure rate of 16.27%
  - based rates of chronic wound closure on a structured expert elicitation (SEE) that it did for beremagene geperpavec (36.7%). It used literature estimates to inform rates for best supportive care (0.57%; Fulchand et al. 2021) and birch bark extract (3.17%, Davidovic et al. 2026 [PDF only])
  - assumed that a higher proportion of chronic wounds would respond to beremagene geperpavec than to birch bark extract. For beremagene geperpavec, the company used the response rate estimated by clinical experts in the SEE (exact rates are confidential and cannot be reported here). Using data from Davidovic et al. (2026) it modelled that 73% of chronic wounds would respond to birch bark extract.
- The company calculated the proportion of old wounds reopening using the median duration of closure in the GEM-3 open-label extension study for beremagene geperpavec and in GEM-1 for best supportive care. For birch bark extract, it estimated reopening rates using the SEE (exact results are confidential and cannot be reported here).

- It defined a chronic wound as one that fails to close within 8 weeks, and calculated the number of chronic wounds using the reopening rate. The proportion of wounds becoming chronic was lower for beremagene geperpavec (1.19%) compared with best supportive care (29.45%) and birch bark extract (24.16%).

The committee noted that the EAG had concerns about the assumptions and inputs used in the company's PLS and the implausibility of some of its outputs. Specifically, that:

- The PLS predicted everyone having beremagene geperpavec was in the very mild health state (BSAP 0 to less than 5%) by about 2 years in the model. The company explained that wounds were still reopening in this health state but closed rapidly when treated with beremagene geperpavec. But the committee thought that this assumption was not supported by evidence and lacked face validity for a progressive disease like DEB. It thought that this resulted in implausibly low beremagene geperpavec use in the company's model (see section 3.22).
- People having beremagene geperpavec with a wound area exceeding the licensed maximum size of 200 cm^2 (see section 3.20) did not accrue the treatment effect associated with best supportive care for wounds outside of that area, meaning these wounds were effectively untreated.
- Scenarios lowering the response rates of chronic wounds to beremagene geperpavec increased the proportion of people in very mild health states compared with the company's base case. This suggests that the company's modelling lacked face validity.
- The PLS predicted higher and faster healing rates for birch bark extract (that is, more people moving to the very mild health state more quickly) than reported in EASE.
- The company excluded wound-closure data from GEM-3. Instead, it used GEM-1 to inform wound-closure assumptions for recurrent

wounds for beremagene geperpavec and best supportive care. The committee recalled that GEM-1 was small and used a dosing less consistent with the licence for beremagene geperpavec than GEM-3 (see section 3.6).

- There were fewer wounds simulated in the very mild health state in the company's 7-state model after technical engagement than in its original 5-state model.
- The rate of chronic wound closure for beremagene geperpavec and weekly reopening rates for birch bark extract in the PLS were informed by the SEE. The EAG raised concerns about ambiguous SEE questions and implausibly faster closure with birch bark extract compared with best supportive care. It was also concerned about the use of a fixed closure rate in the PLS despite a lack of expert support.

Overall, the committee shared the EAG's concerns that the transitions from the company's PLS lacked face validity and relied heavily on indirect data and multiple assumptions, adding unnecessary complexity. Specifically, it was concerned that:

- NICE's technology appraisal and highly specialised technologies guidance manual states a preference for randomised controlled trial data above expert elicitation if available. This is because of the risk of bias and high uncertainty associated with a SEE. So, the results of the SEE were likely more uncertain than those from GEM-1 or GEM-3.
- The reopening rate for birch bark extract was higher compared with best supportive care alone. The committee was concerned that this was implausible, given that birch bark extract was an add-on to best supportive care in the model.
- The lack of inclusion of GEM-3 wound-closure data and new wound assumptions was a major limitation (see section 3.9).
- More severe DEB cases may be underrepresented in EASE and GEM-1 because of the maximum wound size restrictions.

- GEM-1 used overlapping data because the same people were included in the phase 2a and 2b studies.
- BSAP as an outcome measure may not fully reflect the full quality of life or wound severity associated with DEB.

Based on this, the committee concluded that the company's PLS, using the current inputs and with the current implausible outputs, was not acceptable for decision making.

Committee's preferred approach for treatment effectiveness

3.16 The EAG did an ITC to estimate the relative effectiveness for beremagene geperpavec compared with birch bark extract (see section 3.10). Its base case used transition probabilities for birch bark extract and best supportive care derived from EASE. It then applied the relative risk from the ITC to the birch bark extract transitions to estimate transition probabilities for beremagene geperpavec. The company raised concerns that the EAG's approach relied on approximated transitions from EASE, because the direct transition data preferred by the committee in HST28 were confidential. But the EAG noted that using direct transitions would likely give less favourable outcomes for beremagene geperpavec. This was because they were less favourable to birch bark extract than placebo compared with the approximated values. The committee recalled its concern that duration of closure and reopening of wounds was not captured in the EAG's approach, so it likely underestimated the full benefits of beremagene geperpavec (see section 3.10). It noted the EAG's scenarios that varied the relative risk to 2 and 10 had a large effect on the cost-effectiveness results. It agreed these were helpful in demonstrating the uncertainty around this parameter. But the EAG emphasised that the company's PLS results lacked face validity and that there was a lack of trials capturing outcomes for beremagene geperpavec at the whole-patient level. Because of this, it preferred to base clinical effectiveness on existing transition data from EASE. The committee acknowledged limitations with both the company's and EAG's approaches

to clinical effectiveness (see section 3.10 and section 3.15). It thought that the EAG's ITC had the advantage of being simpler, more transparent, using the available trial data and avoiding the many assumptions included in the PLS. But it recalled that the ITC may underestimate some key benefits of beremagene geperpavec compared with birch bark extract. This is because it did not directly consider duration of wound closure or wound reopening (see section 3.11). Also, the committee had concerns about anchoring the relative effectiveness to the birch bark extract transitions because:

- applying the relative risk derived from treating an individual wound in GEM-3 to the full BSAP affected in the model, assumed that relative treatment effects were constant across the whole BSAP affected. The committee found this unrealistic given the application limit for beremagene geperpavec set out in its license. So, the relative risk derived from the ITC may be overly optimistic when applied in the model
- not everyone has birch bark extract in clinical practice (see section 3.5). So, applying the treatment effect from beremagene geperpavec to the birch bark extract transitions may not be appropriate.

The committee noted that both the company's and the EAG's models assumed constant treatment effect with age. But DEB is a progressive condition with increasing wound burden over time and subgroup results from GEM-3 suggested the greatest treatment effect in people under 12 years (see section 3.2). The clinical experts at the meeting supported this, noting benefits were likely to be larger in younger people because stem cells remain available for wound healing and scarring is less advanced. The committee noted that the company modelled a lifetime horizon, but wounds become harder to close as people get older (see section 3.2). So, the committee agreed that the full benefits of beremagene geperpavec in young children and the lesser effect in adults

was likely not captured by the company's and EAG's approaches (see section 3.11 and section 3.15). So, it agreed that any data around treatment effect by age should be provided at consultation to make sure the model captures the natural history of the condition. The committee acknowledged that beremagene geperpavec is highly likely to be more effective than birch bark extract and best supportive care, but decided that the exact treatment effect was highly uncertain. It recalled that the company's PLS was not appropriate for decision making because the outputs lacked face validity (see section 3.15). So, given the options available, it was minded to use the EAG's ITC estimate in its decision making, which used the GEM-3 data and an anchored comparison. But it noted that the ITC, overall, may have underestimated the treatment effects, though it was difficult to quantify this. It also noted that, should the company still prefer the PLS, substantial corrections should be made at consultation. The corrections should ensure inputs and estimated outputs are clinically plausible and address the concerns outlined by the EAG and committee. The committee concluded that the EAG's ITC should be used for decision making, but the limitations of the ITC should be addressed at consultation.

Stopping treatment in the model

3.17 The company assumed that 1% of people would stop treatment with beremagene geperpavec every year. Because no one stopped treatment in GEM-1 and GEM-3, this was based on the stopping rate used in HST28. The company applied the same stopping rate of 1% annually for birch bark extract across all cycles, except for the first cycle in which a stopping rate of 8.3% was applied. The company assumed that people stopping beremagene geperpavec or birch bark extract would transition to health states based on the distribution observed in the best supportive care arm. The committee was concerned that the long-term stopping rate of 1% for beremagene geperpavec was low and unsupported by evidence. It noted that varying this assumption had a large impact on the cost-effectiveness results. It agreed that scenarios assuming alternative

long-term stopping rates should be provided at consultation as well as further rationale and data for these scenarios. The committee noted that people could also stop treatment because they had chronic wounds that did not respond to treatment, with stopping rates for beremagene geperpavec estimated in the SEE (see section 3.15). The committee recalled the uncertainty associated with the SEE estimates (see section 3.15). It noted that GEM-3 may provide evidence on short-term response rates with beremagene geperpavec (67% of wounds closed at 6 months and 71% at 3 months). It thought that the company should provide further details at consultation about the modelling of responders and non-responders and consider whether the available trial data could be used to inform the modelling. The committee concluded that additional justification for the stopping assumptions with beremagene geperpavec should be presented at consultation. This should include why people stop beremagene geperpavec, long-term annual stopping rates and initial stopping because of non-response to treatment, as well as an exploration of alternative data sources.

Utility values

Source of utility values

3.18 After technical engagement, the company's and EAG's base cases both used health-state utility values obtained by applying a generalised linear model to the 24-month data from the EASE open-label extension study. This was preferred by the committee in HST28. The model also captured the quality-of-life impact on carers, based on the assumed number of carers per person in each health state in HST28. This included multiple carers for people in the worst health states. The committee recalled the high quality-of-life burden associated with DEB and agreed that this was appropriate. It concluded that the company's utility values were acceptable for decision making.

Mortality

3.19 The company emphasised the lack of trial data to inform mortality estimates for people with DEB. Because of this, it used mortality estimates from Petrof et al. (2022) for people with RDEB. Different survival estimates for severe and non-severe RDEB were applied to the modelled health states based on the BSAP affected. Long-term mortality was extrapolated using a Gompertz curve in the company's base case after technical engagement. By reducing wound burden (that is, moving people to health states associated with a lower risk of death), the company modelled a mortality benefit for beremagene geperpavec compared with the comparators. The committee noted that 37% of the modelled population had DDEB and 63% had RDEB. It noted that general population mortality was assumed for people with DDEB, making subgroup distribution important for overall life years. The committee recalled that the proportion of people with each subtype who would have beremagene geperpavec in clinical practice was highly uncertain (see section 3.9). It noted that the EAG had explored a scenario in which the excess mortality associated with RDEB was applied to the entire modelled population, which effectively assumed that everyone had RDEB. But the committee found this assumption unrealistic, because some people with DDEB would also be expected to have beremagene geperpavec in clinical practice. So, the committee concluded that, during consultation, the impact of varying the proportions of people with RDEB and DDEB should be examined. These analyses should be done alongside an assessment of any limitations or loss of robustness associated with modelling these subgroups separately.

Costs

Beremagene geperpavec vial usage

3.20 The committee noted that the licence for beremagene geperpavec limited the maximum dose permitted by age to:

- a total of 1 ml (2 syringes) to treat 100 cm^2 of open wounds in children 3 years old and under
- a total of 2 ml (4 syringes) to treat 200 cm^2 of open wounds in people over 3 years old.

Further dose limitations were defined based on total wound surface area, with smaller maximum doses specified for wounds under 60 cm^2. Because there was no trial data using beremagene geperpavec for all open wounds from which to determine usage, the company used the PLS to predict the number of vials per cycle. It thought this was appropriate because the PLS tracks use over time in dynamic wounds. PLS also reflects the induction phase (when there are open wounds requiring high levels of vial use) and maintenance phase (when only wounds that reopen are treated). But the EAG was concerned that the PLS underestimated the number of vials of beremagene geperpavec used. This was because it predicted low vial usage in people in the very mild health state. This did not align with:

- the half-life of the COL7A1 protein, which is around 3 months, suggesting the need for repeat dosing to maintain wound closure. The committee noted this was consistent with the 103-day wound-closure duration reported in GEM-1 but there is wide variability across studies, indicating substantial uncertainty in this parameter
- the average dosage from the GEM-3 open-label extension of 0.72 vials per week (during 86 weeks of follow up).

The clinical experts indicated that wound closure with beremagene geperpavec may persist beyond the COL7A1 protein's half-life, because blistering can be prevented even if around 50% of COL7A1 levels remain. But the committee recalled that the PLS transitions estimated that everyone having beremagene geperpavec would be in the very mild health state by year 2, which appeared implausible given the available clinical data (see section 3.15). So, it was concerned that the overall vial usage for the modelled population was severely underestimated. It noted

that the EAG's base case used the same minimum beremagene geperpavec vial usage as that observed in the open-label extension, equivalent to 9.36 vials per 13-week model cycle. This was to ensure plausible vial usage in all health states (but especially the milder states). The committee noted that, even with the limitation on minimum vial usage, the EAG's model predicted a substantial reduction in vial usage over time. The clinical experts explained that initially people would be treating wounds sequentially as they heal, with treatment shifting to new wounds once the current ones close. So, they were likely to initially be on the maximum dose of beremagene geperpavec. The clinical experts emphasised that beremagene geperpavec is not curative, so ongoing use is expected. They thought there was potential for reduced frequency of dosing over time, especially if wound burden could be controlled with early treatment. But they agreed that any reduction in overall drug use would be modest. The committee considered NHS England comments submitted at technical engagement. These suggested that people would likely be having the maximum available dose of beremagene geperpavec. The committee decided this was plausible because people having beremagene geperpavec were likely to have a large proportion of their body covered with wounds. It also noted that Raymakers et al. (2024) estimated substantially higher usage so much higher costs for beremagene geperpavec than those in the company's submission. So, it agreed that a scenario in which everyone was assumed to have the maximum available dose should be submitted at consultation. The committee would have preferred to see real-world evidence to inform the vial usage for beremagene geperpavec and stated this should be explored at consultation. It agreed that the company's approach underestimated the overall vial usage for the modelled population and that the EAG's approach may do so as well. It agreed that the company should explore alternative approaches to modelling vial usage for beremagene geperpavec at consultation, including a scenario using the maximum licensed dose.

Home administration of beremagene geperpavec

3.21 The company assumed that everyone having beremagene geperpavec would have it at home after their first dose. At the first administration, the company assumed a one-off cost for 30 minutes of nurse time, which would be used to train people on self-administration. Costs for homecare delivery were then included for weekly doses. NHS England comments submitted at technical engagement suggested that the company's current administration costs were considerably underestimated, because:

- initial estimates using standard NHS England homecare delivery charges for aseptic preparation and delivery (which may be underestimated because of compounding of gene therapies) were considerably above the company's modelled costs
- based on current experience with beremagene geperpavec, people would likely need more training and clinical time than modelled for initial training in self-administration.

The patient experts at the meeting stressed the importance of enabling home administration. They emphasised that weekly travel to 1 of the 4 specialist centres to have treatment has a large quality-of-life impact. The clinical experts also emphasised that people with DEB and their carers are highly experienced in wound care. The clinical experts expressed support for providing beremagene geperpavec for use at home, because this gives more flexibility. They believed this could be implemented in the NHS. Patients often spend hours a day dressing wounds, so would be able to administer beremagene geperpavec at home after initial training. The NHS England representative emphasised support for enabling home access for people with DEB. But they emphasised a lack of precedent for home administration of gene therapies. They explained that significant implementation challenges are associated with home administration. They also emphasised a lack of hospital aseptic pharmacy capacity for treatment preparation and the complex distribution requirements. It is also unclear whether the company would provide funding for a central

manufacturing unit to do the aseptic preparation and distribution. Until these challenges are addressed, they agreed that the ability to deliver treatment safely at home was uncertain. The committee noted that NHS England had provided costs for beremagene geperpavec administration assuming it is administered weekly as a hospital day case by 2 nurses. The committee considered the EAG's scenarios applying these costs to 100% and 50% of people having beremagene geperpavec in the model. The committee acknowledged that home access to beremagene geperpavec is important for people with DEB. But it noted the uncertainty about how this wound be funded and the fact that beremagene geperpavec is currently administered in specialist centres. So, it preferred the scenario in which all people incur the higher costs associated with hospital-based administration. The committee decided that the company should clearly define the costs associated with home administration at consultation and confirm how these would be funded. It agreed that, if applicable, any arrangements between NHS England and the company should be in place so the committee is aware of which costs are relevant for the evaluation. The committee concluded that the feasibility and costs of home administration remain uncertain.

Beremagene geperpavec vial-sharing assumptions

3.22 The summary of product characteristics for beremagene geperpavec states that 1 vial of 1-ml extractable volume of suspension provides a total of 2.5 ml when mixed into gel before administration. This constitutes 4 syringes of 0.5 ml when mixed into gel before administration, covering a maximum open wound area of 50 cm^2. The company assumed that the remaining 0.5 ml of beremagene geperpavec would be wasted because of potential remaining pockets of air during the preparation phase. So, 1 vial provides the maximum licensed dose per week for people aged over 3 years (see section 3.20). The company recalled that children 3 years old and under and those with wound areas under 60 cm^2 would have lower doses (see section 3.20). So, the company considered that there was potential for vials to be shared among these people. In its base case, the

company assumed that vial sharing would occur for 80% of people having beremagene geperpavec. It supported this assumption with clinical expert feedback and UK data showing the plausibility of vial sharing for oncology drugs. It also provided beremagene geperpavec specific data from France that suggested current vial sharing levels of 35%. But the EAG questioned the plausibility of vial sharing in NHS clinical practice. It noted that the current stability data stated that a syringe kept under refrigeration should be used within 7 days if mixed under aseptic conditions and within 24 hours otherwise. It considered that the company had assumed that everyone having beremagene geperpavec would have treatment at home after their first dose (see section 3.21). It agreed that, with home administration, vial sharing was unlikely to be possible because mixed syringes would need to be transported to different people to allow use within the stability timeframe. The company emphasised a proposed licence variation based on new data that suggested beremagene geperpavec could be stored in a domestic freezer for 42 days. It considered this would enable vial optimisation for a high proportion of people because they could keep a long-term supply at home. But the committee recalled NHS England input that stated that most people would be on the maximum dose of beremagene geperpavec, which was 1 whole vial (see section 3.20). It noted that the company's and EAG's base cases both assumed vial wastage of 20% (0.5 ml), and considered a company scenario that assumed reduced wastage. The committee recalled the uncertainty around the feasibility of home administration and its preference to assume that all people would have beremagene geperpavec in specialist centres (see section 3.21). It agreed that, without further clarity on the feasibility of home administration, the potential for vial sharing was highly uncertain. It stated that the company should quantify the impact of vial sharing and drug wastage assumptions when outlining its proposed homecare administration model. Also, the potential implications of any future licence variation in relation to storage requirements should be clearly reflected in both the anticipated benefits

and associated risks. The committee concluded that the company should submit additional information at consultation to clarify the feasibility of vial sharing and wastage in clinical practice.

Birch bark extract tube usage

3.23 In the company's base case after technical engagement, birch bark extract tube usage was estimated using the PLS. The EAG noted that the model predicted extremely high birch bark extract usage with an average 927 tubes per person in year 1, reducing to 516 tubes by year 10. The patient expert explained that, because birch bark extract is administered at each dressing change, higher usage was expected compared with beremagene geperpavec, which is administered weekly. The clinical expert also supported the plausibility of a modest reduction in use over time, because some wounds close with birch bark extract treatment (see section 3.5). But the EAG was concerned that the company's predicted tube usage was considerably higher than the mean 29.67 tubes used per month in EASE. It preferred to use this value in its base case, with no reduction over time. The committee agreed that the exact number of birch bark extract tubes used in clinical practice was uncertain. But it found the EAG's assumption to be more appropriate because it was based on direct trial evidence and aligned with its preferred source of clinical-effectiveness data for birch bark extract. The committee concluded that the birch bark extract usage rate from EASE was preferred for decision making.

Beremagene geperpavec in combination with birch bark extract

3.24 The summary of product characteristics permits beremagene geperpavec to be used on wound areas of up to 200 cm^2 per week. The committee acknowledged the clinical experts' advice that some people would use birch bark extract at the same time, to treat small and superficial wounds (see section 3.5). At technical engagement, the company stated that modelling the combination of beremagene geperpavec and birch bark extract would require a substantial restructuring of the existing model. It also emphasised a lack of data on combination use, even though there

are countries where both treatments are commercially available.. So, it decided that incorporating such a scenario would introduce significant additional uncertainty. The EAG supported this. It explained that the lack of robust evidence would mean that estimating clinical effectiveness would rely on applying a PLS approach, which it considered methodologically flawed and prone to bias. The committee recognised that the exclusion of combination use from the company's model was a key uncertainty and was associated with additional costs that could be substantial. It thought that the company could, in theory, have included birch bark extract in the PLS for use on untreated wounds in people having beremagene geperpavec. But it decided any attempt to model this scenario would be highly uncertain because of:

- the complexity of modelling combination treatment
- the lack of data on combination treatment's effectiveness and
- uncertainty about which treatment would be used for which type of wound.

The committee acknowledged that DEB is a rare condition with high unmet need for new treatments (see section 3.4). So, in the absence of modelling, it was willing to accept the results without modelling combination use. But it noted that this was likely to bias the results in favour of beremagene geperpavec and remained a key unresolved uncertainty.

Clinical manifestations of DEB

3.25 The committee recalled that DEB is associated with both skin-related and non-skin-related symptoms (see section 3.1). The company assumed that reducing wound burden lowers the prevalence of complications, and so beremagene geperpavec improves outcomes by keeping people in milder health states. Because of this, it considered costs for clinical manifestations in the model. Rates of developing clinical manifestations that are reversible (anaemia, infections and osteoporosis) and irreversible

(complete or partial mitten deformity of foot, complete mitten deformity of hand, and squamous cell cancer) were modelled by health state. This was based on rates reported in people with RDEB in Eng et al. (2021). The EAG advised that the relationship between wound burden and reduction of clinical manifestations was highly uncertain. It noted the limited supporting evidence, particularly given that beremagene geperpavec is a localised treatment. It also emphasised that the company's modelling of irreversible clinical manifestations lacked face validity. This included a higher risk of squamous cell cancer for people using birch bark extract than those having best supportive care alone. So, the EAG's base case excluded costs for clinical manifestations. The clinical experts at the committee meeting stated there was no evidence that beremagene geperpavec has a systemic effect on the body. But they noted that improved wound healing could reduce inflammation-related complications such as anaemia, osteoporosis, and gastrointestinal issues linked to malnutrition, particularly when treatment is started early. The patient experts emphasised that improvements in nutrition and sleep may reduce corneal abrasions, which often occur during nighttime wakings triggered by itching or pain. Better wound closure may also allow time and resources to be redirected to other affected areas (such as the mouth, oesophagus and eyes), supporting additional healing. They also explained that beremagene geperpavec may help maintain functionality of hands and feet by reducing scarring after surgery for mitten deformities, the benefits of which can be short-lived because of the high rate of wound reopenings. The committee thought it was plausible that there would be some benefits for beremagene geperpavec beyond the direct impact on the skin. But the extent of this impact was highly uncertain and not supported by evidence. So, the committee concluded that the model should exclude the cost of clinical manifestations. But it noted that some benefits of using beremagene geperpavec, including functional benefits after surgery, were likely not captured in the model.

Concomitant medications

3.26 The company included costs for concomitant medications used as best supportive care based on prevalence data from Eng et al. (2021). This estimated concomitant medication usage by severity. The EAG noted that statistically significant differences between mild and severe cases were only reported in Eng et al. for opiates, gabapentin and MediHoney. All other medications showed no significant association with severity. Given this, the EAG excluded costs for concomitant medications in its base case. The committee agreed that this exclusion was appropriate for decision making.

Severity

3.27 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to quality-adjusted life years (QALYs), if technologies are indicated for conditions with a high degree of severity. This is called a severity modifier. The company provided absolute and proportional QALY shortfall estimates in line with NICE's technology appraisal and highly specialised technologies guidance manual. The company's base case applied a severity weighting of 1.2 to the QALYs. The absolute QALY shortfall was 17.44 and the proportional QALY shortfall was 0.75. The committee noted that these values were lower in the EAG's base case, which produced an absolute QALY shortfall of 13.98 and a proportional QALY shortfall of 0.60. This was driven by use of the EASE transitions for best supportive care in the EAG's base case, as opposed to the company's preferred values from the PLS. The committee noted that some people will also be using birch bark extract so these QALY shortfalls may be overestimated. The committee recalled that a higher mortality rate only applied to people with RDEB in the model. It also recalled its request for scenarios varying the proportion of people with RDEB and DDEB who would have beremagene geperpavec in clinical practice. This was because of the uncertainty around this

parameter. The committee agreed that the impact on severity estimates should be quantified. The committee noted that all the EAG's scenarios met the criteria for a QALY weighting of 1.2. It concluded that, with the current analyses, a severity weighting of 1.2 applied to the QALYs was appropriate. But the committee acknowledged that the calculations informing the severity modifier should be assessed after consultation if estimates of total QALYs estimated for standard care change.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.28 Because of confidential commercial arrangements for beremagene geperpavec and the comparators, the exact cost-effectiveness estimates are confidential and cannot be reported here. The company's base-case incremental cost-effectiveness ratio (ICER) for beremagene geperpavec was dominant compared with birch bark extract (lower overall costs and higher QALYs). Compared with best supportive care it was within the threshold normally considered a cost-effective use of NHS resources. The committee recalled that clinical-effectiveness data in the company's model came from the PLS. But the EAG preferred to use the EASE transitions with the relative risk from the ITC applied for beremagene geperpavec (see section 3.16). The committee noted that changing this assumption had a large impact on this ICER. This meant that the EAG's base case was considerably over the threshold considered an acceptable use of NHS resources when comparing beremagene geperpavec with best supportive care or birch bark extract.

Uncaptured benefits

3.29 The committee noted that some potential benefits of beremagene geperpavec may not have been included in company's model, including:

- some children with DEB are born with damage to the skin, the severity and persistence of which result in limiting functions including

development of mitten deformities which limits the ability to walk (see section 3.2). The clinical experts explained that early wound closure with beremagene geperpavec has the potential to reduce severe scarring and improve the likelihood of maintenance of hand function and walking in children with severe skin damage in infancy and childhood

- beremagene geperpavec may be part icularly beneficial when used with or after surgery to treat mitten deformities or squamous cell cancer. The clinical experts stressed that reducing post-surgical scarring would help maintain functionality of hands and feet and increase the longevity of the benefits. This is especially true for mitten deformities, because the high rates of wound reopening mean the benefits are short term (see section 3.2). The committee also recalled that wounds are most likely to reopen around points of friction such as the knees, elbows, wrists and ankles, which can limit mobility (see section 3.2). The committee noted that, by promoting wound closure at these points, people may retain mobility and hand function
- treatment effect was modelled to be constant across age groups. But the treatment effect of beremagene geperpavec was likely larger in babies and young children because they have remaining stem cells for wound closure, less scarring, fewer chronic wounds and less fragile skin (see section 3.2). But this benefit is partly offset in older people with harder-to-treat wounds, so the size of any uncaptured benefit was uncertain
- the committee's preferred source for clinical-effectiveness data for beremagene geperpavec (the EAG's ITC) did not directly capture the duration of wound closure. This was because this data was not collected in GEM-3 (see section 3.11). Unlike birch bark extract, beremagene geperpavec directly targets the underlying cause of DEB. So, some incremental benefit in the duration of wound closure is likely
- wound management can be highly burdensome for people with DEB and their carers, often requiring many hours of care each day (see

section 3.3). So, by reducing the area of open wounds, beremagene geperpavec may reduce the time and resources needed for daily wound care. The committee noted that both the company's and the EAG's base cases included cost savings associated with reduced bandage use. But it agreed that the potential quality-of-life benefits associated with reduced wound-care burden were unlikely to have been fully captured.

The committee agreed there may be several uncaptured benefits for beremagene geperpavec. It considered these in its decision making by accepting a higher level of uncertainty.

Acceptable ICER

3.30 NICE's technology appraisal and highly specialised technologies guidance manual notes that, above a most plausible ICER of £25,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically about:

- the proportion of people with DDEB who would have beremagene geperpavec in clinical practice compared with people with RDEB, and how these people are reflected in the clinical evidence
- the clinical effectiveness of beremagene geperpavec compared with birch bark extract and best supportive care
- how the model captured the natural history of the condition
- the proportion of people stopping treatment with beremagene geperpavec in the model
- vial usage for beremagene geperpavec including home administration, vial sharing and wastage

- the impact of using beremagene geperpavec and birch bark extract on different wounds at the same time.

The committee considered whether other factors should be included in its decision making. It recalled that DEB is a rare condition, which may present specific challenges in data collection. It also noted the high level of unmet need for new treatments and uncaptured benefits for beremagene geperpavec. These include the improved functionality after surgery and with use early in life and a longer duration of wound closure. So, the committee agreed that it was appropriate to accept some of the extra uncertainty in the economic modelling. It concluded that an acceptable ICER would be around £35,000 per QALY.

Committee's preferred ICER

3.31 For the model assumptions, the committee preferred to:

- use the baseline distribution by health state from EASE (see section 3.13)
- use the EAG's approach to relative effectiveness (the transitions from EASE for birch bark extract and best supportive care, with the relative risk from the EAG's ITC applied to the birch bark extract transitions for beremagene geperpavec; see section 3.16)
- use the EASE data to inform the tube usage for birch bark extract (see section 3.23)
- apply the costs from NHS England for administration by 2 nurses in a day care unit for all beremagene geperpavec administrations (that is, assume no home administration for beremagene geperpavec; see section 3.21)
- exclude the costs for clinical manifestations of DEB (see section 3.25)
- exclude the costs of concomitant medications (see section 3.26)
- add a severity weighting of 1.2 to the QALYs (see section 3.27).

Because of the uncertainty around home administration, vial usage and discontinuation rates with beremagene geperpavec, the committee could

not establish a plausible ICER. But it noted that most of its preferred assumptions aligned with those in the EAG's base case. So, it concluded that the most plausible ICER for beremagene geperpavec compared with birch bark extract and best supportive care is likely to be substantially above the threshold considered an acceptable use of NHS resources.

Request for further analyses

3.32 The committee noted that there was considerable uncertainty surrounding the cost effectiveness of beremagene geperpavec for wounds associated with DEB. It agreed that during consultation the company should:

- provide details on the population who would have beremagene geperpavec in clinical practice, including:
  - the proportion of people with RDEB and DDEB having beremagene geperpavec in clinical practice and scenarios exploring any alternative plausible distributions
  - the criteria for identifying people with DDEB for treatment, including any wound-burden thresholds for treatment
  - the differences between baseline characteristics of people with DDEB in clinical practice and the GEM populations (see section 3.9)
  - an assessment of any limitations or loss of robustness associated with modelling subgroups separately (see section 3.19)
- attempt to address the limitations associated with the committee's preferred approach, which is to use the EAG's ITC for the source of clinical-effectiveness data (see section 3.16)
- make substantial corrections to the PLS if it remains the company's preferred source of clinical-effectiveness data, including:
  - using the PLS directly to generate cost-effectiveness outcomes, eliminating the need for a separate Markov model
  - allow for increases in BSAP affected by wounds from baseline
  - exploring alternative sources for wound dynamic data to ensure clinically plausible outputs, including addressing the committee's and EAG's face validity concerns (see section 3.18)

- provide data on beremagene geperpavec by age and ensure the model accurately captures the natural history of the condition over time
- provide additional justification for stopping assumptions with beremagene geperpavec, including:
  - further details on the modelling of responders and non-responders and exploring use of the available trial data to model response rates
  - scenarios assuming alternative long-term stopping rates (see section 3.17)
- explore alternative approaches to modelling vial usage for beremagene geperpavec, including a scenario in which everyone is assumed to have the maximum dose with no reductions over time (see section 3.22)
- provide a breakdown of the costs associated with home delivery and confirm with NHS England how these would be funded, including the impact on vial sharing and wastage and any licence variation (see section 3.23)
- consider if vial sharing is possible when beremagene geperpavec is administered at home, and outline the rationale if assuming any vial sharing in this setting (see section 3.23)
- update the calculations informing the severity modifier to assess the impact of any new assumptions (see section 3.27).

Managed access

Recommendation with managed access

3.33 Having concluded that beremagene geperpavec could not be recommended for routine use in the NHS, the committee then considered if it could be recommended for use during a managed access period for treating skin wounds associated with DEB. The committee noted that the company had not submitted a managed access proposal. It also noted that GEM-3 has completed, but there is an ongoing post-authorisation study that may provide further data. The committee agreed that further real-world evidence data collection may help address some of the high

uncertainty surrounding the outputs of the PLS. These include beremagene geperpavec vial usage in the NHS and concurrent use of birch bark extract and beremagene geperpavec (see section 3.20 and section 3.24). The committee concluded that a managed access proposal would be welcomed at consultation.

Other factors

Equality

3.34 The committee considered that some people with skin wounds associated with DEB may meet the criteria for disability because of limited mobility from progressive scarring leading to hand or foot abnormalities. Disability is protected under the Equality Act 2010. The company emphasised that families caring for children with DEB often face substantial financial and practical burdens including high care costs, challenges accessing health and social care, and broader financial strain. This may be particularly pronounced in some ethnic minority groups. Stakeholders and a patient expert emphasised that restricting beremagene geperpavec to outpatient treatment at specialist centres could exacerbate inequalities. This is because the need to travel regularly for treatment may increase time and cost burdens, particularly for people living far from centres, on low incomes, or facing language barriers. The committee considered these issues. But, because its recommendation applies to the whole population in the license for beremagene geperpavec, it agreed these were not potential equalities issues that could be addressed by this evaluation. The committee concluded that all equalities issues for beremagene geperpavec had been considered in its decision making.

Conclusion

Recommendation

3.35 The committee noted the important uncertainties in the cost-effectiveness evidence. This meant it was not possible to reliably estimate the cost

effectiveness of beremagene geperpavec. The most likely cost-effectiveness estimates were substantially above the threshold considered a cost-effective use of NHS resources. So, beremagene geperpavec should not be used. The committee concluded that the company should provide additional information for consideration at the next evaluation committee meeting to:

- reduce the very high levels of uncertainty in the analysis
- enable plausible model outputs to be produced and
- allow a more accurate estimate of the cost-effectiveness of beremagene geperpavec.

4 Evaluation committee members and NICE project team

Evaluation committee members

This topic was evaluated as a single technology appraisal by the highly specialised technologies evaluation committee. The highly specialised technologies evaluation committee and the 4 technology appraisal committees are standing advisory committees of NICE. Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Paul Arundel

Highly specialised technologies evaluation committee

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager, and an associate director or principal technical adviser.

Emma Douch
Technical lead

Alan Moore
Technical adviser

Thomas Feist
Project manager

Christian Griffiths
Principal technical adviser

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