National Institute for Health and Care Excellence

Health Technology Evaluation

Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959] Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Krystal Biotech	Krystal Biotech considers appropriate the appraisal of the clinical and cost-effectiveness of Beremagene geperpavec within its marketing authorization. We suggest modifying the sentence: "EB is usually diagnosed in babies and children and is thought to affect 1 in 17,000 births with around 5,000 people affected in the UK. Of these, around 1,250 people have DEB. There is currently no cure for EB." with "DEB prevalence in England is estimated to be 10.7/million (0.535/50,000), which translates to 569 people with DEB in England," reported by Petrof G et al., 202215 publication to ensure consistency.	Thank you for your comment. The scope has been updated to include the prevalence estimate of DEB in England.
	British Association of Dermatologists	The evaluation is appropriate as there is currently an unmet need for effective treatments of wounds in epidermolysis bullosa (EB). Current treatment strategies in EB involve management of symptoms such as pain and itch, management of complications such as anaemia, oesophageal stenoses, constipation, or wound management with dressings and topical antimicrobials. Beremagene geperpavec (B-VEC) differs from these	Thank you for your comment. No change to the scope made.

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		approaches as it offers the opportunity to restore functional protein to wounds to enhance healing and maintain healed skin.	
	Genetic Alliance	Genetic Alliance UK believes that this technology is suitable to be routed through the HST route rather than the STA route. The population number stated in the draft scope is likely to be an overestimate and therefore it would fulfil the first two criteria for routing via the HST pathway. See more details in the population section of this response. The severity of the condition is evident in the description and the lack of alternative treatments means that this technology also fulfils criteria 3 and 4.	Thank you for your comment. HST routing was considered by NICE but the HST criteria were not met. See the HST checklist here: https://www.nice.org.uk/guidance/indevelopment/gid-ta10868/documents
	Great Ormond Street Hospital	I do not understand why B-Vec is going through STA and not the HST as birch bark went through? It makes no sense to any of us as EN national experts. None of us have been consulted – patients with RDEB are desperate for this treatment which has been avaible in uSA now since June 2023	Thank you for your comment. HST routing was considered by NICE but the HST criteria were not met. See the HST checklist here: https://www.nice.org.uk/guidance/indevelopment/gid-ta10868/documents
	DEBRA	It is appropriate.	Thank you for your comment. No change to the scope made.

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	NHS England	It is the opinion of NHS England that it is appropriate that NICE appraise this technology.	Thank you for your comment. No change to the scope made.
Wording	Krystal Biotech	No. The anticipated marketing authorization is [redacted]	Thank you for your comment. The scope cannot include confidential wording and identifies that the technology will be appraised within its marketing authorisation. No change to the scope made.
	British Association of Dermatologists	The wording is appropriate.	Thank you for your comment. No change to the scope made.
	Great Ormond Street Hospital	I do not indertsnd how b-vec can be compared to birch bark which is not disease modifying just a wound gel? Would it not be useful to be looking at validated outcome measures ie iSCOREB?	Thank you for your comment. Birch bark extract is licensed and recommended by NICE as a treatment option for dystrophic and junctional epidermolysis bullosa. It is part of established clinical management. The committee will consider the relevant

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			comparators during the appraisal. A specific outcome measure such as iSCOREB will be covered by the generic outcome measures included in the scope. No change to the scope made.
	DEBRA	Yes	Thank you for your comment. No change to the scope made.
	NHS England	Yes, the remit does address the clinical issues and the cost effectiveness	Thank you for your comment. No change to the scope made.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Krystal Biotech	The Company would like to delete the following text: "Dystrophic epidermolysis bullosa (DEB) – accounts for around 25% of cases and can be either dominantly or recessively inherited. DEB is a group of diseases in which blisters heal with dystrophic scarring. Milia (tiny white spots), result from damage to hair follicles."	Thank you for your comment. The scope has been updated to include the prevalence data highlighted.

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		Instead, the scope should reflect the most recent publication (Petrof G et al., 2022), where the prevalence of DEB and DDEB vs RDEB for England and Wales is reported with data in March 2021 as stated below: According to the most recent epidemiologic study in England and Wales (Petrof G et al., 2022), by March 2021, 2,594 individuals were registered, of whom 2361 were living, which yielded a prevalence of 34.8 per million of the population for all EB types leading to a prevalence of 1.74 in 50,000 in England and Wales. Also, Petrof G et al., 2022, also estimate that the prevalence of Recessive DEB (RDEB) and Dominant (DDEB) is 3.3/million and 6.8/million, respectively, with a remaining 0.6/million prevalence non-specified between RDEB and DDEB.15 We suggest modifying the sentence: "EB is usually diagnosed in babies and children and is thought to affect 1 in 17,000 births with around 5,000 people affected in the UK. Of these, around 1,250 people have DEB. There is currently no cure for EB," with "DEB prevalence in England is estimated to be 10.7/million (0.535/50,000), which translates to 569 people with DEB in England," 15 reported by Petrof G et al., 2022 publication to ensure consistency.	
	British Association of Dermatologists	Some of the information is incorrect. Dominant dystrophic epidermolysis bullosa (DDEB) does not always appear at birth with generalised blistering; it can present at birth, usually with localised blistering although it can be more widespread. It can also present later in the first few months of life. The degree of severity of recessive dystrophic epidermolysis bullosa (RDEB) depends largely on the location and nature of the mutations in COL7A1. EB does not usually affect the stomach but can affect the oesophagus. More should be made of the profound impact of EB on patients' daily lives. For example, more severe forms of EB, especially RDEB, are associated with the presence of many chronic wounds. These need specialised atraumatic	Thank you for your comment. The wording for DDEB has been updated in the scope. Reference to damage to the stomach has been removed and the existence of chronic

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		dressings which may take several hours each day for the patients and their carer to change. The costs of dressings and paid care in severe RDEB cost, on average, is almost £100K per annum (Pillay EI et al. J Eur Acad Dermatol Venereol 2020, 100 (Suppl. 220): 58). Patients experience significant pain and itch from their wounds, and this has a negative impact on their quality of life (Eng et al. J Am Acad Dermatol 2021; Tang et al. Orphanet J Rare Dis 2021). It is important to emphasize the link between the presence of wounds and impact on quality of life (QoL)/disease burden since a therapy like B-VEC is aiming to reduce wounds and thereby improving symptoms and QoL.	wounds have been added.
	Great Ormond Street Hospital	adequate	Thank you for your comment. No change to the scope made.
	DEBRA	While the description of EB and the main subtypes is accurate, it doesn't convey the full impact of this condition on the patients and their families. Dystrophic EB is characterised by a life of extreme pain and functional challenges, which impacts on every element of life, from interacting with peers, schooling, ability to work and relationships. This is not only due to the excruciating pain and the strong morphine-based pain killers often needed to mitigate it, or the effects that constant blistering, tearing and scarring have on the body. But also due to the time it can take to change dressings to prevent blistering, or to protect open wounds across the entire body. Our members report dressing changes taking several hours every day. The impact of this condition on physical and mental health cannot be over-estimated. Our members talk of the "constant grinding you down" of the daily painful management of this condition. And the people changing dressings, and therefore inflicting pain on those living with EB, are usually family members; parents, siblings.	Thank you for your comment. The scope includes a summary of the physical symptoms of the condition. It has been updated to include the chronic nature of the wounds. Committee will consider submissions from patient and clinical experts during the appraisal to assess the quality-of-life impacts.

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		EB can also create extreme difficulties with the everyday tasks we take for granted. Eating; swallowing even small particles of food can cause huge discomfort and make it difficult to swallow. Sleeping; those living with EB can injure their bodies, faces, eyelids in the night simply by moving in their sleep. Talking; if EB has caused trauma to the mouth or throat, combined with the additional effect of often strong painkillers, talking can become difficult. Cost of living; household goods are often used more than in an average household. For example, at DEBRA we provide hardship grants and often need to replace washing machines to manage the additional burden of washing dressing retention garments and of multiple bedding changes as those living with EB are frequently injured at night. The reality of living with EB is not just simply trauma or friction causing the skin to blister and tear easily, but large areas of skin may simply be missing, raw and bleeding requiring hours of specialised dressing changes daily. This invariably worsens with age as the inflammation and scarring associated with this condition take hold. Chronic pain is a key factor with most people experiencing pain every day – specifically at dressing changes at a level often requiring morphine-based pain relief. They experience intractable itch with the continued healing, wounding, and scarring process. Patients invariably have mitten hands and feet rendering them useless as the digits are fused together reducing hand function and ability to walk. EB is chronically disabling.	
	NHS England	Background notes suggest that given the complex needs of children with epidermolysis bullosa (EB), birch bark extract treatment is usually carried out by a multidisciplinary team. The clinical experience is that after an initial period of treatment that birch bark administration is managed by patients and families at home with product delivered via homecare. Clinical oversight is provided by the highly specialised EB services.	Thank you for your comment. The scope has been updated to include the option of home treatment.

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Population	Krystal Biotech	Krystal Biotech considers the population as described in the scope to be appropriate.	Thank you for your comment. No change to the scope made.
	British Association of Dermatologists	It should state the age of patients to be treated, unless “people” refers to all ages.	Thank you for your comment. “People” in the scope refers to people of all ages. No change to the scope made.
	Genetic Alliance	The prevalence of DEB is likely to be less than what is quoted in the draft scope and therefore this technology should be routed via the HST pathway instead of the STA pathway. Orphanet quotes a global prevalence of DEB to be 1-9/1,000,000 which equates to a UK population of 67- 603 people affected by DEB. It also states a European prevalence of DEB to be 1/120,000 - 350,000 which would roughly equate to 191- 558 people in the UK*. *Assuming a UK population of 67 million Source: https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=8623&Disease_Disease_Search_diseaseType=ORPHA&Disease_Disease_Search_diseaseGroup=303&Krankheite(n)/Krankheitsgruppe=DEB&title=DEB&search=Disease_Search_Simple Additionally GeneReviews states a prevalence of dominant DEB to be 1.49 per one million live births and recessive DEB to be 1.35 per million live births. Source: www.ncbi.nlm.nih.gov/books/NBK1304/	Thank you for your comment. HST routing was considered by NICE but the HST criteria were not met. See the HST checklist here: https://www.nice.org.uk/guidance/indevelopment/gid-ta10868/documents

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		A recent epidemiology study has also estimated the prevalence of DEB across the UK to be 10 per million. Source: www.pubmed.ncbi.nlm.nih.gov/34927719/ These estimations are no substitute for formal registry data or patient organisations data however they provide useful estimates. They clearly show that the estimated prevalence of DEB is significantly lower than the 1,250 quoted in the draft scope. The ranges quoted here clearly meet the first HST criteria (less than 1,100 people in the UK affected by the condition) and are likely to meet the second criteria (normally, no more than 300 people in England are eligible for the technology in its licensed indication and no more than 500 across all its indications). Given that this technology is an innovative delivery route for a gene therapy to treat a very rare condition, it would be a strong candidate to be flexible with the HST criteria.	
	Great Ormond Street Hospital	Suggest limit to RDEB only	Thank you for your comment. The marketing authorisation is not yet available so the population is wide to accommodate the final population in the marketing authorisation. No change to the scope made.
	DEBRA	Yes	Thank you for your comment. No change to the scope made.

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	NHS England	The population is appropriately defined.	Thank you for your comment. No change to the scope made.
Subgroups	Krystal Biotech	The scope suggests two subgroups: DDEB and RDEB patients. We also recommend considering pediatric and adult patients, given that B-VEC is indicated for all patients with DEB, starting at birth. Treatment of newborns can potentially prevent the devastating sequelae of DEB (such as fibrosis and scarring, deformities like mitten hands and feet, squamous cell carcinoma (SCC), and reduce the risk for early mortality).	Thank you for your comment. The scope identifies the population as people which includes adults and children. No change to the scope made.
	British Association of Dermatologists	Agree that DDEB and RDEB should probably be treated separately. In DDEB, introducing COL7A1 in B-VEC aims to deliver an excess of normal copies of the gene to overcome the dominant negative effect of the mutant allele. In RDEB, B-VEC provides functional copies of the gene to overcome a null allele(s). It is appropriate to include both sub-types, but they may differ in effectiveness.	Thank you for your comment. No change to the scope made.
	Great Ormond Street Hospital	Severe patients with DDEB would benefit but need to identify from DDEB cohort	Thank you for your comment. No change to the scope made.
	DEBRA	The subgroups suggested in the scope are appropriate.	Thank you for your comment. No change to the scope made.
	NHS England	The subgroups are appropriate.	Thank you for your comment. No change to the scope made.

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Comparators	Krystal Biotech	Best supportive care (BSC) is the main comparator, given the current standard of care. The draft scope also suggests birch bark extract (Oleogel-10), which NICE highly specialized technology guidance recommends as an option for treating partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa in people 6 months and older, as a comparator. However, in the topic selection phase of birch bark extract, the TSOO acknowledged that individuals would only be eligible for treatment if they met the inclusion criteria outlined in the EASE pivotal trial, that is, for treatment of patients with target wounds over 3 weeks old and between 10cm² and 50cm² in size. Based on these criteria, the estimated size of the eligible population was between 100 and 150 individuals, including those with DEB, JEB, and KS. This figure is significantly lower than the 569 DEB patients in England identified by Petrof et al., 2022.15 The estimated size of the eligible population by the TSOP indicates that, unlike B-VEC, which is suitable for and can benefit all DEB patients as evidenced by the TSOP conclusion that the target population for BVEC is all DEB patients, birch bark extract is limited to treating a substantially smaller proportion of DEB patients, representing approximately 17% of the DEB population in England. Current clinical practice in England supports that assessment, as clinicians report that less than 100 patients have been treated since NICE recommended birch bark extract in September 2023. Based on the design of the EASE trial of birch bark extract and the GEM3 trial of B-VEC and their results, these two products are not comparable. Data from the EASE trial reflect that birch bark extract does not have an effect on the underlying cause of EB, with no disease-modifying effect shown and no clinically significant benefit observed at 90 days (a key secondary efficacy	Thank you for your comment. Birch bark extract is licensed and recommended by NICE as a treatment option for dystrophic and junctional epidermolysis bullosa. It is part of established clinical management. The committee will consider the relevant comparators during the appraisal. No change to the scope made.

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		endpoint).16 Additionally, only a modest significant effect on wound closure, defined as the first complete closure of the EB target wound within 45±7 days of treatment, was observed at 45 days.16 Although data from the EASE trial suggest that birch bark extract helps wounds heal faster within 45 days, it does not result in sustained wound healing, as evidenced by its lack of clinically significant benefits at the 90-day point.16 On the other hand, GEM3 data show that B-VEC addresses the root cause of the disease at the molecular level, as evidenced by clinically significant and durable improvement in complete wound closure at 3 and 6 months compared to placebo.4 This effect was observed despite a much stricter definition of complete wound closure used in GEM3 than in the EASE trial. In GEM-3, wounds had to be completely closed precisely at 3 and 6 months and must have remained closed for two weeks in a row to be considered completely closed.4 In summary, it is important to highlight that birch bark extract has an unknown mechanism of action and no impact on the core physiopathological mechanism of DEB, while B-VEC has demonstrated to promote collagen 7 expression and anchoring fibril assembly at the basement membrane level, correcting the hallmark of DEB physiopathology and restoring skin integrity, which translated clinically to be the only therapy that showed in double-blind, placebo-controlled clinical trial a significant and clinically meaningful impact in the proportion of patients with durable wound closure at 3 and 6 months, differently from birch bark extract, which failed to demonstrate a sustained effect on wound closure, with only a marginal benefit at 45 days of therapy and no significant differences to placebo at 90 days. In France, the Haute Autorité de Santé (HAS), in the Access Precoce evaluation, assessed that B-VEC allows wounds to be closed for up to 12 months, further highlighting the disease-modifying effect and the duration of	

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		closure. HAS is the EMA Co-Rapporteur in the B-VEC regulatory clinical and safety assessment. In conclusion, given the differences between the two trials, the targeted population, the expected benefits from the usage of the drugs (acceleration of wound closure for birch bark extract vs. durable wound closure for Vyjuvek), and the low use of birch bark extract in clinical practice, birch bark extract is not an appropriate comparator.	
	British Association of Dermatologists	Standard of care is wound dressings, measures to reduce wound colonisation and infection, management of symptoms like pain and itch, management of complications, e.g. anaemia, impaired nutrition.	Thank you for your comment. No change to the scope made.
	Genetic Alliance	In 2022, Birch bark extract was going through a NICE appraisal and was therefore not widely available and it is not guaranteed to be widely available. Additionally, beremagene geperpavec is a different type of treatment compared to birch bark extract as beremagene geperpavec is a gene therapy that addresses the cause of blistering skin rather than purely addressing symptom management.	Thank you for your comment. Birch bark extract is licensed and recommended by NICE as a treatment option for dystrophic and junctional epidermolysis bullosa. It is part of established clinical management. The committee will consider the relevant comparators during the appraisal. No change to the scope made.

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	Great Ormond Street Hospital	Not appropriate as there are none	Thank you for your comment. Birch bark extract is licensed and recommended by NICE as a treatment option for dystrophic and junctional epidermolysis bullosa. It is part of established clinical management. The committee will consider the relevant comparators during the appraisal. No change to the scope made.
	DEBRA	The comparators listed in the scope are “treatments which can help ease and control infections, pain and other aspects of EB” and “birch bark extract”. We would not consider these to be true comparators. There are no treatments designed specifically for EB that significantly reduce their pain, wound care, or scarring. The management of the symptoms of EB (bandaging, barrier creams, topical medicine to prevent infections) are not comparators to a treatment for the condition itself. What is more, the care of severe wounds inflicts further pain and distress. The birch bark extract is a different technology to Beremagene geperpavec. This technology is an innovative topical gene therapy specifically designed to	Thank you for your comment. Birch bark extract is licensed and recommended by NICE as a treatment option for dystrophic and junctional epidermolysis bullosa. It is part of established clinical management. The committee will consider the relevant comparators during the

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		treat EB. Birch bark extract is a treatment to promote wound healing, originally used for burns and skin grafts.	appraisal. No change to the scope made.
	NHS England	The comparators are appropriate.	Thank you for your comment. No change to the scope made.
Outcomes	Krystal Biotech	Krystal suggests rephrasing the following outcomes: - "Closures of unhealed target wounds" should be phrased as "proportion of complete wound healing." -"percentage of the surface area of wound healed" and "change in total body wound burden" should be merged into a single outcome, "percentage of body surface area with wounds." Our rationale is that the first outcome (interpreted as a change in wound size over time) is less relevant since the treatment aims to promote durable wound closure. Also, the mortality outcome will be assessed through surrogate endpoints, given the long timeframe needed to collect direct evidence on mortality. We also recommend evaluating caregivers' quality of life, given that BSC is mainly administered by parents or caregivers.	Thank you for your comment. The scope has been updated as suggested.
	British Association of Dermatologists	Yes.	Thank you for your comment. No change to the scope made.
	Great Ormond Street Hospital	Please add iSCOREB	Thank you for your comment. A specific outcome measure such

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			as iSCOREB will be covered by the generic outcome measures included in the scope. No change to the scope made.
	DEBRA	The outcomes as defined are all relevant to patients, what are harder to define are the qualitative improvements and impact on the wider family. For example, if less time were spent changing dressing for family members, it would mean more time to spend with other children, the possibility of returning to work in some capacity, or a positive impact on the mental health of the whole family.	Thank you for your comment. As outlined in the scope, the NICE reference case stipulates that impacts on the outcomes of carers can also be included when relevant. This is covered under the 'health-related quality of life' outcome in the scope. No change to the scope made.
	NHS England	The outcomes are appropriate	Thank you for your comment. No change to the scope made.
Equality	Krystal Biotech	The Company has not identified inequalities	Thank you for your comment. No change to the scope made.

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	British Association of Dermatologists	No concerns.	Thank you for your comment. No change to the scope made.
	DEBRA	DEBRA UK has a community support team that help families gain access to appropriate healthcare, the correct financial state benefits and supporting with school applications, housing, and access to work. Equality for patients with EB impacts hardest on those that have least and who may be culturally disadvantaged. Those with fewer resources always struggle the most to access the care they need, due to costs associated with organising travel to treatment centres or accessing the appropriate specialist healthcare likely to be aware of this product	Thank you for your comment. Equality issues that are raised during the appraisal will be considered by the committee. No change to the scope made.
	NHS England	Patients are particularly impacted by EB because of the high costs imposed by modifications to everyday life. Equity of access to treatment and the challenges presented by travel by fragile-skinned RDEB patients to specialised medical centers should be considered in the scope, recognising the disability burden experienced by patients.	Thank you for your comment. Equality issues that are raised during the appraisal will be considered by the committee. No change to the scope made.
Other considerations	Krystal Biotech	No additional considerations	Thank you for your comment. No change to the scope made.
	British Association of Dermatologists	Please consider evaluating the costs of dressings and paid carer time, and time spent on dressings.	Thank you for your comment. As outlined in the scope, the NICE reference case stipulates costs will be

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			considered from an NHS and Personal Social Services perspective. Impacts on the outcomes of carers can also be included when relevant. No change to the scope made.
	NHS England	It would be helpful to consider the delivery model for this product to ensure that the maximum clinical benefit for patients can be achieved in a patient group for whom we need to minimise travel to healthcare settings. It is expected that the management of patients will continue to be by the highly specialised EB centres with beremagene geperpavec prescribed and monitored by highly specialised centres.	Thank you for your comment. No change to the scope made.
Questions for consultation	Krystal Biotech	Where do you consider beremagene geperpavec will fit into the existing care pathway for dystrophic epidermolysis bullosa? Would beremagene geperpavec be used instead of, before, or after birch bark extract? Currently, patients with DEB do not have access to a disease-specific treatment option. B-VEC is a disease-modifying gene therapy that addresses the root cause of DEB and is expected to benefit all patients with DEB. Given that B-VEC can slow down disease progression, initiating treatment as early as possible has the potential to prevent the devastating sequelae of DEB. Given the debilitating nature of DEB and the potential disease-modifying ability of B-VEC, B-VEC should be made available to patients at diagnosis. In the topic selection phase of birch bark extract, the TSOO acknowledged that individuals would only be eligible for treatment if they met the inclusion criteria	Thank you for your comment. No change to the scope made.

		outlined in the EASE pivotal trial, that is, for treatment of patients with target wounds over 3 weeks old and between 10cm² and 50cm² in size. Based on these criteria, the estimated size of the eligible population was between 100 and 150 individuals, including those with DEB, JEB, and KS. This figure is significantly lower than the 569 DEB patients in England identified by Petrof et al., 2022.15 The estimated size of the eligible population by the TSOP indicates that, unlike B-VEC, which is suitable for and can benefit all DEB patients as evidenced by the TSOP conclusion that the target population for B-VEC is all DEB patients, birch bark extract is limited to treating a substantially smaller proportion of DEB patients, representing approximately 17% of the DEB population in England. Current clinical practice in England supports that assessment, as clinicians report that less than 100 patients have been treated since NICE recommended birch bark extract in September 2023. Data from the EASE trial reflect that birch bark extract does not have an effect on the underlying cause of EB, with no disease-modifying effect shown and no clinically significant benefit observed at 90 days (a key secondary efficacy endpoint).16 Additionally, only a modest significant effect on wound closure, defined as the first complete closure of the EB target wound within 45±7 days of treatment, was observed at 45 days.16 Although data from the EASE trial suggest that birch bark extract helps wounds heal faster within 45 days, it does not result in sustained wound healing, as evidenced by its lack of clinically significant benefits at the 90- day point.16 On the other hand, GEM3 data show that B-VEC addresses the root cause of the disease at the molecular level, as evidenced by clinically significant and durable improvement in complete wound closure at 3 and 6 months compared to placebo.4 This effect was observed despite a much stricter definition of complete wound closure used in GEM3 than in the EASE trial. In GEM-3, wounds had to be completely closed precisely at 3 and 6 months and must have remained closed for two weeks in a row to be considered completely closed.4 In summary, it is important to highlight that birch bark extra has an unknown mechanism of action and no impact on the core physiopathological mechanism of DEB, while B-VEC has demonstrated to promote collagen 7 expression and anchoring fibril assembly at the basement	

		membrane level, correcting the hallmark of DEB physiopathology and restoring skin integrity, which translated clinically to be the only therapy that showed in double-blind, placebo-controlled clinical trial a significant and clinically meaningful impact in the proportion of patients with durable wound closure at 3 and 6 months, differently from birch bark extract, which failed to demonstrate a sustained effect on wound closure, with only a marginal benefit at 45 days of therapy and no significant differences to placebo at 90 days. In conclusion, based on both product mechanisms of action, different endpoints, impact on clinical outcomes, and no comparability, together with the low adoption of birch bark extract in the UK, the data of the EASE and GEM3 trials, and the difference in the eligible target population for both products, we consider the B-VEC will be as a first-line treatment. Will beremagene geperpavec be used in the same population as birch bark extract for DEB? B-VEC was designed and specifically targeted for the treatment of DEB (i.e., RDEB and DDEB), while birch bark extract is indicated for the treatment of JEB, KS, and DEB. Therefore, the population of patients eligible for B-VEC treatment does not necessarily overlap with those eligible for birch bark extract. Moreover, as raised above, in the topic selection phase of birch bark extract, the TSPO acknowledged that individuals would only be eligible for treatment if they met the inclusion criteria outlined in the EASE pivotal trial, that is, for treatment of patients with target wounds over 3 weeks old and between 10cm² and 50cm² in size. Based on these criteria, the estimated size of the eligible population was between 100 and 150 individuals, including those with DEB, JEB, and KS. This figure is significantly lower than the 569 DEB patients in England identified by Petrof et al., 202215 . The estimated size of the eligible population by the TSOP indicates that, unlike B-VEC, which is suitable for and can benefit all DEB patients, as evidenced by the TSOP conclusion that the target population for B-VEC is all DEB patients,	

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		birch bark extract is limited to treating a substantially smaller proportion of DEB patients, representing approximately 17% of the DEB population in England. Current clinical practice in England supports that assessment, as clinicians report that less than 100 patients have been treated since NICE recommended birch bark extract in September 2023. B-VEC has been specifically designed to address the underlying pathophysiology in DEB, restoring collagen VII production to promote wound healing and break the cyclical nature of wounding, healing, and reblistering.3-5 Individuals with DEB who initiate B-VEC early in the disease course are expected to have fewer recurrent and chronic wounds, less fibrosis and scarring, less potential to develop highly disabling consequences, and reduced risk for early mortality. Birch bark extract does not address the genetic root of DEB. Its mechanism of action is unknown; it is not gene-specific and is used as a symptomatic treatment rather than a curative or genetic therapy.1,2 Therefore, B VEC is expected to provide the most benefit earlier in the disease pathway, as it can prevent DEB-related complications. In addition, the requested indication for B-VEC will address patients suffering from DEB from birth. This is an important differentiating factor between the two therapies, given that, as indicated above, patients in the early stages of the disease are expected to derive the greatest benefit from treatment. Availability of B-VEC starting at birth is expected to address the genetic root of the disease and consequently prevent (or at least reduce) serious complications associated with more severe stages of the disease. Initiation of treatment soon after birth may enable children to engage in regular activities of daily living and avoid the disability associated with severe DEB.	

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		Please select from the following, will beremagene geperpavec be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention Regarding prescribing and routine follow-up, we expect it to be other (letter D). DEB is an extremely severe disease that is and will continue to be managed in the four highly specialized centers in England. The treatment (B-VEC) administration, as per the expected SmPC, may take place at the center or the patient's home. Krystal Biotech is committed to working with NHSE to design the service to provide optimal access to patients. Would beremagene geperpavec be a candidate for managed access? We do not believe the B-VEC will meet the criteria to be selected for consideration of managed access. Do you consider that the use of beremagene geperpavec can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? QALY data were not available from clinical trials of B-VEC and were based on the published literature. Given that DEB is a rare disease, published data were limited and do not fully capture the true burden of disease. DEB is a	

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		devastating disease that often presents at birth or within the first year of life, and has lifelong impacts on patients and their caregivers.6-8 Due to the nature of DEB, many aspects of HRQoL were not captured in the QALY calculation. For example, most patients with DEB are diagnosed in childhood, and complications of the disease accumulate over their lifetime. Consequently, DEB affects every aspect of the patients', their caregivers', and family members' lives, impacting their emotional and psychological well-being.9-12 It is essential that these impacts on caregivers are fully considered in NICE's review of B-VEC, as has been the case in other STA and HST assessments and in line with NICE's established methods. Additionally, DEB has broader societal impacts, as patients often need special accommodations for daily activities. For example, children with DEB may not be able to attend school regularly, or schools may have to provide special accommodations for them.13 Given the lifelong nature of DEB, the full value of this innovative therapy will become apparent only over time. The long-term benefits, such as preventing severe disease complications like hand and foot deformities, can only be measured over extended periods. Additionally, as the first disease-modifying therapy for DEB, B-VEC offers hope to patients facing a devastating and progressive disease with limited treatment options. Although the value of hope is not typically included in QALY assessments, it is recognized in studies as a critical component of the value of novel therapies.14 Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.	

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		Although data showing the value of B-VEC are limited, the devastating nature of DEB is well documented. Currently, patients with DEB do not have access to a disease-modifying treatment option, and there is a substantial unmet need for innovative therapies that address the root cause of the disease and potentially prevent serious complications. Therefore, the paucity of available data should be considered in the context of disease severity and a lack of available disease-modifying treatment options. Please indicate if any of the treatments in the scope are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics. The expected EMA indication for B-VEC is for treating wounds in patients with DEB with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene from birth. B-VEC is administered topically once a week, and the label allows patients and caregivers to self-administer it at home. Wounds should be treated weekly until closed, with previously treated re-opened wounds prioritized if possible. Each vial of B-VEC contains 2.5 mL extractable volume of 5×109 (5 billion) PFU per mL. For patients 3 years and older, the weekly dose is up to 4.0×109 PFU of B-VEC, i.e., four syringes of 0.5 mL each can be used for those patients. The weekly dose for patients under 3 years is 2.5×109 PFU (2.5 billion) of B VEC. The maximum dose for this last group of	

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		patients will be two syringes of 0.5 mL each. To optimize the use of B-VEC and patient experience, it is expected that unused syringes (4 syringes of 0.5 mL each per vial of B-VEC) are used instead of being discarded after a single use. B-VEC can be stored in the refrigerator for 7 days. Therefore, unused syringes can be used in multiple patients or the same patient multiple times, as has been the case with patients currently treated in Europe, such as France, under early access programs.	
	British Association of Dermatologists	Where do you consider beremagene geperpavec will fit into the existing care pathway for dystrophic epidermolysis bullosa? This is a novel technology, and no similar approaches are currently available for EB. By delivering functional COL7A1 to wounds it aims to restore collagen 7 to the skin and result in wound healing that should persist for longer than normal DEB wounds stay healed. It is something that can be applied easily by patients/carers at their normal dressing changes and can be used alongside other standard of care treatments. As such, it fits well into the existing care pathway for DEB. Does this differ when considering children, adolescents or adult populations? No – it would be a feasible and appropriate intervention for all age groups. In theory, treating children from an early age should reduce the number of chronic wounds and sequelae such as scarring, deformities and, perhaps, the tendency to develop aggressive skin cancers over time. In which EB populations and under which circumstances would treatment with beremagene geperpavec be considered?	Thank you for your comment. No change to the scope made.

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		Any form of DEB. It is specific for delivering COL7A1 so would not be appropriate for other types of EB where other genes are affected. What genes may be affected in dystrophic epidermolysis bullosa? Is dystrophic epidermolysis bullosa always associated with mutations in the COL7A1 gene? If not, would people who did not have mutations in the COL7A1 gene be eligible for treatment with beremagene geperpavec? All forms of DEB are caused by COL7A1 mutations. Other forms of EB have other genes affected and therefore B-VEC would not be appropriate. Would treatment with beremagene geperpavec be used for all DEB wounds or would treatment be limited to only certain types or wounds? It could be used on all cutaneous wounds, both acute and chronic ones. It is not developed for mucosal lesions, e.g. in the mouth or eye. Are the outcomes listed in scope appropriate? Are there any other outcomes which should be considered? They are appropriate. As mentioned above, given the high costs of wound dressings and paid (and unpaid) care in DEB, a measure of this in a subset of patients might be warranted and lend weight to economic grounds for any benefit from B-VEC. Also, looking at any reduction in time spent doing dressings would be a potential patient-centred and relevant measure; each hour a week not spent doing dressings is an hour of normal life back for the patient and their carer. What is a meaningful clinical difference in terms of time spent doing dressings	

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		has not been formally evaluated (to our knowledge) but it is something tangible that could be a helpful measure of value to the patient. Are the subgroups listed in the scope appropriate? Are there any other subgroups which should be considered separately? They are appropriate. Would beremagene geperpavec be a candidate for managed access? As a novel therapeutic modality with uncertain health-related QoL benefits in the longer term, and a relative paucity of evidence underpinning the health economic case for its use, this would be an ideal candidate for a managed access program incorporating routine data collection and assessment of real-world cost and clinical effectiveness on the NHS. Do you consider beremagene geperpavec to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Yes – it is a totally different approach, whereby the faulty/missing protein is replaced, encouraging wound healing. Also, since it is expressed for a time after the wound has healed, making the skin less fragile, so less likely to blister. The effects, and collagen 7 expression, do wane with time, so the skin would eventually blister again, but could be re-treated with B-VEC when it does. Improving healing and maintaining intact skin will have an impact of symptoms, complications and QoL for patients, and will reduce the costs and time of care.	

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		Do you consider that the use of beremagene geperpavec can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? There are likely to be significant health-related QoL benefits uncaptured by the available health economic and clinical modelling. Specifically, the impact on educational attainment and reduction in social stigma (and consequent decrease in health-related burden on NHS services that have been clearly shown to arise from that stigma) are likely to be considerable, but not captured. The long-term outcomes for patients with often debilitating wounds are known to be poor, and their healthcare utilisation high; reduction of this at an early stage would be predicted to have an expansionary impact downstream, with reduced healthcare burden imposed by carers, patients themselves and their dependents due to improved independence and self-care. Introduction of COL7A1 into areas of chronic wounds with subsequent healing may well reduce the risk of squamous cell carcinoma. Severe RDEB patients spend an average of 18 hours per week on dressing changes. Half of all RDEB working age adults are unemployed and 39% of carers are unable to do any paid work (PT or FT) due to their carer commitments. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. See the added references in the background section.	
	Great Ormond Street Hospital	Where do you consider beremagene geperpavec will fit into the existing care pathway for dystrophic epidermolysis bullosa? It should be avaible for all patients with RDEB in uk	Thank you for your comment. No change to the scope made.

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		Would beremagene geperpavec be used instead of, before, or after birch bark extract? There is comparison with birch bark which is just a wound gel and 50% patients don't find it helpful so it. Can be used with birch bark or better instead of as. Its clearly much more effective as its gene therapy Will beremagene geperpavec be used in the same population as birch bark extract for DEB? No just in RDEB Please select from the following, will beremagene geperpavec be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): only the 4 national EB centres For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. Would beremagene geperpavec be a candidate for managed access? Not sure	

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		Do you consider that the use of beremagene geperpavec can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Reduce disease severity and long term reduction in SCC	
	NHS England	The questions to address the place of this product in the care pathway are important to understand better the priority for treating different wounds. Treatment options for EB are limited. If product can be administered at home, it is expected that beremagene geperpavec would become first line therapy as the first DEB-specific treatment that addresses the underlying cause of the disease for patients.	Thank you for your comment. No change to the scope made.
	DEBRA	These question are best answered by the clinicians.	Thank you for your comment. No change to the scope made.
	Great Ormond Street Hospital	This treatment works, its very expensive, the issues are cost, practically of how it will be delivered , what staff and rescourses are needed and this will need a lot of planning and additional staff. Its aviable in USA for over a year, in Europe too now privately- we need to leran from their experience. If possible make allow carers tp administer in home setting as its weekly therapy at least initially	Thank you for your comment. No change to the scope made.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

The British Society for Cutaneous Allergy