27 February 2025
EMA/98574/2025
Committee for Advanced Therapies (CAT)
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vyjuvek

International non-proprietary name: beremagene geperpavec

Procedure No. EMEA/H/C/006330/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse event
AET	Analytical evaluation threshold
AF	Anchoring fibril
AQL	Acceptable quality limit
BMZ	basement membrane zone
BSA	Bovine serum albumin
BSE	Bovine spongiform encephalopathy
BSM	Berkshire Sterile Manufacturing
CCI	Container closure integrity
cDNA	Coding DNA
CFU	Colony forming units
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CMV	Cytomegalovirus
COC	Cyclo-olefin copolymer
COL7	Collagen type VII
CPE	Cytopathic effects
CPP	Critical process parameter
CQA	Critical quality attribute
CSR	clinical study report
Ct	Cycle threshold
CV	Coefficient of variation
DDEB	dominant dystrophic epidermolysis bullosa
DEB	dystrophic epidermolysis bullosa
DLS	Dynamic light scattering
DMEM	Dulbecco’s modified Eagle Media
DP	Drug Product
DPBS	Dulbecco phosphate buffered saline
DS	Drug Substance
EB	epidermolysis bullosa
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOPC	End of production cells
EU	Endotoxin unit
FBS	Foetal Bovine Serum
FDA	Food & Drug Administration
GC/MS	Gas chromatography mass spectrometry
GLP	Good laboratory practice
GMP	Good manufacturing practice
HBV	Hepatitis B Virus
HCP	Host cell protein
HCP	health care provider
HCV	Hepatitis C virus
HEK	Human embryonic kidney

HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HIV	Human immunodeficiency virus
HMW	High molecular weight
HPMC	Hydroxypropyl methylcellulose
HPRA	Health Products Regulatory Authority
HRP	Horseradish peroxidase
HSV	Herpes simplex virus
HSV-1	herpes simplex virus type 1
ICH	International Conference on Harmonisation
ICP	Inductively coupled plasma
IGA	Investigator's Global Assessment
IP	investigational product
IPC	In process control
ISO	International Organisation for Standardisation
ISS	integrated safety summary
ITT	intent-to-treat
IU	Infectious unit
KB103	beremagene geperpavec
kGy	kiloGray
LAL	Limulus amebocyte lysate
LC-MS	Liquid chromatography – mass spectrometry
LMW	Low molecular weight
LOD	Limit of detection
LOQ	Limit of quantitation
LTFU	long-term follow-up
MAA	Marketing authorisation application
MAO	Monoamine oxidase
MCB	Master Cell Bank
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MO	Major Objection
MOI	Multiplicity of Infection
MoS	Margin of safety
MRA	Mutual Recognition Agreement
MW	Molecular weight
NC	non-collagenous
NMT	Not more than
NOR	Normal operating range
NTC	No template control
OC	Other concern
OD	Optical density
OLE	open-label extension
PBS	Phosphate buffered saline
PDE	Permitted daily exposure
PdI	Polydispersity index
PFU	Plaque forming unit

PP	per-protocol
PPQ	Process performance qualification
PRO	patient-reported outcome
PV	Process validation
QA	Quality attribute
QP	Qualified person
qPCR	Quantitative polymerase chain reaction
rcHSV	Replication competent HSV
RDEB	recessive dystrophic epidermolysis bullosa
RS	Reference standard
RSD	Relative standard deviation
SAE	serious adverse event
SCC	squamous cell carcinoma
SD	Standard deviation
SmPC	Summary of product characteristics
TFF	Tangential flow filtration
TIC	Total ion current
TRIS	Tri(hydroxymethyl)aminomethane
TSB	Tryptone soya broth
TSE	Transmissible spongiform encephalopathy
TTC	Threshold of toxicological concern
UF/DF	Ultrafiltration/ diafiltration
US	United States
USP	United States Pharmacopoeia
UV	Ultraviolet
v/v	Volume/ volume
VAS	visual analog scale
Vg	Vector genome
WCB	Working cell bank
WFI	Water for injections
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Krystal Biotech Netherlands B.V. submitted on 30 October 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Vyjuvek, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 March 2023.

Vyjuvek, was designated as an orphan medicinal product EU/3/18/2012 on 16 April 2018 in the following condition: treatment of epidermolysis bullosa.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Vyjuvek (beremagene geperpavec) as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Vyjuvek

The applicant applied for the following indication: treatment of patients from birth with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the *collagen type VII alpha 1 chain (COL7A1)* gene.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that beremagene geperpavec was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0024/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the P/0249/2023 was not yet completed as some measures were deferred.

1.3. Information relating to orphan market exclusivity

1.3.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is an authorised orphan medicinal product for a condition related to the proposed indication.

1.4. Applicant's requests for consideration

1.4.1. New active substance status

The applicant requested the active substance beremagene geperpavec contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. PRIME

Vyjuvek was granted eligibility to PRIME on 28 March 2019 in the following indication: treatment of dystrophic epidermolysis bullosa. Eligibility to PRIME was granted at the time in view of the following:

- The unmet medical was agreed considering that Dystrophic Epidermolysis Bullosa is a serious debilitating disease for which no available treatments are available.
- Topical administration in non-clinical studies in xenograft mice and in heterozygous hypomorph mice showed functional collagen VII expression and structural correction of the skin.
- The phase II clinical study showed that administration of the product closed wound as an average of 87.4% at Day 30 with 5 of the wounds achieving 100% closure, 2 of the wounds with closure over 75%, and one wound with 35% closure in comparison to placebo which was 27.1% at Day 30.
- Overall, although data were lacking at present on tendency of recurrence, chronicity and persistence of wound closure, the nonclinical data and observed clinical effect on wound closure were supportive of proof of concept and potential to bring a major therapeutic advantage.

Upon granting of eligibility to PRIME, Maura O'Donovan (later replaced by Joseph deCourcey) was appointed by the CAT as rapporteur.

A kick-off meeting was held on 16 July 2019. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

The applicant was recommended request Scientific Advice on quality (batch comparability, process validation, aseptic process, control and compounding of final formulation) and non-clinical (non-clinical package, justification for non-GLP studies to evaluate biodistribution and toxicity) development.

The applicant was recommended to request Scientific Advice on clinical development (design of pivotal study, in particular choice of control, dose selection for paediatric development, and data to support possible conditional MA).

1.6. Protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
28 June 2018	EMEA/H/SA/3850/1/2018/PA/SME/ADT/II	Hans Ovelgönne, Susan Cole, Jan Mueller-Berghaus

28 May 2020	EMEA/H/SA/3850/1/FU/1/2020/PA/SME/ ADT/PR/III	Sheila Killalea, Rune Kjeken, Carin Bergquist, Paolo Foggi
14 October 2021	EMA/SA/0000064052	Sheila Killalea, Silvijus Abramavicius

The protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- Acceptability of the proposed MCB, MVB and GMP batch release assays, the proposal to use the drug substance and drug product manufactured under GMP in the US at clinical sites in the EU, acceptability of the proposed stability program; the release assays and specifications for B-VEC drug substance and drug product; suitability of Krystal's Ancoris facility to manufacture material intended for use within the EU; suitability of the current B-VEC manufacturing process for a topical gene therapy product intended for use in the EU; the aseptic process simulation strategy to assure sterility; the approach for raw materials and components used in the B-VEC manufacturing process; the plan to utilise a WCB and WVB to produce B-VEC commercial product; the comparability plan for evaluating process changes for B-VEC Drug Product; the classification of 3.75% METHOCEL gel, intended to be mixed with the B-VEC Drug Product at the time of preparation of the clinical dose, as an excipient; the proposed stability program in order to establish an expiration period; suitability of foetal bovine serum (FBS) for commercial manufacture of B-VEC; whether the addition of a sterile filter at the clarified bulk step is an acceptable solution to overcome the requirement of an aseptic processing strategy for the B-VEC manufacturing process; whether the downstream process achieves a sufficient clearance of residual impurities in the B-VEC manufacturing process; the proposed approach for defining the commercial B-VEC manufacturing control strategy; the proposed specification for the Plaque Titre Assay for B-VEC Lot Release; whether the date of manufacture is sufficient on the label in lieu of an expiry date.

- Adequacy of the non-clinical development program to support a MAA; the approach to justify the absence of carcinogenicity studies.

- The phase 1 study design; the overall phase 3 study design (i.e., a randomised block design in which each patient serves as a block to receive all of the treatment conditions) and plan proposed; the primary endpoint; the secondary and exploratory endpoints; the Safety Monitoring Plan; the proposal not to perform biopsies in the phase III trial; the rationale to include data from previously treated patients in the statistical analysis of the pivotal phase III study data.

1.7. Steps taken for the assessment of the product

The CAT Rapporteur and Co-Rapporteur appointed by the CHMP were:

CAT Rapporteur: Joseph DeCourcey CAT Co-Rapporteur: Violaine Closson Carella

CHMP Coordinator (Rapporteur): Finbarr Leacy CHMP Coordinator (Co-Rapporteur): Jean-Michel Race

The application was received by the EMA on	30 October 2023
The procedure started on	23 November 2023
• As the ATMP is a combined ATMP, the CAT agreed to consult the national Notified Bodies on the Environmental Risk Assessment of the GMO as the ATMP is a gene therapy product. The consultation	28 February 2024

procedure closed on	
The CAT Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	12 February 2024
The CAT Co-Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	26 February 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	26 February 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CAT during the meeting on	07 March 2024
The CAT agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 March 2024
The applicant submitted the responses to the CAT consolidated List of Questions on	12 August 2024 21 August 2024
A GMP inspection at ''Krystal Biotech, Inc., 2100 Wharton Street Suite 701, Pittsburgh, PA 15203, USA'' was performed 22nd-24th February 2024. The outcome of the inspection carried out was issued on 22nd May 2024.	22 May 2024
The CAT Rapporteur circulated the Joint Assessment Report on the responses to the List of Questions to all CAT and CHMP members on	17 September 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	03 October 2024
The CAT agreed on a list of outstanding issues to be sent to the applicant on	11 October 2024
The applicant submitted the responses to the CAT List of Outstanding Issues on	06 November 2024
The CAT Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CAT and CHMP members on	21 November 2024
The CAT agreed on a 2nd List of Outstanding Issues to be sent to the applicant on	06 December 2024
The applicant submitted the responses to the CAT 2nd List of Outstanding Issues on	22 January 2025
The CAT Rapporteurs circulated the Joint Assessment Report on the responses to the 2nd List of Outstanding Issues to all CAT and CHMP members on	06 February 2025
The CAT, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a	21 February 2025

marketing authorisation to Vyjuvek on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Vyjuvek on	27 February 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Dystrophic epidermolysis bullosa (DEB) is a serious ultra-rare genetic blistering disease caused by mutations in COL7A1, the gene encoding type VII collagen (COL7) and is inherited in an autosomal dominant (DDEB) or autosomal recessive (RDEB) pattern depending on the subtype. The disease, which can present itself as early as at birth, is characterised by skin fragility, separation of the epidermis from the dermis (blister formation), milia, and scarring. DEB-associated blisters and erosions affect skin as well as certain mucosa exposed to disruptive external environments, including the oropharynx, oesophagus, rectum, genitourinary system, and eyes. Healing of erosions can result in debilitating scarring.

2.1.2. Epidemiology

At the time of designation, epidermolysis bullosa affected 0.7 in 10,000 people in the European Union (EU). This was equivalent to a total of around 36,000 people. The most reliable estimates of the prevalence of epidermolysis bullosa (EB) are derived from the National Epidermolysis Bullosa Registry, a cross-sectional and longitudinal epidemiological study of 3,300 patients with confirmed EB across the entire continental United States (US) from 1986 to 2002. Based on this 16-year analysis of registry data, the prevalence of recessive DEB (RDEB) in the US was estimated to be 1.35 persons *per* million inhabitants and the prevalence of dominant DEB (DDEB) was estimated to be 1.49 persons *per* million inhabitants.

2.1.3. Biologic features

The most severe form of DEB is RDEB, in which COL7 protein expression is severely diminished or completely absent in the patient's skin due to null mutations in the COL7A1 gene.

2.1.4. Clinical presentation, diagnosis

A systematic literature review of the disease burden in patients with RDEB that included 65 studies was recently published. It was reported that 60% of patients had wounds covering more than 30% of their bodies, with pain and itch seen with the larger wounds. Commonly reported symptoms and complications included lesions and blistering, anaemia, nail dystrophy and loss, milia, infections, musculoskeletal

contractures, strictures or stenoses, constipation, malnutrition/nutritional problems, pseudo-syndactyly, ocular manifestations, and dental caries.

Persistent blistering begins at birth and contributes to the high mortality risk due to bacterial infection. In a study of 41 RDEB patients, pneumonia and sepsis resulted in the death of 14.6% and 9.8% of these patients, respectively. Patients who survive bacterial sepsis during early infancy are at a high risk of later developing severe complications such as growth retardation due to gastrointestinal involvement, multifactorial anaemia, oesophageal strictures, corneal scarring and/or progressive blindness, post streptococcal glomerulonephritis, renal failure, progressive hand and foot deformities such as pseudo-syndactyly, muscle contractures that restrict movement, microstomia, obliteration of the oral vestibule, dysphagia, rapid tooth decay, nail deformities, and hair loss. Additionally, patients suffering from RDEB have a high risk of developing squamous cell carcinoma (SCC), which is highly aggressive and life-threatening. The risk of SCC was 76%, with mortality from SCC reading 84% by age 40. There is significant mortality associated with RDEB; nearly 10% of the patients died before age 10, almost 40% by age 20, and 72% before the age of 30. These deaths occur despite aggressive tumour resection. While not as prevalent as in RDEB, SCC also poses a significant risk for patients with DDEB, with tumours occurring later in life and tending to be less aggressive.

Given the severity of DEB, its associated mortality and morbidity, and the lack of effective disease modifying treatment options, there is a need for therapies that focus on the root cause of the debilitating symptoms and that can be administered in a minimally invasive way.

2.1.5. Management

There are no approved corrective treatments for DEB patients. For most patients, management is supportive in nature and is mainly limited to palliative care. Current standard of care is focused on reducing trauma and infections while managing the symptoms associated with multiple wounds of varying duration, size, and healing stage. Regimented personal hygiene and skincare are necessary to promote wound healing and to prevent infection and wound growth. Pain medications are commonly used. Surgery is indicated for co-morbidities such as pseudo-syndactyly, oesophageal strictures, and skin cancer. The burden of wound care for RDEB is substantial, requiring daily changes of wound dressings that can take several hours. Thirteen to 54% of patients report daily dressing changes and 15% to 40% report spending up to 3 hours *per* change.

In June 2022, Filsuvez, topical birch bark extract, received marketing authorisation in the EU for the treatment of dystrophic and junctional EB.

2.2. About the product

Beremagene geperpavec is a gene therapy medicinal product, i.e. it is an engineered, replication-incompetent herpes simplex virus type 1 (HSV-1)-based vector coding human COL7A1 that is applied topically to promote functional COL7 expression in the skin. As it is non-integrating, its genes remain physically separate from the host cell chromosome, it does not carry the potential risk of insertional mutagenesis, nor the resulting possibility of disrupting essential host genes and triggering oncogenesis. Through the deletion of essential viral immediate early genes, beremagene geperpavec is rendered completely replication-incompetent in non-complementing cells, thus, eliminating its ability to replicate within HSV-1's natural environment, the human body.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as a suspension and gel for gel containing 5×109 Plaque Forming Units (PFU)/mL of beremagene geperpavec as active substance.

Other ingredients are:

Excipients in beremagene geperpavec suspension: glycerol (E422), sodium chloride, disodium phosphate (E339), potassium chloride (E508), dipotassium phosphate (E340).

Excipients in gel: hypromellose (E464), trometamol, sodium chloride, disodium phosphate (E339), dipotassium phosphate (E340).

Each carton of Vyjuvek contains one single-dose vial of Vyjuvek suspension and one single-dose vial of gel. The suspension is available in a cyclo-olefin copolymer vial with a thermoplastic elastomer closure and green cap and the gel is available in a separate Type-1 glass vial with a bromobutyl elastomer stopper and blue cap.

The finished product manufacturing process is essentially part of a continuous process from the end of active substance manufacture, therefore certain sections of the dossier (e.g. active substance specifications and stability) are not applicable as they are controlled on the finished product level, which is discussed in detail further in this report.

2.3.2. Active substance

2.3.2.1. General information

The active substance of Vyjuvek is beremagene geperpavec (INN), (also referred to as KB103 in the dossier and this report) and it is a replication-incompetent, non-integrating HSV-1-based vector engineered to express full-length, functional human collagen VII (COL7). The vector was generated by deleting both copies of the viral immediate early (IE) gene ICP4 from the KOS genome, and then inserting a copy of a human COL7A1 into each ICP4 locus. These copies of COL7A1 are each separately under the control of a human cytomegalovirus (hCMV) promoter and bovine growth hormone (bGH) polyadenylation signal to allow for constitutive expression of COL7 upon cellular infection. In addition, KB103 was completely deleted for the IE gene ICP22 to further reduce any potential cytotoxic effects of the engineered virus. Because ICP4 is deleted, KB103 is non-replicating and does not grow in non-complementing cells lacking exogenous ICP4. Information provided on the nomenclature, structure and general properties is sufficient.

2.3.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The applicant has updated the manufacturers responsibilities during the procedure to provide detail on the specific testing carried out by each site. All the sites are appropriately authorised and adequate GMP compliance has been demonstrated.

The active substance manufacturing process has been adequately described. The KB103 active substance manufacturing process consists of working cell bank (WCB) thawing, cell expansion, virus infection and production, bulk harvest, and purification.

The infection conditions and duration are defined. As the viable cell count cannot be determined, it is also not possible to determine the amount of virus to add by the multiplicity of infection (MOI).

The active substance container closures system is adequately described. The specifications include sterility, biocompatibility, endotoxin and particle contamination. The site of sterilisation for the container closure is registered in the dossier. Identification of the container closure components is considered adequately addressed in the registered specifications.

Compatibility of the container closure is supported by the hold time studies for the active substance described in sections S.2.4 and S.2.6 of the dossier. A risk assessment of the leachables is provided and supported with supplier extractables studies and a leachables study. The conclusion that there is little risk posed by the use of the selected active substance container is adequately supported.

Control of materials

Materials determined to be critical materials used in the manufacture of the active substance are listed identifying where each material is used in the manufacturing process. Information provided in the dossier on the control of raw materials is sufficient. The qualitative components of each media used in routine manufacturing and compendial status are registered. Filters used in the manufacturing process are registered and manufacturer/catalogue numbers are provided.

The starting materials described include the Vero master cell bank (MCB) and WCB, and the master virus banks (MVB) and working virus banks (WVB). Details on the critical reagents used in development of the cell and virus banks are provided. The manufacturing and characterisation of the cell banks is in line with the principles described in ICH Q5D, and the relevant Ph. Eur. monographs and general texts. Qualification of both new WCB and WVB is described and a protocol is provided. Adventitious agents testing is addressed in A.2 section of the dossier and found acceptable.

KB103 is deleted for ICP4, required for HSV-1 growth. Therefore, a complementing cell line expressing ICP4 in trans was generated from a parent VERO cell line. History and establishment of the complementing cell line from Vero cells is sufficiently described. The sequence of the plasmids has been provided in accordance with ICH guideline Q5B. Data are provided to demonstrate that the ampicillin resistance gene is present in the complementing cell line but not in KB103 finished product and therefore release testing for residual ampicillin resistance gene is not required. Sufficient data have been provided to demonstrate the genetic stability. The manufacturing of MCB in 2017, WCB in 2019 and WCB in 2020 is described. Overall, the characterisation of MCB and WCBs is acceptable.

The generation of the KB103 construct is well described. KB103 was deleted for viral immediate early (IE) gene ICP4 to inhibit viral replication. A copy of COL7A1 was inserted in each ICP4 locus under the control of a human cytomegalovirus (hCMV) promoter and bovine growth hormone (bGH) polyadenylation signal to allow for constitutive expression of COL7 upon cellular infection. KB103 was also deleted for IE gene ICP22 to reduce potential cytotoxic effects. Overall, provided that the proposed transgene and resultant protein are demonstrated to be safe and efficacious in the pivotal studies, no queries are raised on the proposed transgene and variants.

The original virus seed stock was obtained from KB103 vector construct by limiting dilution and used to produce the first MVB. Second and third MVB batches were manufactured using the first MVB batch and subsequently the second batch to make the third. These 3 MVBs were used to manufacture KB103 finished product batches for phase 1, phase 2 and phase 3 trials, respectively. The manufacturing process of MVBs

and WVBs is sufficiently described. Specifications of MVBs and WVBs are clearly presented in the dossier. The specifications presented in the certificates of analysis (CoAs) are overall acceptable.

Control of critical steps and intermediates

The process parameters were identified based on risk assessment and process development data. A list of controls for critical quality attributes (CQAs) that are implicit in the design of the manufacturing process is presented. The control strategy parameter classifications are provided and includes critical process parameters (CPP), process performance parameters (PPP), in process limits (IPL), and in-process release tests which are defined. A clearer definition of the IPL and its role in the control strategy was provided and is acceptable.

In-process release tests are limited to sterility, and mycoplasma and adventitious agents. Sterile filter integrity testing is described.

Process validation

The active substance and finished product process were validated in conjunction as the finished product is a singe vial filling operation that follows active substance manufacturing in the same facility (Krystal Biotech, Inc., USA).

In general, all the batches met the pre-determined release specifications, CPP, and in-process limits. Graphical representations of the data are provided. Some deviations were observed, and these have been sufficiently addressed by the applicant. These deviations are not determined to have an impact on the process, product quality, or suitability of the batches for validation purposes. Sterile filter validation is provided for the sterile filters and is considered acceptable. Validation is in accordance the Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015). Membranes are single use, and no lifetime studies are required. Overall, based on the information provided it is considered that the process is under control.

Manufacturing process development

There are GMP process iterations described, and all were used to manufacture clinical batches. Comparability is sufficiently demonstrated. Comparability has been demonstrated by analytical comparability testing to the release specifications and demonstrating statistical equivalence of the potency and transgene assay, and this is considered acceptable. In general, the results provided demonstrate comparability. In-process data from batches included in the comparability studies between processes have been included in the updated version of Module 3.2.S.2.6 of the dossier. Comparability on stability has been sufficiently addressed. Further optimisation was performed

The information provided is considered sufficient to support the proposed strategy and no further considerations are raised. As part of the overall microbial control strategy a risk assessment is provided. Additional information was provided to ensure that all possible worst-case conditions have been included

Development of the control strategy is described, and failure rate ranges and historical rate ranges were calculated to determine process parameters.

The maximum recommended hold times were established. In general, the proposed process intermediate hold times are considered adequately supported.

Analytical development history

The different methods used during development were presented. All methods were validated. Comparability studies between the qualified and the validated methods were performed and the data support method changes and comparability.

Characterisation

Initially, the applicant provided a high-level description in characterisation of the active substance, and minimal data were provided. Upon request, sufficiently detailed information has been presented on the characteristics of the viral particle, including morphology, glycoprotein composition, ratio of the different proteins and size of the genome. The full DNA sequence and COL7A1 transgene sequence are discussed. Characterisation of the biological activity of KB103 is considered sufficient and is supported by the non-clinical and clinical data. Overall, the information provided in S.3.1 of the dossier is considered sufficient to demonstrate a comprehensive picture and knowledge of the product. The beremagene geperpavec active substance has been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure of a replication-defective Herpes Simplex Type-1 HSV-1-based gene therapy vector. The analytical results are consistent with the proposed structure.

The applicant has included adequate information on the capacity and consistency in clearance of the identified process- and product- related impurities from the active substance manufacturing process in S.3.2 section of the dossier with relevant data from historical batches. Details of the residual raw materials e.g. culture residues have been provided and the risk assessment of the raw material used in the manufacturing process have been cross referenced. The applicant concludes that the impurity levels in purified KB103 active substance do not present a patient safety risk, and this statement can be supported.

2.3.2.3. Specification

No specifications, analytical procedures, reference standard or batch analysis are registered for the active substance but are addressed in the finished product as the finished product manufacture is a singe vial filling operation that follows active substance manufacturing in the same facility (Krystal Biotech, Inc., USA). Cross-reference is made to the corresponding 3.2.P section of the dossier. A description and summary of the active substance testing is provided and considered acceptable.

2.3.2.4. Stability

Long term storage of the active substance is not proposed, and no stability data are provided. No section is presented on the stability of the active substance. Cross-reference is made to the corresponding 3.2.P section of the dossier, which is found acceptable.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

Description of the product

KB103 finished product suspension is a white to off-white, opalescent, sterile suspension, preservative free, supplied in 1.15 mL single- dose cyclic olefin copolymer vials (1mL extractable) at a concentration of 5×10^9 plaque-forming units (PFU) per mL.

KB103 finished product is the active substance (HSV 1-COL 7 in 10% glycerol DPBS) which is filled aseptically. All formulation unit operations for the finished product occur during manufacture of the active substance with no additional components added during the manufacture of the finished product.

The finished product needs to be mixed with 1.5 mL of the excipient gel (hydroxypropyl methylcellulose (HPMC) 4% formulated in Tris/PBS buffer) prior to topical application to wounds. The function of the HPMC gel is to simplify dosing by increasing the viscosity of the product for ease of application. Increasing the viscosity prevents product from running off the wound prior to covering the application site.

Pharmaceutical development

KB103 finished product is manufactured by dispensing the KB103 active substance into vials without additional formulation or dilution. The target fill volume is 1.15 mL to ensure full withdrawal of 1 mL of KB103 finished product.

Hydroxypropyl methylcellulose (HPMC) excipient gel is supplied as a sterile solution in a separate vial and is mixed with KB103 prior to topical administration.

Several different formulations were used throughout development between the Phase 1/2 and Phase 3 studies. The percent of HPMC was changed to increase the thickness of the mixed product for better containment of the product to the wound during application. For commercial use the mixing ratio of KB103 finished product: excipient gel is standardised to 1 finished product :1.5 gel and the product application is standardised to 4 administration syringes (that are not supplied with the product) with a 0.5 mL fill.

A high-level summary of the finished product formulation development studies has been provided. Formulation development was also studied in several non-critical studies. The principles of the EMA Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2) have been followed. The applicant has sufficiently demonstrated that the exact viscosity of the HPMC gel is not critical, as it does not impact the delivery of the finished product.

The administration information in the SmPC requires that once the finished product is added to the excipient gel it should be shaken vigorously for 10 seconds. In-use data have been provided to demonstrate that shaking for 10 seconds is sufficient to evenly disperse the finished product within the excipient gel. The suspension must be mixed into the gel in a pharmacy setting prior to administration.

Excipients

The excipient formulation buffer is 10% glycerol in Dulbecco's phosphate buffered saline (DPBS). Glycerol is added to the final formulation buffer to act as a cryoprotectant to ensure long-term stability in freezer storage, and to protect the vector across temperature changes in the supply chain to ensure equivalent potency from the time of fill to patient administration. The finished product suspension is mixed with HPMC gel prior to topical application to wounds.

The specifications for 10% glycerol in DPBS include endotoxin, pH, specific gravity, sterility, and appearance. The registered control strategy is considered acceptable.

As stated in the EMA Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container (EMA/CHMP/CVMP/QWP/850374/2015); for excipients required to be sterile (i.e. those subsequently used in an aseptic manufacturing process) the sterilisation of an excipient is a critical process, and the sterility of the excipient is a critical quality attribute to ensure the sterility of the finished product. The manufacturing process for the DPBS glycerol has been appropriately validated.

Stability data have been provided for the 10% glycerol DPBS.

The HPMC excipient gel is mixed with the finished product prior to topical application to wounds, its purpose is to keep the finished product within the treatment area. The gel consists of tromethamine (tris base), potassium dihydrogen phosphate, NaCl, sodium hydrogen phosphate heptahydrate, and hydroxypropyl methylcellulose (HPMC). HPMC gel is a commonly used mixture of excipients in medicinal products including creams, ointments and ophthalmic preparations, therefore its use is not considered to be novel, and information is presented in section 3.2.P.4 of the dossier.

The manufacturing process of the excipient gel involves sterilisation of materials, washing, depyrogenation and steam sterilisation of vials, formulation, clarification, aseptic filling, terminal sterilisation, and visual inspection. Filled vials can be stored at 2–8 °C for up to 60 days and are then stored frozen. Some changes have been made to the manufacturing process of the HPMC gel between the Phase 3 and commercial process. As the excipient gel is comprised of chemical components, ICH Q5E is not applicable and therefore comparability data to support these changes is not requested.

Controls are registered for the manufacturing process and they are considered appropriate. All methods apart from visual appearance and concentration are conducted in accordance with the Ph. Eur.

The container closure for the HPMC gel is a glass vial with a bromobutyl rubber stopper. The container closure system complies with Ph. Eur. 3.2.1 Glass containers for pharmaceutical use, and Ph. Eur. 3.2.9 Rubber closures for containers for aqueous parenteral preparations. An extractables and leachables report has been provided. Components used in the process are pre-sterilised or washed and depyrogenated or sterilised by autoclave. All three PPQ batches successfully passed validation. All in-process tests and release tests met acceptance criteria. Batch release data is provided for the 3 PPQ batches. Stability data are presented for the 3 PPQ batches. The provided data was sufficient to support the overall shelf life for the product and it was found acceptable.

Manufacturing process development

No additional finished product comparability data are required. Details of comparability can be found in S.2.6 of the dossier and these are found acceptable.

Only a high level summary of the process characterisation was provided in section P.2 of the dossier, however since the finished product manufacturing process comprises only vial filling, no additional finished product process characterisation is considered necessary.

Container closure

The container closure is a closed vial composed of cyclic olefin copolymer and a stopper composed of thermoplastic elastomer and a high-density polyethylene (HDPE) vial cap. The vial complies with Ph. Eur. 3.1.3 Polyolefins, and the stopper conforms with Ph, Eur. 3.2.9 Rubber Closures. Container closure integrity testing in accordance with Ph. Eur. 3.2.9 has been performed by the vial vendor using the methylene blue ingress test. A simulated leachables study was also carried out and no volatile, semi-volatile, or non-volatile compounds were identified above the Analytical Evaluation Threshold (AET) in this study. No elemental impurities were reportable in this study. The applicant justified that the simulated use study at ambient temperature is sufficiently representative of the possible leachables when the finished product is stored at -20 ˚C for 2 years and up to 1 month in a refrigerator and this conclusion is agreed. The Applicant has presented release specifications for the closed vial, the vial body and the stopper. Sterilisation is performed with a dose range which meets the minimum requirements of Ph. Eur. 5.1.1. The name and address of the sites of sterilisation have been registered in the dossier.

Compatibility

Reference is made to a pre-clinical study report in Module 4.2.1.1 of the dossier to support compatibility with 10% glycerol DPBS formulation buffer. References to further pre-clinical reports are provided for compatibility with the excipient gel, which includes compatibility with 3% HPMC (Phase 1 and 2) with 4% methocel. Data from a pharmacology study in mice is presented in the dossier to support comparable efficacy between KB103 mixed with 3% or 4% methocel.

A report was provided outlining where excipient gel from three different suppliers was tested with a representative finished product batch. Issues around compatibility with the excipient gel are further addressed in the pharmaceutical development section and in the stability section.

The compatibility of KB103 with a 4% methocel in 1xDPBS with 7.5 mM Tris was evaluated during 24 hours at room temperature. KB103 is compatible with the excipient gel during 8 hours at room temperature.

Another study was performed at 2-8 °C. The applicant claims that the mixed finished product/excipient gel in the filled syringe remains stable, both for strength and potency, for up to 168 hours when stored at 2-8°C (cf comment in the stability section of this report).

2.3.3.2. Manufacture of the product and process controls

Manufacture

The finished product is manufactured and tested at Krystal Biotech, Pittsburgh, PA, USA, and an EU GMP certificate has been provided for this site during the procedure, after a major objection has been initially raised on the missing GMP certificate. EU batch release takes place at ProPharma Group, Leiden, Netherlands, this site has a valid MIA. A QP declaration for EU GMP compliance is provided and includes active substance manufacturing and the preparation of the cell banks and the virus banks.

Third party vendors manufacture the excipient gel and the 10% glycerol DPBS. These sites have not been inspected by an EEA competent authority; however they have been inspected by FDA, and it has been confirmed by the Supervisory Authority that in consideration of the GMP compliance history of the sites, including all previous inspections and FDA inspection reports/outcomes, an EU GMP inspection is currently not required.

For the current MAA, the applicant is proposing to confirm the identity of the finished product upon importation.

In conclusion, the Applicant has provided a detailed and well-structured discussion of the impact that repeat testing in the EU would have on the availability of this medicine for EU patients. It is agreed that the Applicant has satisfactorily addressed the individual points raised in the Major Objection and repeat testing in the EU can be exceptionally omitted in this case given the small batch size and the impact to availability due to repeat testing.

The batch formula has been registered in terms of concentration per volume as well as the overall amounts per batch. This is based on a fill volume target of 1.15 ml.

The finished product manufacturing process is essentially part of a continuous process from the end of active substance manufacture. Finished product manufacturing consists of storage of the active substance overnight at 2 – 8 °C and aseptic filling into pre-sterilised vials. There are no formulation or dilution steps. After filling, the vial is sealed and then capped. Visual inspection for cosmetic defects and bulk packaging is performed

concurrently. The filled cryoboxes are placed into -80 °C (±10 °C) for storage. The final packaging/labelling process is performed at -80 °C. Sufficient stability has been demonstrated for both the -80 °C storage condition as well as -20 °C storage condition which is the intended finished product storage condition. Vials undergo 100% visual inspection.

Process controls

The overall control strategy for the finished product manufacturing process can be agreed. The claimed hold times of the active substance are the following: 2 hours at room temperature and 24 hours at 2-8 °C.

Data supporting the applicability of the ranges/limits established for operating parameters have been provided.

Process validation

The active substance and finished product processes were validated in conjunction, as they are essentially continuous. Following the manufacture of the initial three PPQ batches, the manufacturing process was changed for the active substance TFF2 step and therefore an additional three consecutive PPQ batches were manufactured. All finished product validation acceptance criteria were met for the batches, and release testing results for all six batches are provided showing results which are consistent across batches. Batch homogeneity has been demonstrated. Full process validation reports have been provided, which include details of deviations noted during PPQ and the related CAPAs. The deviations do not impact the conclusion that the finished product manufacturing process is in a validated state.

A high level overview is provided on the media fill studies/aseptic process simulation (APS). Four consecutive media fills using tryptic soy broth were successfully performed for initial validation of the fill step between August and November 2019. Following initial validation, media fills were performed periodically to maintain the validated state (twice a year). Three consecutive media fills were also successfully performed for initial validation of the fill step using the L1 filler. The overall duration of the media fill runs is greater than the filling times of the commercial process and therefore acceptable.

Details of the future planned finished (secondary) packaging qualification are provided. This qualification will leverage existing packaging validation carried out at a different site and is acceptable. Transport validation data were provided to support the transport of the finished product from the site of finished product manufacture to the distribution centres and warehouses in the EU. The applicant confirms that the temperature is monitored throughout shipping.

2.3.3.3. Product specification

The active substance release is not independent of the finished product release since the KB103 process is continuous. One Certificate of Analysis (CoA) is prepared per KB103 lot. The tested parameters are identity, quality, potency, strength, purity, and safety. Sterility, mycoplasma, and *in vitro* viral testing are performed as in-process tests.

Analytical method numbers are included in the specifications which provides a link to the method description and method validation. Many of the specification acceptance criteria have also been clinically justified.

Regarding the control of genetic identity and integrity, the applicant highlights that whole genome sequencing has been carried out on 9 finished product batches which confirmed genetic identity of KB103.

There are no proposed release tests for empty particles or co-packaged sequences. In the 2021 Scientific Advice, the applicant highlighted that since the manufacturing process is an infection process, rather than a transfection based process, empty particles or particles containing co-packaged unwanted genetic sequences are not expected. The justification was considered acceptable in the Scientific Advice and therefore it is acceptable that there is no release test for empty particles or co-packaged sequences.

Tests for process related impurities include host cell DNA, HCP, and total protein. However, the Applicant has justified that the risk posed by residual DNA is low due to the demonstrated low systemic exposure.

Safety related release tests include sterility, endotoxins, sensitivity, and replication competent HSV. General tests include colour, clarity, pH, extractable volume and visible particles. No test for sub-visible particles is proposed, however considering that the pharmaceutical form is a suspension and gel for gel, the omission of a sub-visible particle test is acceptable; this was previously agreed in the 2021 Scientific Advice. There is no test for osmolality proposed in the release specifications. This was addressed in the 2021 Scientific Advice where it was agreed that osmolality is not relevant for batch release of this topically administered product. The applicant proposes acceptance criteria for visual inspection, as vials may contain inherent proteinaceous particles. The possible presence of inherent proteinaceous particles is addressed in the product information.

The potential presence of elemental impurities in the finished product has been appropriately discussed and it is considered acceptable.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed following a raised major objection. The risk assessment considering all suspected and actual root causes is in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

In conclusion, the testing panel of the finished product component generally meets the requirements of the EMA Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014) and it is considered appropriate.

Analytical procedures

The in-house analytical methods are generally described in sufficient detail and appropriate system suitability tests (SSTs) are registered.

Regarding testing for colour and opalescence, no reference solutions are used which means that the assigned colour and opalescence might be influenced by subjectivity during analysis. However, the applicant has committed to complying with Ph. Eur. 2.2.1 and Ph. Eur. 2.2.2 for appearance testing post approval of the application; this is included as a quality recommendation.

Sterility is conducted in accordance with Ph. Eur. 2.6.1 using the membrane filtration method. Mycoplasma is tested using Ph. Eur. 2.6.7. The *in vitro* adventitious virus test using a 28-day assay with tests for cytopathic effects, hemadsorption and hemagglutination.

Endotoxin testing is in accordance with Ph. Eur. 2.6.14 using the kinetic chromogenic technique in the LAL assay. The Applicant has started the process of development of an endotoxin assay based on recombinant Factor C to eliminate the need for horseshoe crab derived material.

For the identity method, identity is confirmed by presence of the COL7 band in reference to the Protein Ladder and KB103 Reference Standard.

Particle size is measured. This is a dynamic light scattering method that measures the Brownian motion of particles in a dispersion.

The HSV-1 plaque titre assay involves incubating cells with dilutions of the test sample. Cells are covered in a layer of methylecellulose and focal zones are measured as plaques using crystal violet.

The principle of the potency ELISA is based on the interaction between collagen VII and one of its native binding partners in the skin. This interaction plays a crucial role in anchoring the epidermis to the underlying dermis, contributing to the overall stability and functionality of the skin. The potency assay involves transducing Vero cells with KB103 at a defined MOI; a negative mock-transduced control is also used. Cell lysate is prepared from these cells and added to assay plates pre-coated with the native binding partner. Binding is then measured and compared to a standard curve constructed using recombinant COL7 as input. The result obtained for the test sample is normalised taking into account the historical mean value of the reference standard and the reference standard result obtained during the run.

Residual DNA is detected by qPCR.

Host cell protein (HCP) is measured using a commercial ELISA.

Total protein is measured using a standard microBCA.

Replication competent HSV (rcHSV) is tested by inoculating Vero cells in 6-well plates at MOI of 1 and after culturing, cells are observed for cytopathic effect.

Genes are assayed using a standard qPCR approach and the acceptance criteria of "not detected" is based on the limit of detection (LOD) of the assay. The information provided on this assay is considered acceptable.

The analytical methods have been shown to be suitably validated in accordance with ICH Q2(R1).

Batch analysis

In total, twenty batches have been manufactured during development. This includes one toxicology batch, one Phase 1 batch, one Phase 3 batch, one engineering batch, eight Phase 3 baches, two batches used for reference material, and six PPQ batches. All results from these batches are within specification and show consistency from batch to batch.

Reference standards

Primary reference standards are in use, rather than a primary and secondary reference standard. The approach has been appropriately justified. Stability data at -80 °C are presented for both lots, respectively at 48 months and 24 months. The data meet the specifications.

A protocol for qualification of the next reference standard is provided. Both release and characterisation methods are utilised during qualification. The statistical approach for assigning potency to new reference standards is described and controls are in place to avoid reference standard drift over time.

2.3.3.4. Stability of the product

The proposed shelf life is 24 months at -20±5 °C. To support the claimed shelf life, stability data is presented for nine finished product lots. These include the six PPQ lots and three reference standard batches. Up to 24 months stability data are currently available for the primary stability batches. The finished product batches were stored at -80 ± 10 °C, -20±5 °C (long-term storage), and at 5 ± 3 °C (accelerated storage condition). The batches were tested for quality, identity, potency, strength, and sterility. The stability data provided so far indicate that the finished product is stable for up to 24 months and no significant trends were noted in any of the assays.

The stability data at 2-8 °C support the statement in Section 6.4 of the SmPC that the carton can be refrigerated at 2 to 8 °C for up to 1 month.

In the SmPC, the instructions for use describe how the Vyjuvek suspension is mixed with the gel, then 0.5 ml of the mixed Vyjuvek gel is withdrawn using an administration syringe. In-use stability studies were carried out at room temperature to examine the impact on potency when the finished product is combined with the gel.

In use data have been provided to support storing the finished product - gel mix for up to 168 hours at 2-8 °C. The proposed 7 day in-use storage period is not considered appropriate from a microbial contamination perspective and therefore further wording has been added to the SmPC to clarify that the product should be used immediately.

The shelf life of the finished product is 2 years when stored in the freezer. After thawing, if a freezer is not available, the carton(s) may be stored in a refrigerator (2°C to 8°C) for up to 1 month. Once stored in the refrigerator, the medicinal product should not be re-frozen. After mixing, chemical and physical in-use stability has been demonstrated for 168 hours (7 days) at 2-8°C. Syringes can be stored at room temperature for up to 8 hours.

2.3.3.5. Adventitious agents

Control of mycoplasma, bacteria and fungi is through testing of raw materials and control of the manufacturing process. All in-house prepared solutions are sterile filtered (0.2µm) prior to use in the KB103 manufacturing process and filters are integrity tested post-use. Each KB103 batch is tested for sterility, endotoxin and replication-competent virus, mycoplasma, and *in vitro* adventitious agent testing are carried out at the bulk harvest. The KB103 manufacturing process is performed aseptically through the use of closed sterile single-use pathways with aseptic connections. Aseptic processing is employed downstream of the sterile filtration unit process immediately after clarification and upstream of the TFF and filling processes. Aseptic process simulations for the active substance process support the aseptic manufacturing.

Material of biological origin are identified, and clarification is provided on the source of the used material in the generation of the starting materials and the routine manufacturing. A sample CoA is provided in the dossier and is considered sufficient. Many different batches used for the manufacture of the MCBs and WCBs, the MVB and WVBs or the finished products are mentioned. The batch number, the manufacturer, and the use in the manufacturing process (cell banks, virus banks or finished products manufacture) of each batch has been provided in a tabular format and supporting documentation for the batches is provided.

TSE statements of compliance are provided in 3.2.R of the dossier for single use product contact materials and are acceptable. A certificate of analysis and a TSE/BSE certificate has been provided.

A summary of the testing carried out on the MCB, WCB, MVB, and WVB is provided. In addition, testing of the limit of in vitro cell age (LIVCA) cells is summarised. Testing of the cell and viral banks is considered to be in accordance with ICH Q5A. A risk assessment was performed to determine the suitability of the adventitious agent testing strategy for the cell and viral banks, and the LIVCA cells. The conclusions that the testing strategy is sufficient is supported. Viral clearance studies were not performed since KB103 is a gene therapy product derived from HSV-1 and this is acceptable.

Overall, the adventitious agents are considered to be adequately addressed with regards to TSE and viral safety.

2.3.3.6. GMO

Based on the environmental risk assessment (ERA) provided and following consultation with the relevant GMO competent authorities, it can be agreed that the environmental risk associated with beremagene geperpavec can be considered negligible.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Vyjuvek (beremagene geperpavec, also known as KB103) is a replication-incompetent, non-integrating HSV-1-based vector engineered to express full-length, functional human collagen VII (COL7). The KB103 active substance manufacturing process consists of working cell bank (WCB) thawing, cell expansion, virus infection and production, bulk harvest, and purification. The downstream purification process consists of clarification filtration (0.45 µm), endonuclease treatment, sterile filtration (0.2 µm), 2 tangential-flow filtration (UF/DF) steps and final filtration (0.45 µm) chased with 10% glycerol DPBS until target active substance volume is reached. The sterilisation filtration process step is upstream of purification and the proposed microbial control strategy is considered acceptable. The applicant has committed to introduce in-process endotoxin testing and this is included as a recommendation. Risk mitigation includes routine aseptic process simulations and qualification of operators. The proposed approach and the result of the APS runs support the aseptic processing downstream of the sterile filter. The active substance and finished product processes were validated in conjunction as the finished product is a singe vial filling operation that follows active substance manufacturing in the same facility (Krystal Biotech, Inc., USA). Overall, based on the information provided it is considered that the process is under control.

The generation of the MCB, WCB, MVB and WVB are adequately described. The qualitative components of each media used in routine manufacturing are registered. The applicant initially provided a high-level description in characterisation of the active substance. Additional information has been provided and is considered sufficient. The applicant has addressed the capacity and consistency in clearance of the identified process- and product-related impurities from the active substance manufacturing process in S.3.2 with relevant data from historical batches. The applicant has concluded that the impurity levels in purified KB103 active substance do not present a patient safety risk, and this statement is supported. The active substance container closures system is adequately described.

Vyjuvek finished product is a sterile suspension, preservative free, supplied in single dose vials at a concentration of 5×10^9 plaque-forming units (PFU) per mL. The finished product is mixed with a hydroxypropyl methylcellulose (HPMC) excipient gel prior to use. The finished product manufacturing process is essentially part of a continuous process from the end of active substance manufacture.

The information provided on the formulation development is considered brief but sufficient to support the chosen formulation. Changes to the finished product manufacturing process during development have been minor. There were several changes in the excipient gel used during clinical development, and this was supported by appropriate data.

The applicant has requested a temporary exemption from release testing in the EU. Based on the arguments out forward by the applicant and the plan for a staged implementation of EU release testing, the proposal is considered acceptable.

During the procedure a major objection was raised on manufacturer of the finished product for which a GMP certificate was not provided. Following submission of the GMP certificate, the major objection was resolved.

The finished product manufacturing process involves filling of active substance into vials, sealing, capping, visual inspection and storage at -80 ˚C. The control strategy is acceptable.

The commercial finished product manufacturing process has been validated based on successful completion of three process performance qualification batches. Batch data has been provided for twenty batches.

The panel of release tests and acceptance criteria is acceptable. A major objection was raised on the provided nitrosamines risk assessment, and the major objection was resolved following the provision of requested data.

The container closure uses standard materials and complies with the Ph. Eur.

The finished product has been shown to be stable for up to 24 months and the proposed shelf life is agreed.

Overall, the adventitious agents are considered to be adequately addressed with regards to TSE and viral safety and queries raised on the use and source of the FBS have been adequately addressed.

In conclusion, Vyjuvek is considered approvable from a quality perspective. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

The CHMP endorses the CAT assessment regarding the conclusions on the chemical, pharmaceutical and biological aspects as described above.

2.3.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CAT recommends the following points for investigation:

The CHMP endorses the CAT assessment regarding the recommendations for future quality development .

2.4. Non-clinical aspects

2.4.1. Introduction

Beremagene geperpavec is a gene therapy developed for the treatment of wounds in patients with DEB. The most relevant initial readout for a gene therapy attempting to treat DEB is COL7 expression, deposition in the

basement membrane zone (BMZ), and anchoring fibril (AF) formation. The key objective in the design of the non-clinical programme was to demonstrate that the vector could efficiently transduce clinically relevant skin cells and secrete COL7 and deposit it along the BMZ in immunocompetent animals, including a DEB disease animal model. With this overarching objective, the rationale of primary pharmacology studies was to address the following specific goals:
1. Evaluate the transduction efficiency of beremagene geperpavec and functionality of its encoded human COL7 *in vitro* in clinically relevant primary RDEB skin cells.

2. Determine whether beremagene geperpavec could be applied to RDEB skin, or a relevant surrogate, *in vivo* to achieve COL7 expression at the dermal-epidermal junction using both topical and intradermal routes of delivery.

3. Assess the ability of beremagene geperpavec to establish ultrastructural changes (AF formation) in the skin of a disease animal model (COL7 hypomorphic mice) that are suggestive of drug efficacy.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

In the initial *in vitro* experiments, the ability of the KB103 to express COL7 protein was assessed in fibroblasts and keratinocytes derived from skin biopsies of patients with RDEB or controls. The control cells were derived from a different anatomical site (breast) to that of the RDEB patients (axilla), however, any theoretical differences in COL7 between these sites are unlikely to be of concern. Immunofluorescence staining results suggested that KB103 increased expression of COL7 in the fibroblasts and keratinocytes derived from RDEB patients. Western blot analysis of samples similarly indicated that KB103 resulted in expression of full length COL7 in fibroblasts and keratinocytes from RDEB patients with no appreciable COL7 expression detected in samples not transduced with KB103. In fibroblasts and keratinocytes derived from control patients (without known *COL7A1* mutations) expression of COL7 was evident in non-transduced cells, however, levels increased after transduction with KB103. Quantitative PCR (qPCR) was also used to measure the expression of *COL7A1* mRNA after KB103 transduction and suggested an increase in mRNA levels with increasing MOI in the patient samples. No qPCR data is presented for the normal control fibroblasts and keratinocytes transduced with KB103, although the qPCR data for the RDEB patients was normalised to levels in normal control fibroblasts and keratinocytes. Expression of the *COL7A1* mRNA was detected in untransduced fibroblasts and keratinocytes derived from RDEB patients, albeit at lower levels compared to normal control fibroblasts and keratinocytes. This is likely due to the inability of the PCR primers used to differentiate between normal and mutated *COL7A1* mRNA. With increasing MOI, there was increased *COL7A1* mRNA detected.

Downstream of COL7 expression, several markers assessing the functionality of the expressed COL7 were examined. Expression of Thromospondin-1 (*TSP-1)* was decreased and lysyl hydroxylase 3 (*LH3*) increased by KB103. This correlated with increased adhesion of KB103 transduced cells RDEB keratinocytes to fibronectin and Collagen 1 coated plates in a plate adhesion assay. Taken together, these results suggest that the expressed COL7 protein was functional, as further corroborated in a 3D organotypic culture model where KB103 transduced cultures displayed COL7 expression in the BMZ.

These *in vitro* data suggest that KB103 can increase the expression of COL7 protein in both keratinocytes and fibroblasts derived from patients with DREB and control patients. The expressed COL7 is seen to increase the ability of keratinocytes from RDEB patients to functionally interact with fibronectin and Collagen-1.

The initial *in vivo* study was performed with a single administration in BALBc mice *via* intradermal injection at 2 dose levels or using topical application in a gel formulation to a surgical wound or abraded skin. The results suggest that the expression and retention of *COL7A1* transcript in the skin is similar following either intradermal injection or topical dermal application to a wound. The differences in detected levels of *COL7A1* DNA and transcript levels between Day 3 and Day 6 support the assertion that KB103 persistence is short-lived. Although immunofluorescence staining for COL7 was performed, the results are not easy to interpret because the staining antibody does not differentiate between the endogenous mouse COL7 and the exogenously KB103 expressed human COL7. Of note, with intradermal injections COL7 was detected in deeper layers of the skin which may have been a result of the injection being subcutaneous rather than intradermal.

An *in vivo* study was also performed in a mouse model of DEB, which expresses COL7 at ~10% of normal levels and has a phenotype displaying aspects seen in humans. An intradermal injection to the back of the mice was given, with each mouse receiving one control injection (PBS or HSV-GFP) and three sites injected with KB103 at 4.6 x 10^7 pfu/50 µl/injection site on Day 1. One of the mice received a second dose of KB103 on Day 3. The mice were sacrificed on either Day 3 or 7 and the injection sites biopsied and processed for qPCR analysis and microscopy. Although the animal numbers utilised are low, the qPCR data suggested that the levels of *COL7A1* DNA and transcripts were very similar across the KB103 administered sites in each animal. Measured levels on Day 7 were lower than on Day 3 signifying short-lived persistence. Electron microscopy was also performed on sections from KB103 transduced animals and showed that AF were formed. A similarly designed experiment was performed in *COL7A1* heterozygous mice, but animals received either a low dose 4.6 x 10^6 pfu/50 µl/injection site or high dose 4.6 x 10^7 pfu/50 µl/injection site. Measured *COL7A1* transcript levels showed some dose dependence. Overall, the study data suggest that KB103 can transduce dermal cells and increase expression of COL7 protein, which is able to form fibrils anchoring epidermis and dermis layers.

In addition to the two main proof of concept *in vivo* studies, four additional studies on changes in production processes or excipient formulations were provided. Study KB103-IVV-010 investigated potential differences when production was changed from a flatware-based upstream process to a scalable adherent cell bioreactor. BALBc mouse received intradermal injections with batches produced *via* either process, with the expression of *COL7A1* transcripts as well as immunofluorescence staining investigated. The applicant suggested that KB103 transduction efficacy is similar with batches from both methods and no significant differences were seen. The three other studies investigated different excipient gel formulations with varying levels of HPMC with and without additional surfactants or a formulation with PluroGel. In summary, the changes in the excipients investigated did not significantly alter the efficacy of KB103 in the mouse skin samples after dermal application.

2.4.2.2. Secondary pharmacodynamic studies

The absence of studies on secondary pharmacodynamics is acceptable considering the type of product, as was concluded by the CAT and CHMP.

2.4.2.3. Safety pharmacology programme

No standalone safety pharmacology studies were performed. This is acceptable to the CAT and CHMP considering that the drug product is locally administered and is a gene therapy product with a limited distribution outside the site of application.

2.4.2.4. Pharmacodynamic drug interactions

No drug interaction studies were performed, which is acceptable from a nonclinical perspective.

2.4.1. Pharmacokinetics

As Vyjuvek is a gene therapy medicinal product, traditional studies on absorption, distribution, metabolism and excretion have not been performed. Biodistribution following administration *via* the dermal route to a wound, and following repeated intra-dermal injection, has been assessed in mice as part of the GLP toxicity studies; and the findings are discussed in the toxicology section (see below). Collected samples were analysed for KB103 by qPCR using a validated method fit for purpose with appropriate sensitivity and precision.

2.4.2. Toxicology

2.4.2.1. Single dose toxicity

Two single dose studies with KB103 were completed using different routes of administration: intravenous (IV) injection and dermal application.

Study details	**No:Sex/ Group**	**Dose**	**Major (alt. Salient) findings**
BALB/cAnNCrl mice; single dose with 28 days recovery; IV injection; GLP/Study ID KB103-GLP-001/ 8378961	6 M/F *per* group	Vehicle; or 3.45 X 10^7 pfu/day	No KB103-related mortality or clinical observations. Lower body weight gain in KB103 group in period interval from Day 1 to 8 without correlative changes in food consumption. Clin chem: higher globulin and total protein concentrations; higher glucose conc. in single male. Organ weights: increased spleen (both sexes), and liver weight (females); decreased testis weights. Histopathology: Minimal to slight lymphocyte hyperplasia in spleen and lymph nodes ((axillary and/or inguinal); minimal extramedullary haematopoiesis in the liver
Study details	**No:Sex/ Group**	**Dose**	**Major (alt. Salient) findings**
BALB/cAnNCrl mice; single dose with 2 or 34 days recovery; Topical application to skin wound;	12 F *per* group	Control or 3.48x10^7 pfu	No KB103-related mortality, clinical observations, effects on body weight or body weight gain. Haematology: Mildly to moderately higher total white blood cell count and absolute neutrophil, lymphocyte, and large unstained cell counts on Day 3. Due to errors no haemotology testing could be performed on Day 35 samples. Clin chem: minimally higher blood glucose concentration on Day 3 and 35 in KB103 dosed animals. Organ weights: Lower thymus weight in KB103 dosed animals on Day 3.

GLP/Study ID KB103-GLP-003/ 8420430			Histopathology: Limited to the treated skin site, were considered consistent with the surgically created wound, and were, therefore, considered not KB103 related. Biodistribution: vector DNA was detected in all KB103-treated skin dose sites, with concentrations between 2.36 $x10^6$ and 1.54 $x10^7$ copies/µg DNA. No vector DNA was detected in blood from KB103 treated animals at Day 3 or Day 35. On Day 3 the majority of organs tested were negative with the exception of an animal which had bone marrow levels of 9.36$x10^2$ copes/µg DNA and another 2 sample from other animals had detectable levels but below the LLOQ.

Whilst the route of administration in the IV study in mice differs from the clinical administration route, it can be seen as a potential worst-case scenario, should all the administered topical dose be absorbed and released into the circulation. No mortality or AEs were seen; only an initial decrease in body weight gain, which reversed by Day 30. Pathology findings of higher serum protein as well as the microscopic findings of minimal to slight lymphocyte follicular hyperplasia in the spleen and minimal to slight lymphocyte hyperplasia in the axillary and/or inguinal lymph nodes were consistent with an inflammatory response to KB103.

The second study was a GLP compliant, single dose dermal application study with a combined biodistribution analysis in mice. It was performed exclusively in females and utilised a full thickness wound with the gel applied to the wound bed and included an interim analysis after Day 3 with the remainder of the animals sacrificed on Day 35. The dose was formulated in an excipient gel containing 3% Methylcellulose with control animals just receiving the excipient gel. Whilst the dose and formulation differ from the final clinical formulation, the efficiency of KB103 delivery into cutaneous wounds of healthy animals was determined to be functionally equivalent when the vector was formulated in either 3% or 4% Methylcellulose. No KB103 related mortality, clinical observations, changes in body weight or food consumption were seen. A single animal in the treated group was euthanised in a moribund condition, with the cause of death being abdominal perforation, unrelated to KB103. There was limited evidence of systemic effects, with only limited pathology changes suggestive of an inflammatory response to KB103 (minimally higher blood glucose concentrations and mildly to moderately higher total white blood cell counts and absolute neutrophil, lymphocyte, and large unstained cell counts).

Biodistribution was assessed by qPCR for blood and a limited number of organs (site of administration, bone marrow, brain, heart, kidney, liver, lung, ovary, axillary and inguinal lymph nodes). Although the tissues are not fully in-line with those suggested in the relevant ICH S12 guideline, this is acceptable considering the route of administration. In blood samples of the treated animals, no KB103 was detected at Day 3 or 35. In the tissues analysed from the Day 3 interim sacrificed animals, KB103 vector DNA was detected at the skin dose site in all KB103 treated animals. In addition, two control animals had detectable levels of KB103 vector DNA; this was attributed to cross-contamination as they were shipped to the test site in the same box as the KB103 dosed samples. Outside of the site of treatment, there was limited evidence of biodistribution with a single animal positive for KB103 vector DNA in the bone marrow, and 2 additional animals with KB103 vector DNA detected in the kidney or inguinal lymph nodes but at levels below the LLOQ.

Persistence of KB103 at the site of application following topical administration is unclear, as only samples from the interim analysis were investigated and none from the terminal sacrifice. However, the results of the

repeat dose intradermal injection study, in which the mice received 5 weekly injections, suggested very little persistence at the injection site 30 days after the last injection. Persistence at Day 35 following a single topical administration of Day 1 appears unlikely.

2.4.2.2. Repeat dose toxicity

Study details	**No:Sex/ Group**	**Dose**	**Major findings & NOAEL**
BALB/cAnNCrl mice; Once weekly for up to 5 doses (Day 1, 8, 15, 22 and 29) Interim analysis on Day 4; Necropsy on Day 30; recovery group at Day 30 post dose completion Intradermal injection GLP Study ID KB103-GLP-002/8373246	18 M/F	Vehicle, $6.9x10^6$ pfu or $3.45x10^7$ pfu	No KB103-related effects were noted on mortality, food consumption, or body weight. Clinical observations of KB103 related dose site scabbing which was generally resolved at the end of recovery. Clin pathology: Day 30 of the dosing phase, KB103-related haematology differences included mildly higher total leukocyte, absolute neutrophil, and absolute lymphocyte counts in females administered 3.45 x 107 pfu. Evidence of partial reversibility on Day 30 of the recovery phase. Clin chem: On Day 30 of the dosing phase minimally higher globulin concentration and minimally lower albumin:globulin ratio in males administered 3.45×10^7 pfu/day and females administered $\geq 6.9 \times 10^6$ pfu/day. Evidence of partial reversibility on Day 30 of the recovery phase. Organ weights: KB103-related increased spleen weight parameters were noted at the interim, terminal, and recovery necropsies. Macroscopic observations: KB103-related macroscopic finding of scab was noted at the intradermal dose site of one male and two females administered 3.45×10^7 pfu/day. Microscopic observations: KB103-related mixed cell inflammation, haemorrhage, erosion/ulcer, and/or epidermal hyperplasia were noted at the intradermal dose site of animals administered $\geq 6.9 \times 10^6$ pfu/day at interim and terminal necropsies. Biodistribution: From interim or terminal necropsy intervals all samples from animals administered $\geq 6.9 \times 10^6$ pfu/day were positive at the injection site. Positive in blood from 2 animals administered $6.9x10^6$ pfu and 5 animals at $3.45x10^7$ pfu. Positive tissue samples were identified across a number of animals administered $\geq 6.9 \times 10^6$ pfu/day, mainly in the axillary and inguinal lymph nodes, with occasional positive samples in

			the spleen and brain, one positive sample in the bone marrow, and one positive sample in the testis. From the recovery phase necropsy, KB103 positive samples were found in two injection site samples, lymph nodes of one animal administered, and kidney of one animal. **NOAEL = 6.9 x 10^6 pfu**

A GLP compliant repeat dose study using intradermal injection was completed where mice received up to 5 weekly doses. An interim sacrifice group was included, with animals sacrificed on Day 4. The remaining animals were sacrificed on Day 30 or allowed to recover for an additional 30 days following completion of dosing. Where possible, the same intradermal injection site was utilised for all injections. No KB103 related mortality or clinical events were seen. Changes in haematological parameters, minimally higher globulin concentration and minimally lower albumin:globulin ratio were seen. Increases in spleen weight were noted. At the site of injection, scabbing, microscopic findings of mixed cell inflammation, haemorrhage, erosion/ulcer, and/or epidermal hyperplasia occurred. These effects are likely to be a result of an inflammatory response to KB 103 and the expressed COL7. In general, the findings at least partially reversed in the recovery group. The low dose of 6.9 x 10^6 pfu was considered as the NOAEL.

Biodistribution of the vector was assessed using qPCR. At the site of injection, all KB103 dosed animals were positive with measured values between 10^4 and 10^9 copies/µg of DNA. In the recovery group, only 2/23 KB103 dosed animals were positive at the site of injection suggesting a limited persistence. Levels measured on Day 4 and Day 30 were largely comparable, suggesting no accumulation. Blood samples from 2 of the low dose group and 5 of the high dose group were positive at Day 4 or 30, but none in the recovery group. Outside of the site of injection and blood, other sites where KB103 vector DNA was detected was mainly in the lymph nodes and spleen with 2 samples positive in the kidney, brain and a single sample in the testis.

2.4.2.3. Genotoxicity

No traditional genotoxicity studies were performed. The applicant stated that since HSV-1 does not integrate and hence, the risk of insertional mutagenesis is negligible.

2.4.2.4. Carcinogenicity

No carcinogenicity studies were performed, and the applicant provided a weight of evidence risk assessment, based on a literature search up to July 2024. This did not identify any association or risk factor identification for HSV-1 infection and cancer.

In-line with the CHMP's "Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014)" the absence of standard rodent carcinogenicity studies is acceptable. The risk of insertional mutagenesis is considered low and the expressed COL7 protein is not expected to provide a proliferative advantage to cells. Whilst epithelial hyperplasia was seen in the intradermal toxicity studies in mice, this is not considered to be a preneoplastic change but rather a local inflammatory reaction to the injection. Lymphocyte hyperplasia was also seen in the single dose IV study which was also likely an immune/inflammatory related reaction. The product is applied locally with limited apparent distribution outside the site of application when used dermally. The patient population has already a predisposition for skin cancers and hence, will be frequently monitored for such risks.

2.4.2.5. Reproductive and developmental toxicity

No specific studies were performed. Taking into consideration the topical route of administration with limited evidence of systemic exposure *via* this route, this is acceptable. With the exception of minimally decreased testis weight (without histological correlates) when KB103 was administered *via* the IV route, there were no significant effects on reproductive organs in the non-clinical toxicity studies. Biodistribution was assessed following a single dose dermal application or repeat dose intradermal injection. A positive signal for KB103 was detected in the testes of a single animal in the intradermal studies. The dermal application study was only performed in females, however, there was no vector detected in the ovaries in the animals in that study. Considering that HSV-1 is seen as a non-integrating vector, the fact that the presence of KB103 was only detected in 1/17 KB103 dosed samples at a low copy number of 4.95×10^2 copies/µg, and *via* the intradermal route which differs from that used clinically, the absence of further investigation appears appropriate.

2.4.2.6. Toxicokinetic data

Not applicable.

2.4.2.7. Local tolerance

Local tolerance was assessed as part of the overall toxicity studies.

2.4.2.8. Other toxicity studies

Not applicable.

2.4.3. Ecotoxicity/environmental risk assessment

Based on the submitted ERA, Vyjuvek is proposed to be used under controlled conditions. HSV-1 is a well characterised virus and is a suitable source of vectors for gene therapies. Beremagene geperpavec is engineered so that it cannot replicate, nor integrate into the genome of host cells. It is expected to survive in the infected cell until natural cell death and no adverse effects on the environment from the use of this medical treatment are foreseen. Hence, it is agreed that the environmental risk associated with beremagene geperpavec can be considered negligible.

2.4.4. Discussion on the non-clinical aspects

Pharmacology: As well as the conducted *in vitro* and i*n vivo* proof of concept studies, there is a clear scientific rationale suggesting that a gene therapy delivering a functional COL7 protein to the skin of DEB patients could provide benefit for their wound healing. This is supported by *in vitro* data, based on both 2-D and 3-D cell-based assays, which suggests that KB103 can increase the expression of COL7 protein in both keratinocytes and fibroblasts from patients with RDEB, without toxicity. The expressed COL7 increased the ability of keratinocytes from RDEB patients to functionally interact with fibronectin and Collagen-1. Similarly, the *in vivo* studies in wild-type BALB/c mice and the hypomorphic DEB mouse model provided evidence that KB103 can transduce dermal cells and increase expression of COL7 protein, which is able to form anchoring fibrils. These can fix the epidermis and dermis layers with comparable levels of COL7 expression after topical

vs intradermal administration. Although the study in the hypomorphic DEB mouse model has some limitations in that the administration route differs from the clinical route and that effects on the relevant disease parameters for the proposed indication were not assessed, it does provide sufficient evidence for the underlying mechanism of action of the therapy (delivery of functional COL7).

Pharmacokinetics: Traditional PK studies are not warranted for a topically applied gene therapy product. Biodistribution studies were performed as part of the toxicology programme (single dose topical application to the dorsal skin of female mice; repeated ID injection of a low (6.9×10^6 PFU/day) or a high dose (3.45×10^7 PFU/day) into intact dorsal mice skin). The results confirm a transient transfer of the HSV1 KB103 vector in animals. After 30 days of recovery, positive samples were still found in lymph node and kidney in some animals. The clinical route of administration is topical (injured skin); hence, systemic distribution cannot be excluded. No non-clinical studies investigating excretion of KB103 were conducted, and vector shedding was studied in the clinical setting.

Toxicology: Considering the nature of the product and the toxicities seen, the use of a single species (mice) for the toxicity studies is considered acceptable and in line with the "Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014)". A justification for the choice of mice is not specified, other than the suggestion that this species is historically used in toxicity studies. Given that the skin of mice is dissimilar to that of humans in terms of skin structure, studies in minipigs may have been preferable; however, considering that a wound model was used for the dermal toxicity studies, this choice is acceptable.

In general, KB103 was well tolerated, irrespective of the route of administration, with only systemic effects linked to inflammation/immune responses, likely related to the vector and/or expressed human transgene, which is foreign in mice. KB103 ID injection provoked mixed cell inflammation, haemorrhage, and/or epidermal hyperplasia at the intradermal dose site and follicular hyperplasia in the spleen and/or lymph nodes. Although the duration of studies appears limited, considering the treatment duration for patients, it is acknowledged that the nature of the product (gene therapy expressing a foreign protein) would limit the conduct of longer non-clinical studies. Furthermore, when considered in the context of the limited toxicities observed, it can be agreed that further studies of longer duration are not warranted. While the clinical data do not suggest a potential impact of immunisation against the HSV-1 vector and/or transgene on the efficacy of KB103 (notably similar response regardless of the HSV-1 sero status in patients were observed), the impact of re-administrations on efficacy was initially unclear. Hence, the applicant was asked to discuss the risk of possible compromise of efficacy over time, and the risk of cross reactivity of the COL-7A1 ADA with host proteins or other types of collagens. In response, it was indicated that efficacy was not altered in patients having received up to 2.2 years of KB103 administration as part of an open label extension study. Of note, active monitoring for anti-COL7 antibodies was not performed in this study, in order to minimise the discomfort of patients with DEB owing to their inherent skin fragility and difficulty to draw blood. Furthermore, the applicant explained that neutralising autoantibodies raised against COL7 were found in epidermolysis bullosa acquisita (EBA) patients and sera from these patients do not appear to interact with host proteins in human skin samples outside of the dermal-epidermal junction.

The currently proposed patient population includes paediatric patients from birth. The age of the mice used in the intradermal injection and dermal toxicity studies was around 6 to 7 weeks of age, approximately reflective of an adolescent population. However, considering the toxicities noted and the developmental stage of the skin at birth, no juvenile animal studies are considered necessary, as agreed at the time of the PIP.

The biodistribution studies *via* dermal route did not identify significant distribution outside the site of administration. Whilst biodistribution was not measured in the IV study, the intradermal injection study

measured some limited levels of KB103 in blood samples, lymph nodes, spleen, kidney, brain and a single sample in the testis. The applicant suggested that the risk of dissemination throughout the body *via* circulation, and particularly, delivery to the brain across the blood brain barrier, is low due to the topical application and the absence of measurable KB103 in clinical blood samples. Furthermore, it was stated that the potential of retrograde transport from infected peripheral neurons to the CNS is eliminated due to genetic engineering strategy employed during KB103 construction. The intradermal injection likely increases the potential for biodistribution compared to the topical dermal application. Importantly, there was no evidence of accumulation with repeated administration. With the removal of the ICP4 genes found in wild type HSV-1, KB103 has been rendered replication incompetent. No new toxicities were noted in animals from the interim sacrifice and those who received all 5 doses.

As agreed in the scientific advice (see section 1.6), no dedicated studies on developmental and reproductive toxicity (DART) were performed. Considering the local administration, effects on reproductive parameters are not expected. KB103 vector was detected in the testis of only a single animal, in the high dose group, in the intradermal injection study. No biodistribution to the gonads was seen in the dermal toxicity study, however, only female mice were used in this study. One patient urine sample (1/31 patients) collected in the clinical trial was positive for the vector, but the applicant argued that this positive signal in testis is not persistent, as the observation occurred on a single occasion, one day after the fifth intradermal injection of KB103. This is in-line with the "Guideline on non-clinical testing for inadvertent germline transmission of gene transfer vectors (EMEA/273974/2005)", which requires three consecutive positive timepoints to be considered as persistent. As the vector backbone is claimed to be non-integrating and non-replicating, it is accepted that the risk for potential germline transmission is negligible and additional DART studies are not required.

Furthermore, a literature search performed on a potential HSV-1 integration revealed that the natural infection of HSV-1 is associated with a lack of genomic integration and supported the assumption of negligible risk for HSV-1 integration. The absence of traditional rodent carcinogenicity studies or other related studies is therefore considered acceptable. The weight of evidence for the risk of carcinogenesis provided by the applicant did not find any association or risk factor for HSV-1 infection and cancer.

Relevant information on non-clinical findings was reflected in section 5.3 of the SmPC.

Environmental risk assessment: Based on the provided ERA and the results/comments from the consultation with the relevant GMO competent authorities, it can be agreed that the environmental risk associated with beremagene geperpavec can be considered negligible. No further updates to the ERA are required.

The CHMP endorse the CAT discussion on the non-clinical aspects as described above.

2.4.5. Conclusion on the non-clinical aspects

The non-clinical programme designed to support the MAA of Vyjuvek in the treatment of patients from birth with dystrophic epidermolysis bullosa with mutation(s) in the collagen type VII alpha 1 chain (*COL7A1*) gene is sufficient to support the MA granting.

The CHMP endorse the CAT discussion on the non-clinical aspects as described above.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study Number	Study Type	Study Objectives	Study Design	Key Inclusion Criteria	Sample Size Gender Age (Years)	Treatment	Study Status	Study Report Location
KB103-001	Phase 1/2 safety/efficacy, controlled	To evaluate safety, demonstrate molecular correction of the disease, and assess proportion of wounds with complete wound closure	Single-center, open-label, intrasubject randomized, placebo-controlled	≥2 years of age; diagnosis of RDEB confirmed by genetic testing, IF, IEM, and confirmed *COL7A1* mutations; wounds Phase 1: ≤10 cm^2; Phase 2a and 2b: ≤20 cm^2; and Phase 2c: ≤50 cm^2	12 subjects[a] 9 M/3 F 10 to 35 years (mean 20.3)	Topical treatment with B-VEC or placebo (vehicle) gel Unit dose varied by study phase, ranging from 1×10^8 to 6×10^8 PFU per ≤20 cm^2 wound area	Complete	Module 5.3.5.1
B-VEC-03 (GEM-3)	Phase 3 safety/efficacy, controlled	To determine whether administration of B-VEC in addition to standard of care improved wound healing as compared to placebo in children, adolescents, and adults with DEB	Multicenter, double-blind, intrasubject randomized, placebo-controlled	≥6 months of age; diagnosis of DDEB or RDEB confirmed by genetic testing including *COL7A1*; 2 cutaneous wounds similar in location and appearance	31 subjects[b] 20 M/11 F 1 to 44 years (mean 17.2), including 19 subjects ≤ 18 years	Topical treatment with B-VEC or placebo (vehicle) gel Dose/wound varied by wound area: 4×10^8 PFU for <20 cm^2 8×10^8 PFU for 20 to 40 cm^2 1.2×10^9 PFU for 40 to 60 cm^2 Maximum weekly dose varied by age: 1.6×10^9 PFU for ≥6 mos to <3 yrs 2.4×10^9 PFU for ≥3 yrs to <6 yrs 3.2×10^9 PFU for ≥6 yrs Treatment duration: once weekly for 26 weeks	Complete	Module 5.3.5.1
B-VEC-EX-02	Open-label extension, uncontrolled, safety	To provide continued access to B-VEC for subjects who completed B-VEC-03, to provide the use of B-VEC to DEB-diagnosed subjects who did not participate in B-VEC-03, and to record safety outcomes of subjects while on B-VEC	Multicenter, open-label treatment extension for subjects who completed B-VEC-03 and treatment naive subjects with DEB	From birth; diagnosis of DDEB or RDEB confirmed by genetic testing including *COL7A1*	47 subjects enrolled (24 rollover, 23 naive) 0.5-45.9 years (mean 16.5), including 26 subjects <18 years	Topical treatment with B-VEC gel Maximum weekly dose per subject = 10^9 PFU/mL Subjects <3 yrs received half the volume of subjects ≥3 yrs Treatment duration: Up to 112 weeks	Complete	Module 5.3.5.2

DEB=dystrophic epidermolysis bullosa; DDEB=dominant DEB; F=female; IEM=immunoelectron microscopy; IF=immunofluorescence; M=male; PFU= plaque forming units; RDEB=recessive DEB; yrs=years.
a: Includes 3 subjects who were re-enrolled in a later phase for treatment of different wounds after approximately a 3-month washout.
b: Includes 5 subjects who were treated in study KB103-001 for different wounds at least a year prior to study B-VEC-03.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Bioanalytical methods

Neutralising antibody method: The method describes the quantitative assessment of neutralising anti-HS virus type 1 antibodies in serum, harvested pre- and post-KB103 exposure. The aim is to detect serum reduction in KB-103 PFU as a result of neutralising antibodies. The method was suitably validated.

Genome copy number qPCR: The qPCR method was validated in accordance with ICH Q2 and is acceptable.

Anti- human type VII collagen IgG: The method describes the procedure for evaluating IgG anti-drug antibodies targeting human type VII collagen (COL7) *via* enzyme-linked immunosorbent assay (ELISA) using a commercially available CE-IVD Anti-COL7 ELISA, which is a CE-marked IVD used as *per* its intended purpose**.**

Plaque titer assay: This plaque titer assay procedure is used for quantifying the number of infectious viral particles present in skin swabs obtained pre- and post-KB103 administration. The applicant clarified that the method for quantifying infectious KB103 particles is the same as that used for release testing of the drug product and the method validation data was also provided. Specificity, sensitivity, accuracy, precision, and linearity of the method were demonstrated. Upon request, the applicant presented data to show that the bioanalytical method is also valid for skin swab samples, thus, it is considered appropriate.

Absorption

Not applicable

Distribution

Biodistribution was assessed in the phase 1/2 and phase 3 studies by monitoring vector shedding in blood, urine, and skin. Methods for the detection of vector genomes in clinical samples were also provided.

- **Phase 1/2 study**

Blood and urine vector shedding: Blood and urine samples were collected pre-dose and on all scheduled visits as often as feasible (respecting the discomfort to DEB patients). No vector DNA was detected in any sample. To minimise subject discomfort, blood and urine evaluations were removed from phase 2a. In the interest of generating additional safety data regarding vector shedding, evaluation of beremagene geperpavec DNA in blood and urine samples resumed in phase 2b. No vector DNA was detected in any phase 2b sample.

Skin vector shedding: Evaluation of skin swabs from treated sites was incorporated into the protocol following phase 1. In phase 2a, subjects were treated daily for 5 consecutive days, and treated sites were swabbed at each visit during the dosing phase. Low levels of vector copies were detected at the treatment site during the daily dosing phase. At the 30-day return visit, minimal qPCR-detectable vector copies were present at the treatment site compared to during the dosing phase. In phase 2b, subjects were treated every 3 days to correspond with bandage changes. Treated sites were swabbed at each visit. Low levels of vector DNA were detected during dosing phase evaluations but the evaluations at Day 30 and 60 return visits indicated no qPCR-detectable vector copies.

Immunogenicity

Evaluation of antibody response to HSV-1: Serum samples collected pre-dose and at scheduled visits were evaluated for antibodies against HSV-1 using a qualified plaque reduction neutralisation test (PRNT) that determines the percent reduction in beremagene geperpavec-mediated plaque formation in complementing cells in the presence of serially diluted subject sera. It is reported as PRNT50, which is the serum dilution at which a ~50% reduction in plaques is observed. An increase in the PRNT50 value over time is suggestive of an increase in anti-HSV-1 antibodies in the sera. Quantification of anti-HSV-1 antibodies in sera is provided in Figure 5. Among subjects who demonstrated an increase in anti-HSV-1 antibodies from baseline, efficacy was still evident as demonstrated by molecular correction and more rapid/durable closure of beremagene geperpavec-treated wounds as compared to those treated with placebo.

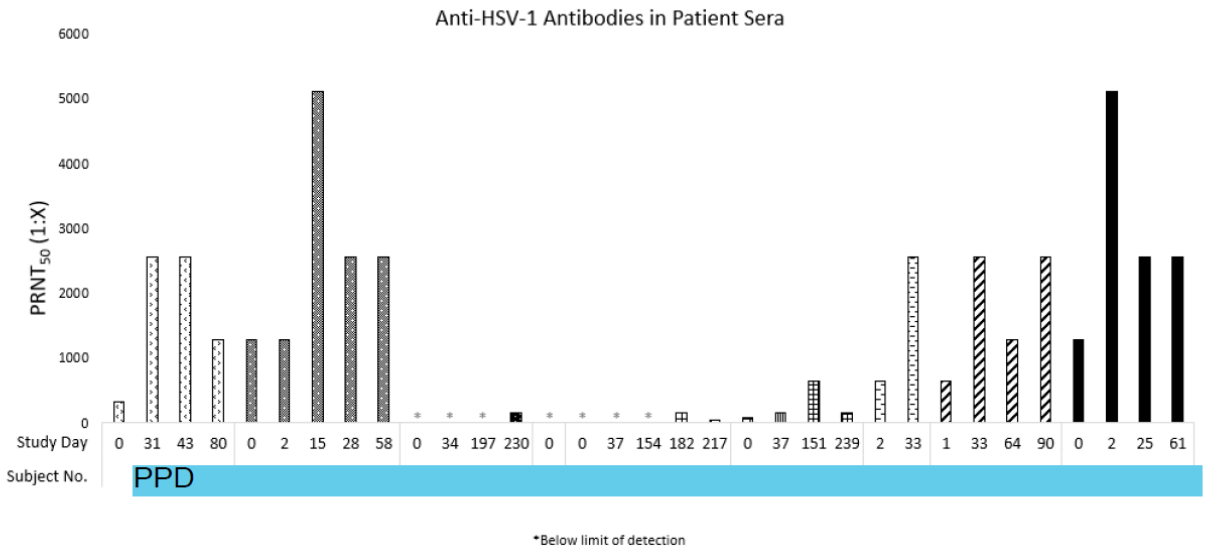


Figure 1 Anti-HSV-1 Antibodies in phase 1/2 Subject Sera

Evaluation of antibody response to COL7: Sera samples collected pre-dose and at scheduled visits were evaluated for IgG anti-drug antibodies targeting COL7 by ELISA, which qualitatively determines the anti-COL7 serostatus of subjects based on a 20 RU/mL threshold. Positivity for anti-COL7 antibodies at baseline was observed for 2 subjects, and 2 other subjects seroconverted post-treatment. In these 4 subjects, efficacy was still evident as demonstrated by and more rapid/durable closure of beremagene geperpavec -treated wounds as compared to those treated with placebo.

- **Phase 3 study**

Evaluation of vector shedding and infectivity: Systemic and environmental exposure assessments (vector shedding) were conducted at weekly clinical site visits, *per* the schedule of events, *via* quantification of beremagene geperpavec genomes in blood, urine, skin swabs, and dressing swabs using a validated qPCR assay, and detection of infectious viral particles in skin swabs using a validated plaque titre assay. All blood samples and all but one urine sample collected throughout the study were below the limit of detection/quantification for all subjects, indicating no significant systemic exposure of the subjects to the vector. Only a very small number of skin swabs (2.42%, 50/2069) contained detectable vector genomes. However, no extracellular infectious particles were detected on the skin surface of any subject at any

timepoint. These data demonstrate that the limited number of vector genomes remaining on the skin surface was non-infectious particles and suggest localised containment and efficient transduction of the cutaneous wounds after topical beremagene geperpavec application. Most wound dressings (67.7%, 483/713) contained detectable vector genomes, although the absolute quantification was variable, ranging from 5.19×10^{2} to 4.16×10^{8} genome copies. Based on the infectivity analysis, it is believed that these dressing-associated genomes are not associated with infectious particles.

Immunogenicity

Evaluation of antibody response to HSV-1: Pre- and post-exposure sera samples were evaluated for anti-HSV-1 specific antibodies using a validated PRNT. Due to the difficulty of blood draws owing to skin fragility, 22 of the 31 subjects (71.0%) were able to provide a serum sample at baseline, and matched serum samples were obtained at the week 26 visit from 19 of these subjects. At baseline, 63.6% of subjects (14/22) were anti-HSV-1 antibody positive, in agreement with seropositivity rates of the general USA population. Six of the 8 seronegative subjects seroconverted by week 26. For baseline seropositive subjects, where quantitative differences at study completion could be calculated, antibody responses varied. A *post hoc* analysis of response rate in primary wound pairs at 6 months among baseline anti-HSV-1 seropositive *vs* seronegative subjects was suggestive of similar efficacy of beremagene geperpavec-mediated durable wound closure, irrespective of antibody status at enrolment, see Table 1.

Table 1 Response Rate, Baseline Anti-HSV-1 Seropositive versus Seronegative Subjects

Immune Status at Baseline	B-VEC Responder	B-VEC Non-Responder	Overall	Difference[a] (95% CI)
Anti-HSV-1 Seropositive				38.6 (5.7, 71.5)
Placebo Responder	3.0 (21.4)	1.1 (7.9)	4.1 (29.3)	
Placebo Non-Responder	6.5 (46.4)	3.4 (24.3)	9.9 (70.7)	
Overall	9.5 (67.9)	4.5 (32.1)		
Anti-HSV-1 Seronegative				41.3 (-8.6, 91.1)
Placebo Responder	0.2 (2.5)	1.1 (13.8)	1.3 (16.3)	
Placebo Non-Responder	4.4 (55.0)	2.3 (28.8)	6.7 (83.8)	
Overall	4.6 (57.5)	3.4 (42.5)		

a The difference was the treatment/discordance difference in percentage of responders, which was the same as the difference in the percentage of treatment responders and the percentage of placebo responders.

Evaluation of Antibody Response to COL7: The same pre- and post-exposure sera samples collected and tested for anti-HSV-1 antibodies were also evaluated by ELISA for IgG ADAs targeting human COL7. One of 22 (4.5%) subjects was determined to be anti-COL7 antibody positive at baseline, and 13 of 18 baseline seronegative subjects with matched week 26 sera samples seroconverted by the end of study. A *post hoc* analysis of response rate in primary wound pairs at 6 months among subjects that did versus did not seroconvert was suggestive of similar efficacy of beremagene geperpavec-mediated durable wound closure in the absence or presence of anti-COL7 antibodies, see Table 2.

Table 2 Response Rate, Anti-COL7 Seropositive versus Seronegative Subject at 6 Months

Immune Status at Baseline	B-VEC Responder	B-VEC Non-Responder	Overall	Difference (95% CI)[a]
Anti-COL7 Seroconversion				40.8 (5.9, 75.6)
Placebo Responder	2.2 (16.9)	1.1 (8.5)	3.3 (25.4)	
Placebo Non-Responder	6.4 (49.2)	3.3 (25.4)	9.7 (74.6)	
Overall	8.6 (66.2)	4.4 (33.8)		
Anti-COL7 No Seroconversion				40.0 (-30.1, 110.1)
Placebo Responder	0.0 (0.0)	1.0 (20.0)	1.0 (20.0)	
Placebo Non-Responder	3.0 (60.0)	1.0 (20.0)	4.0 (80.0)	
Overall	3.0 (60.0)	2.0 (40.0)		

a The difference was the treatment/discordance difference in percentage of responders, which was the same as the difference in the percentage of treatment responders and the percentage of placebo responders.

Elimination

Not applicable.

Dose proportionality and time dependencies

Due to varying wound dimensions, different total doses were administered. Systemic exposure did not correlate with total wound area. Dosing recommendations relate to age, wound size and total weekly exposure to the drug.

Special populations

No dedicated studies were performed in special populations.

Pharmacokinetic interaction studies

There is no data on potential drug interactions with other topical agents. SmPC section 4.5 indicates that concomitant medication should not be administered with Vyjuvek.

Pharmacokinetics using human biomaterials

Not applicable.

2.5.2.2. Pharmacodynamics

Mechanism of action

Beremagene geperpavec is a replication-defective Herpes Simplex Type-1 HSV-1-based gene therapy vector that has been genetically modified to express the human collagen VII protein under the control of the human cytomegalovirus promoter. Hence the mechanism of action is the delivery of functional COL7.

Pharmacodynamics: This was assessed in phase 1/2 study by establishing the presence of functional COL7 expression and the formation of AFs post-administration.

COL7 Analysis by Immunofluorescence: Microscopic detection of COL7's NC1 and NC2 domains, along with observation of linear deposition of both domains at the dermal-epidermal junction, or BMZ, indicates

functional, full-length protein expression. All the subjects' pre-treatment skin biopsies showed presence of NC1 (fluorescence intensity compared to normal human skin %), which is commonly observed in RDEB subjects. All biopsies were NC2 negative at baseline. Following beremagene geperpavec administration, fluorescence intensity was significantly improved; COL7 (NC1 and NC2) expression was clearly detectable; and the was protein correctly localised at the BMZ. Expression of both NC1 and NC2 domains and linear deposition at the BMZ demonstrates production of full-length, functional COL7, see Table 3.

Table 3 IF Microscopy of Subject Biopsies Treated with beremagene geperpavec

Subject	Visit	NC1 IF	NC2 IF
PPD	Baseline	10%	0%
	Week 4	80%	80%
PPD	Baseline	20%	0%
	Week 8	80%	80%
PPD	Baseline	10%	0%
	Week 4	80%	70%
PPD	Baseline[a]	10%	0%
PPD	Baseline	5%	0%
	Week 4	30%	0%
PPD	Baseline	10%	0%
	Week 4	90%	90%
PPD	Baseline	10%	0%
	Week 8	90%	90%
PPD	Baseline	5%	0%
	Week 1	30%	30%
	Week 4	20%	0%
PPD	Baseline	5%	0%
	Week 2	80%	90%
	Week 4	80%	90%
PPD	Baseline	10%	0%
	Week 2	100%	100%
	Week 13	100%	100%
PPD	Baseline[a]	10%	0%
PPD	Baseline[a]	10%	0%

Numbers are expressed as % fluorescence intensity compared to normal human skin
a: Subject PPD dropped out and was unavailable for post treatment skin biopsy, subjects PPD PPD and PPD declined post treatment skin biopsies

Anchoring fibril analysis by immunoelectron microscopy: Detection of mature AFs at the BMZ is indicative of functional COL7 molecular correction. Of the 12 subjects enrolled in the study, post-treatment biopsies were collected for 9 subjects, of which, 6 could not be analysed due to dermal-epidermal separation occurring during overnight transport of unfixed IEM skin biopsies. At baseline, subjects whose biopsies were analysed by IEM showed less than 25% of normal skin NC1 and NC2 staining, while IEM analyses of beremagene geperpavec-treated skin revealed clearly detectable and correctly localised AFs at the BMZ (Table 4). The AFs were observed as early as week 2 and as late as week 13.

Table 4 IEM of Subject Biopsies for AFs

Subject ID	Visit	NC1 IEM	NC2 IEM
PPD	Baseline	less than 25% of normal skin	less than 25% of normal skin
	Week 2	25-75% of normal skin	less than 25% of normal skin
	Week 8	75-100% of normal skin	25-75% of normal skin
PPD	Baseline	less than 25% of normal skin	less than 25% of normal skin
	Week 2	75-100% of normal skin	25-75% of normal skin
PPD	Baseline	less than 25% of normal skin	less than 25% of normal skin
	Week 2	75-100% of normal skin	75-100% of normal skin
	Week 13	75-100% of normal skin	75-100% of normal skin

Representative images from Subject PPD before (Day 0) and after (Day 97) treatment with B-VEC demonstrated increased COL7 NC1 lamina densa localization and prominent COL7 NC2 localization approximately 300 nm below the lamina densa , consistent with their respective localization in normal skin. Mature AFs, absent on Day 0, can be seen on Day 97 post-treatment.

Primary and secondary pharmacology

Primary pharmacodynamic activity was assessed in the phase 1/2 study (KB103-001) as described above. No secondary pharmacology studies were submitted.

2.5.3. Discussion on clinical pharmacology

Standard ADME studies were not conducted due to the nature of the product (topically applied gene therapy). Instead, vector shedding studies examining biodistribution of the vector in blood and treated wounds were performed. These are supported by immunogenicity measurements of antibodies to the vector and the transgene before, and after treatment.

Beremagene geperpavec demonstrated limited biodistribution of the vector beyond the site of application. All blood samples and all but one urine collected sample were below the limit of detection/quantification for all subjects, indicating no significant systemic subject exposure to the vector. Only a very small number of skin swabs contained detectable vector genomes; however, no extracellular infectious particles were seen on the skin surface, hence, the limited number of vector genomes remaining the skin surface were non-infectious.

Baseline HSV-1 antibodies were present in two-thirds of subjects, consistent with the general population. Six of the 8 subjects who were baseline seronegative for HSV-1 seroconverted after treatment. All subjects except one were anti-COL7 negative at baseline. Thirteen of 18 subjects who were seronegative for COL7 antibodies at baseline seroconverted post treatment. This is consistent with expected pharmacologic activity. No clinically relevant immunologic reactions were reported. The protein expression occurs at site of administration, which is different from for instance IV administered AAV, where antibodies to vector might result in clearance before the vector can be delivered to site of action. Treatment response was similar irrespective of baseline HSV-1 serostatus or COL7 seroconversion.

Pharmacodynamics was assessed in the phase 1/2 study by establishing the presence of functional COL7 expression and the formation of AFs post administration. Detection of mature AFs at the BMZ is indicative of functional COL7 molecular correction. Of the 12 subjects enrolled in the study, the limited analysed samples (n=3) showed less than 25% of normal skin NC1 and NC2 staining, while IEM analyses of beremagene geperpavec-treated skin revealed clearly detectable and correctly localised AFs at the BMZ. The presented data are reassuring and support the proof of concept, as well as the limited systemic product absorption assumption. No additional exposure data were provided and the maximum weekly dose as set out in the SmPC is in line with doses given in the pivotal trial without any systemic adverse events. The fixed maximum dose limits the amount and area of wound that can be treated at any one time.

No interactions studies were performed to test whether Vyjuvek interacts with other topically applied drugs. Given that concomitant topical medication was not allowed in the pivotal trial, the SmPC adequately reports the lack of interaction studies. Hence, Vyjuvek should not be administered with other topical medications. No studies were performed in special populations. There is no data for patients older than 44 years and in the elderly population. The SmPC informs the prescribers that no dose adjustment is required in patients ≥ 65 years old.

2.5.4. Conclusions on clinical pharmacology

The clinical pharmacology development supports the proof of concept and the lack of limited systemic absorption of Vyjuvek. The applicant adequately responded to the CAT and CHMP questions raised and the SmPC was updated with statements ensuring delivery of relevant information to the prescribers.

The CHMP endorse the CAT assessment regarding the conclusions on the Clinical pharmacology as described above.

2.5.5. Clinical efficacy

2.5.5.1. Dose response study

KB103-001 was a single-centre (US), open-label, randomised, intrasubject placebo-controlled study to assess safety and efficacy of topical beremagene geperpavec in the DEB treatment. It was divided into 4 phases:

Phase 1 (protocol v1.0): Phase 1 trial enrolled 2 adult subjects. Two wounds ≤10 cm^2 were selected in each subject; 1 wound was treated by beremagene geperpavec, the other by placebo. the first subject was administered beremagene geperpavec at ~1×10^8 PFU on Days 0, 2, 28 and 30 and treatment was well tolerated. The Safety Monitoring Committee (SMC) approved the dosing to proceed to the second subject, which was administered beremagene geperpavec at ~1×10^8 PFU on Days 0, 2, 14, 28, 30, and 42. The SMC reviewed safety data from both subjects before treatment initiation in paediatric subjects.

Phase 2a (protocol v2.2): Phase 2a enrolled 4 subjects: 2 adults and 2 paediatric subjects (aged 13 and 14, respectively). Three wounds ≤20 cm^2 were selected *per* subject with 2 randomised to beremagene geperpavec and 1 to placebo. Each wound randomised to active treatment was administered 3×10^8 PFU of topical beremagene geperpavec/administration day. Subjects were initially administered beremagene geperpavec on Days 1, 2, 3, 4, and 5. One of the adult Subjects was topically administered 6×10^8 PFU/day for the first 5 days, then withdrew from the study. The other adult subject had additional administrations at

Days 30, 44 (unscheduled), and 60. One of the paediatric subjects had an additional administration at Day 30. The other of the paediatric subjects had additional administrations on Days 30 and 46 (unscheduled).

Phase 2b (protocol v3.1): Phase 2b enrolled 5 subjects: 2 paediatric subjects and 3 adults. Three subjects who participated in phase 2a re-enrolled in phase 2b as subjects, and contributed with additional wounds. For the re-enrolled subjects, a washout period of about 3 months passed between treatments in phases 2a and 2b. Three wounds ≤20 cm^2 were selected *per* subject with 2 randomised to active treatment and 1 to placebo. Wounds randomised to topical active treatment received 1×10^8 to 1.2×10^9 PFU/administration day. These subjects were dosed approximately every 2 to 3 days for 2 consecutive weeks and then at Days 30, 60, and 90 if the wounds were open during the visit.

Phase 2c (protocol v4.0): Following completion of phase 2b, the protocol was amended to incorporate a second cycle of beremagene geperpavec to accommodate for administration to large, chronic wounds. The SMC reviewed the safety data and allowed phase 2c to proceed. This enrolled 1 paediatric subject. Two wounds were selected; the wound randomised to active treatment measured 65.29 cm^2 and received 8×10^8 to 1.57×10^9 PFU/administration. The placebo wound measured 36.17 cm^2. The wounds underwent 2 cycles of treatment and placebo administrations: cycle 1 took 25 days and consisted of 20 administrations and cycle 2 was 24 days and consisted of 21 administrations. Due to the large difference in wound sizes between the selected wound pair at baseline, the subject was excluded from the intent-to-treat (ITT) and the per-protocol (PP) population because the beremagene geperpavec wound fell outside of the inclusion/exclusion criteria; however, the subject was observed for safety. After subjects finished the interventional phase of the study and continued into a long-term follow-up period or enrolled into the phase 3 study.

Study Population: By phase, the inclusion criteria for age and wound size/surface area were:

- Phase 1: ≥18 years old with 2 wounds ≤10 cm^2
- Phase 2a: ≥5 years old with at least 3 wounds ≤20 cm^2
- Phase 2b: ≥2 years old with at least 3 wounds ≤20 cm^2
- Phase 2c: ≥2 years old with at least 2 wounds ≤50 cm^2

Other key inclusion criteria were clinical diagnosis of recessive DEB (RDEB), confirmed by genetic testing, immunofluorescence, and immunoelectron microscopy, and confirmed RDEB *COL7A1* mutations. The first 2 adults on the study had to be non-collagenous 2 domain negative and non-collagenous 1 domain positive.

The key exclusion criteria, amongst others, included medical illness expected to complicate participation and/or compromise the safety of this technique, serum antibodies to COL7, active infection, evidence of systemic infection, current evidence or a history of squamous cell carcinoma in the area that would undergo treatment, receipt of chemical or biological study product for the specific treatment of RDEB in the past 3 months, and specific wounds that had previously been administered investigational gene or cell therapy.

Treatment: Investigational product was applied topically on the assigned wounds by the investigator or designee until the wound closed. Placebo was the vehicle gel. Intradermal injections to intact skin for evaluation of molecular correction/mechanistic endpoints were performed by and at the discretion of the investigator. Starting dose selection for phase 1 was based on results from the non-clinical toxicity studies that met the FDA's guidance estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. A topical starting dose of 1×10^8 PFU/day was selected for the first-in-human phase 1 portion of the study. Dose escalation in phases 2a, 2b and 2c was based on established safety data from the various phases of the study and approval by the SMC.

Efficacy Variables and Endpoints: Three analysis populations were defined:

- Safety – all subjects administered IP
- Intent-to-treat (ITT) – all subjects who administered IP and had at least 1 post-dose paired wound assessment
- Per-protocol (PP) population – all subjects who administered IP, had at least 1 post-dose paired wound assessment, and completed the protocol as planned

Primary endpoints:

• The proportion of DEB wound sites with complete wound closure from baseline (≥90% reduction in wound surface from baseline) was analysed using the Cochran-Mantel-Haenszel (CMH) test stratified by the timepoints (weeks 8, 10, and 12). In addition, *p*-values for independence of weekly evaluations (weeks 8, 10, and 12) using the Breslow-Day test were provided.

• Time to wound closure, defined as the time from the first treatment to complete wound closure (≥90% reduction in wound surface from baseline) was summarised by treatment and compared using log rank test.

• The duration of wound closure, defined as the time from the complete wound closure to the first reduction in wound surface from baseline to a value below 90%, was summarised by treatment and compared using log rank test. An Investigator's Global Assessment (IGA) of each wound was performed on a subset of subjects at baseline and Days 3, 5, 15, 30, 60, 90. Wounds were scored according to how healed the wound was compared to baseline: 0% to 49% healed, 50% to 74% healed, 75% to <100% healed.

• Complete closure (100% healed). A patient-reported outcome (PRO) pain scale was completed by the subject at baseline and Days 3, 5, 15, 30, 60, and 90.

Safety assessments: Evaluation of the safety and tolerability of beremagene geperpavec was based on the assessment of AEs, clinical laboratory test results, vital signs, and physical examinations.

Disposition: The study enrolled 9 individual subjects, 3 of whom re-enrolled in a later phase of the study after a washout period. For analysis purpose, these subjects counted separately in the different phases, so the total number of subjects enrolled is 12. All subjects were considered to have completed the study except one, who withdrew after 4 weeks due to an inability to travel, and another one excluded from the ITT and PP populations.

Demographic and baseline characteristics: The majority of subjects (75%) were male, aged 10 to 35 years (mean 20.3), and all subjects were white.

Clinical efficacy: For the primary endpoint of complete wound closure, the proportion of wounds with ≥90% reduction in wound area from baseline in beremagene geperpavec-treated wounds compared to placebo-treated wounds at weeks 8, 10, and 12 showed treatment differences of 82.4%, 41.7%, and 71.4%, respectively ($p<0.0001$ based on CMH test stratified by time points). Beremagene geperpavec-treated wounds demonstrated a shorter median time to wound closure and a longer median duration of wound closure than placebo-treated wounds; the median time to wound closure was 13.5 days for actively treated wounds compared to 22.5 days for placebo ($p=0.0216$), and the median duration of wound closure was 103 days for placebo-treated wounds compared to 16.5 days for placebo-treated wounds ($p=0.0009$).

Secondary efficacy endpoint analyses: For the secondary efficacy endpoint of Investigator's Global Assessment (IGA) scores, beremagene geperpavec-treated wounds had a numerically higher percentage of wound healing compared to placebo-treated wounds over a 3-month period. No formal statistical comparison

was performed on IGA. Regarding the PRO pain scale, beremagene geperpavec-treated wounds had a numerically lower mean pain score than placebo-treated wounds over a 3-month period. No formal statistical comparison was performed on PRO pain scales.

Safety results: No deaths, SAEs, or significant AEs were reported. Beremagene geperpavec was well tolerated and the only AEs determined by the investigator to be possibly related to topical active treatment or placebo administration were mild and included rash, wound discharge, itching, and peculiar taste. Similarly, only mild AEs were associated with IP administration/injection, including fever, swelling, redness, pain, rash, and itching. Although intradermal administration was evaluated in phase 1/2 for the purpose of demonstrating molecular correction, the intradermal route of administration is not intended for further clinical development.

Conclusions: The dosing regimen (4×10^9 PFU of Vyjuvek for ages 3 years and older and 2×10^9 PFU Vyjuvek for ages from birth to 3 years) is based largely on the safety and efficacy results from the phase 3 study (see below); however, it had to be modified for commercial application to account for the dynamic nature of the wounds in this patient population. Extrapolation to the youngest children (birth) was also taken into account. The need for a simple dosing regimen in the intended patient population independent of the number or size of wounds, which can vary significantly from patient to patient, supports the proposed weekly dose of 4×10^9 PFU to be applied evenly to the wounds as described in the administration section of the SmPC.

A range of unit doses and dose frequencies were initially explored in the phase 1/2 study. Wounds measuring ≤20 cm^2 were given a unit dose between 1×10^8 (the first-in-human starting dose) to 1.2×10^9 PFU. The maximum weekly dose *per* subject in phase 2 ranged from 1.2×10^9 PFU/week to 6.0×10^9 PFU/week (median 4.2×10^9 PFU/week). Efficacy was observed in subjects in the phase 2 trial, as evident by wound healing supported by molecular correction with no drug-related safety events. The doses selected for phase 3 were based on exposure in phase 2. For phase 3, subjects were administered a unit dose of 4.0×10^8 PFU *per* 20 cm^2 of wound area, well within the range of 1.0×10^8 to 1.2×10^9 PFU administered in phase 2. In addition to the primary wound pair, treatment of secondary wounds was permitted in phase 3 up to a specified maximum weekly dose. A maximum weekly dose of 3.2×10^9 PFU was selected for subjects ≥6 years in phase 3, roughly equivalent to the median exposure of 4.2×10^9 PFU/week among subjects in phase 2. Since the phase 3 study enrolled younger patients than the phase 1/2 study, the maximum weekly dose was reduced for younger age groups to account for lower average body surface area. The maximum weekly doses used in the phase 3 trial were: ≥6 months to <3 years dosed at 1.6×10^9 PFU/week; ≥3 years to <6 years dosed at 2.4×10^9 PFU/week; ≥6 years dosed at 3.2×10^9 PFU/week. These age-related maximum weekly doses fall within the reported median weekly exposure of 4×10^9 PFU, hence there is no discernible difference between the maximum weekly doses among the 3 age groups.

Overall, the data observed in the subjects administered beremagene geperpavec supported advancing development of this treatment in DEB and provided meaningful insights into the design of the pivotal phase 3 clinical study with respect to sample size and endpoints.

2.5.5.2. Main study

Title of study

GEM-3 was a multi-center, intrasubject randomised, placebo-controlled, double-blind, phase 3 study of beremagene geperpavec for the topical treatment of DEB wounds.

Methods

- **Study Participants**

Inclusion criteria

- The subject or legally appointed and authorised representative must have read, understood, and signed an IRB-approved informed consent or assent form and must have been able to and willing to follow study procedures and instructions.
- Age ≥ 6 months at the time of informed consent.
- Clinical diagnosis of DEB.
- Confirmation of DEB (dominant [DDEB] or recessive [RDEB]) by genetic testing including COL7A1.
- Two cutaneous wounds meeting the following criteria:
    - a. location: similar in size, located in similar anatomical regions, and similar in appearance.
    - b. appearance: clean with adequate granulation tissue, excellent vascularisation, not infected.
- Subjects and caregivers who were able to understand the study, cooperate with the procedures, and willing to return to the clinic for all of the required follow-up visits.
- Male or female of childbearing potential must have used a reliable birth control method throughout the duration of the study and for 3 months after the last dose of IP.
- Negative pregnancy test at Visit 1 (week 1), if applicable.

Exclusion Criteria

- Medical instability limiting ability to travel to the investigative centre.
- Diseases or conditions that could have interfered with the assessment of safety and efficacy of the study treatment and compliance of the subject with study visits/procedures.
- Current evidence or a history of SCC in the area that would undergo treatment.
- Subject was actively receiving chemotherapy or immunotherapy at Visit 1.
- Active drug or alcohol addiction as determined by the investigator.
- Hypersensitivity to local anaesthesia (lidocaine/prilocaine cream).
- Participation in a clinical trial within the past 3 months (not including beremagene geperpavec).
- Receipt of a skin graft in the past 3 months.
- Pregnant or nursing women.
- Any subject was free to withdraw from the study at any time for any reason without prejudice to his or her future medical care by the physician or at the institution. An investigator or sponsor could also withdraw a subject at any time in the interest of safety/other reasons. Criteria for withdrawal included consent/assent was withdrawn; subject refused treatment and/or procedures/observations; occurrence

- **Treatments**

Topically administrated beremagene geperpavec consisted of thawed cryopreserved drug product mixed with an excipient gel. Placebo consisted of excipient gel, mixed with isotonic saline, without the active drug product. The mixed IP was stored at -20°C for up to 6 weeks past the date of mixing. Each primary wound

pair received IP/placebo based on the randomisation schedule. Subjects were dosed topically for up to 26 weeks or until wound closure. Following IP application, the subject was to keep the treated wounds covered for approximately 24 hours. If one wound in the primary wound pair closed completely, it would stop receiving weekly treatment. However, if a neighbouring wound (approximately 2 to 3 cm away from the originally selected wound) opened, that neighbouring wound may have received treatment even if the original primary was determined to be closed. weekly treatment of that primary wound resumed when it was determined to be open by the investigator during a subsequent weekly visit. This dosing regimen was followed throughout the 26-week treatment period. In addition to the primary wound pair, the investigator selected unmatched secondary wounds in each subject to receive open-label beremagene geperpavec. The total dose applied weekly to the secondary wounds did not exceed the remaining weekly dose. The remaining weekly dose was calculated as the difference between the maximum weekly dose (based on age) and the weekly unit dose used to treat the primary wound pair. As with the primary wound pair, the unit dose of beremagene geperpavec for the secondary wounds depended on the area of each wound.

The proposed regimen is a once-weekly dosing immediately after mixing 1mL beremagene geperpavec with 1.5mL of excipient gel. The final concentration is 5×10^9 PFU/mL in a single-use vial. After preparing the product with 1.5mL of excipient gel, the weekly dose is 4×10^9 PFU (in 2mL volume when mixed with excipient gel) for age 3 years and older and 2×10^9 PFU (in 1 mL volume when mixed with excipient gel) for age 6 months to 3 years. Based on experience from the phase 1/2 and phase 3 studies, the proposed dose is sufficient to achieve clinical efficacy while also supported by the safety data collected to date. For discussion on dose-finding, please refer to earlier section (dose response study).

Concomitant and rescue therapies: Medications including prescriptions, herbal and dietary supplements, over-the-counter medications, injections, and topical treatments the subject had taken within 3 months prior to the Visit 1 (week 1) or Screening visit were documented. Medication reviews occurred at subsequent visits, noting if the medication was continuing or if the subject had begun any new medication.

Prohibited therapies: Throughout the study assessment period up to week 26, topical administration of any medication (other than treatment and placebo) to a study target wound was prohibited unless approved in advance by the medical monitor/sponsor. Wounds that were not naturally occurring from the disease (e.g. post-surgery), were excluded from receiving treatment.

Permitted therapies: Topical concomitant medications/treatments necessary for adequate supportive care to non-target wounds may have been prescribed and were documented. Additionally, although prescription of tacrolimus, clobetasol, or becaplermin was permitted *per* protocol, none was applied during the study.

- **Objectives**

The primary objective was to determine whether topical administration of Vyjuvek in addition to standard of care improved wound healing as compared to placebo in DEB patients.

- **Outcomes/endpoints**

The primary endpoint was complete wound healing at 6 months, defined as complete wound closure at weeks 22 and 24 or weeks 24 and 26.

The secondary endpoints were:

- the proportion of primary wound sites with complete wound healing from baseline (as defined in the primary endpoint) in B-VEC *vs* placebo at weeks 8 and 10 or weeks 10 and 12. The wounds had to meet any of the following: healed on week 8 and week 10, or, healed on week 10 and week 12.

- the mean change in pain severity using a VAS score *per* primary wound site associated with wound dressing changes at weeks 22, 24, and 26 for ages 6 and above on the primary wound pair. For ages below 6 years, the Face Legs Activity Cry and Consolability-Revised (FLACC-R) scale was used.

- **Sample size**

The sample size assumed 90% power and a two-sided Type 1 error rate of 5% yielding 24 subjects (i.e., 24 wound pairs) under a McNemar's test, assuming an expected response rate of 75% among wounds randomised to B-VEC and a response rate of 25% among wounds randomised to placebo.

- **Randomisation and blinding (masking)**

The investigator selected 2 matched wounds (primary wound pair) in each subject that were similar in size, located in similar anatomical regions, and had similar appearance. This pair was randomised to treatment with investigational product: one wound received weekly topical treatment and the other placebo. The randomisation schedule was generated using a block size of 6 for 7 sites with a maximum of 72 randomisations *per* site. Randomisations were not stratified, and the schedule was generated by an independent statistician and validated by an independent statistical programmer.

The subjects (incl. caregivers) and (sub-)investigator conducting outcome-related assessments/procedures were blinded to the treatment identity. The unblinded staff, incl. pharmacist and monitor, remained separate from the primary study team and were not involved in any study conduct outside of their functions. All unblinded material was secured in a secondary locked location not accessible to the primary study team. To ensure the integrity of the study blind, if a matched primary wound was determined to be closed at a visit, the remaining dose was not used to treat secondary wounds. In a medical emergency, treatment may have been unblinded. Materials provided to the site for emergency unblinding were kept in a secure location where study personnel access was limited. The investigator had to contact the medical monitor/sponsor directly *prior* to breaking the blind to discuss the need for unblinding. If unblinding had to occurred, the unblinded staff could provide the information to the investigator, which was captured on the eCRF. No unblinding occurred in the study.

- **Statistical methods**

Population analyses were defined as:

- The intent-to-treat (ITT) population included subjects whose primary wounds were randomised regardless of whether they received randomised treatment or not. The ITT population was used for all primary and secondary efficacy analyses and baseline summaries.
- The safety population was defined as all subjects who were administered either beremagene geperpavec or placebo; and was used for all safety analyses.
- The modified intent-to-treat (mITT) population included subjects with primary wounds randomised and received beremagene geperpavec or placebo with at least one post-baseline primary endpoint assessment. The mITT population was used for primary and secondary efficacy sensitivity analyses.
- The per-protocol (PP) population included all safety population subjects who completed study without major protocol deviations; it was used for primary and secondary efficacy sensitivity analyses.

For the primary efficacy endpoint using the ITT population and the primary wound pair, the proportion of DEB primary wound sites with complete wound healing from baseline in beremagene geperpavec -treated and placebo-treated intra-subject wound sites at weeks 22 and 24 or 24 and 26, was analysed. Complete wound

healing was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin re-epithelialisation without drainage. The primary endpoint was defined as responder wounds that: healed on week 22 and 24, or, healed on week 24 and 26. Only wounds that were healed for at least two consecutive weeks were counted as positive responses.

The null hypothesis of interest was the absence of a treatment effect on wound healing the alternative hypothesis was the presence of a treatment effect on wound healing. The null hypothesis was to be tested using a McNemar test statistic using a two-sided type I error rate of 0.05. For subjects with missing primary endpoint data, a multiple imputation approach assuming MAR was to be used. Additional sensitivity analyses of the primary endpoint included an analysis using the PP and mITT populations as well as without any imputations and logistic regression using multiple imputation (MI) methods. For key secondary and other efficacy endpoints similar analyses to the primary outcome were conducted. Common treatment risk differences were to be obtained from conditional logistic regression with covariates age and gender and stratified by subject (matched pair) and multiple imputation approach assuming MAR. Other secondary endpoints were analysed using Analysis of Covariance (ANCOVA).

Results

- **Participant flow**

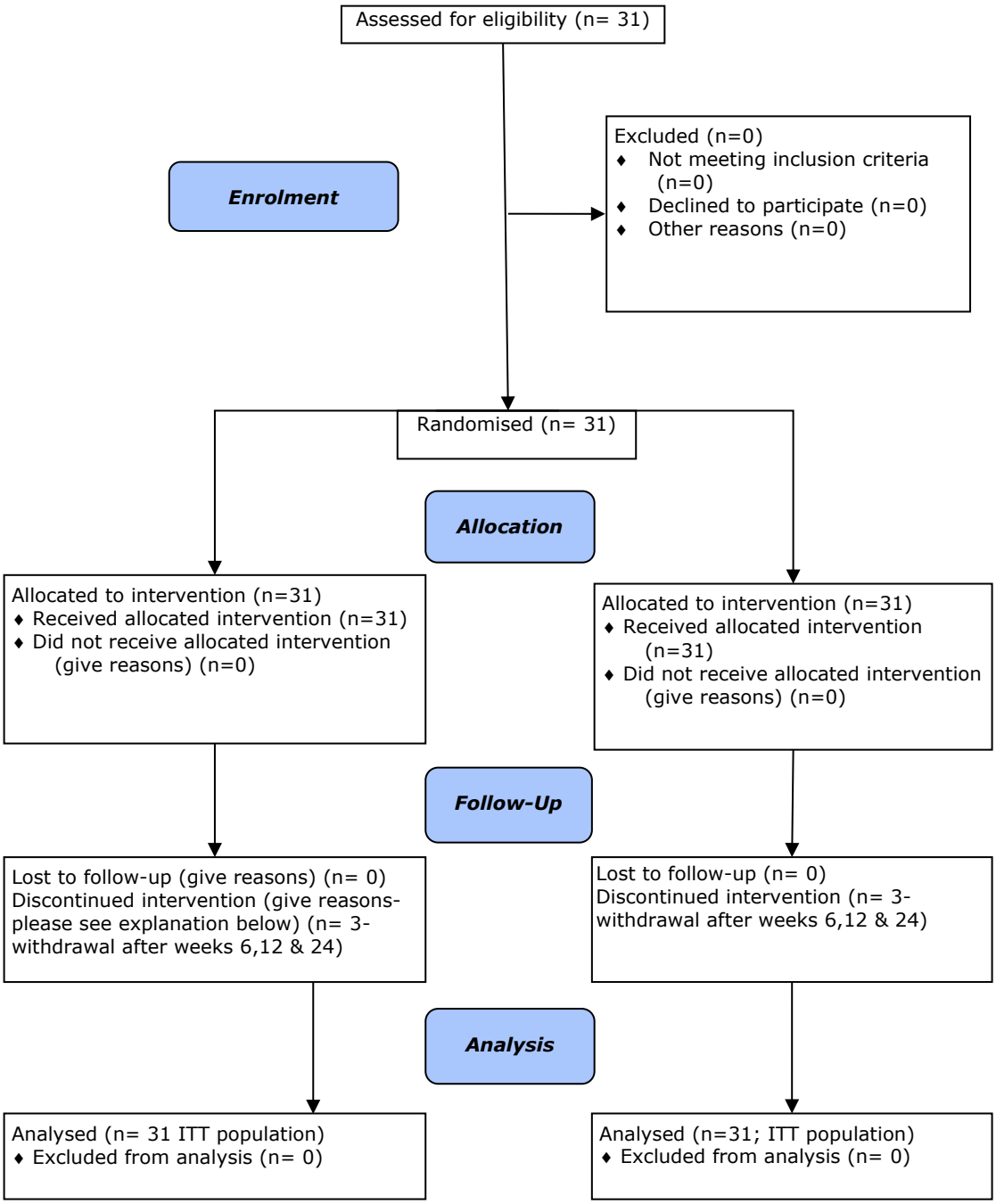


Figure 2 Participant flow

- **Recruitment**

The start date for the pivotal trial was 17th August 2020 and the stop date was 29th October 2021.

- **Conduct of the study**

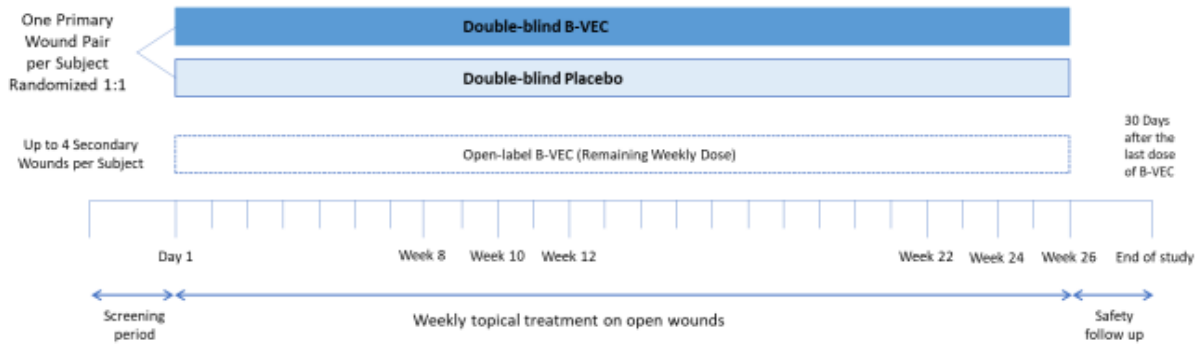


Figure 3 Conduct of the study

The original protocol (v.1.0, 5May 2020) was amended 4 times; enrolment began with v. 1.1 (29June 2020). In v.1.2 (20October 2020), the protocol was amended to reduce the amount of urine and blood collected *per* subject, and the number of dressings collected for viral shedding analysis (min 4 dressing collections). In v.1.3 (10December 2020), the protocol reflected limited wounds to 1 matched pair and secondary unmatched wounds to 4 for subjects enrolled. Weeks 25 and 26 were added to the protocol and the primary efficacy evaluation was changed to weeks 22, 24, and 26 to evaluate wound closure by week 24, and further re-evaluate wound closure for 2 consecutive weeks. Enrolment was increased to approx. 37 subjects due to limiting the intrasubject matched primary wounds to 1 pair based on a Fisher Exact Analysis. The secondary endpoint (proportion of DEB primary wound sites with ≥75% wound healing from baseline) was removed due to the lack of accuracy in measuring of the wounds with the Canfield imaging system. In the final v.1.4 (21April 2022), protocol was amended to update the statistical analysis (use of the McNemar's test) for primary and key secondary endpoints. Clarification was also added pertaining to the assessment of primary wounds. The neighbouring wounds that did not receive treatment during the study would not be included in the assessment. Since a McNemar's test had been used for sample size calculation, the sample size was reduced to 24 subjects (24 wound pairs) assuming a response rate of 75% among wounds randomised to active treatment and a response rate of 25% among wounds randomised to placebo. Due to concerns about the COVID-19 dropouts and burden of weekly visit to the clinical sites, operationally a 20% to 25% dropout rate was assumed. With that estimated dropout rate, a total sample size of 30 to 32 subjects was targeted.

- **Baseline data**

Demographic and baseline characteristics for the ITT/safety population are summarised in the below Table 5. The primary wounds were well matched in size between the treatments with medians of 10.6 cm^2 for beremagene geperpavec and 10.4 cm^2 for placebo. Primary wound sizes varied in size from approx. 2.3 cm^2 to over 50 cm^2. Large secondary wounds exceeding 100 cm^2 were also treated with beremagene geperpavec.

Table 5 Summary of Demographic and Baseline Characteristics

Characteristic	All Subjects (N=31)
Age (years)	
Mean (SD)	17.2 (10.70)
Median (min, max)	16.1 (1, 44)
Age by category, n (%)	
≤12 years	10 (32.3)
>12 and ≤18 years	9 (29.0)
>18 years	12 (38.7)
Sex, n (%)	
Male	20 (64.5)
Female	11 (35.5)
Race, n (%)	
White	20 (64.5)
Asian	6 (19.4)
American Indian or Alaska Native	5 (16.1)
Ethnicity, n (%)	
Hispanic or Latino	16 (51.6)
Not Hispanic or Latino	15 (48.4)
Genotype, n (%)	
Dominant DEB	1 (3.2)
Recessive DEB	30 (96.8)
Primary Wound Area (cm^2) – B-VEC	
Mean (SD)	14.4 (12.7)
Median (min, max)	10.6 (2.3, 57.3)
Primary Wound Area (cm^2) – Placebo	
Mean (SD)	15.6 (12.1)
Median (min, max)	10.4 (2.3, 51.5)
Primary Wound Area – B-VEC, n (%)	
<20 cm^2	23 (74.2)
20 to <40 cm^2	6 (19.4)
40 to 60 cm^2	2 (6.5)
Primary Wound Area – Placebo, n (%)	
<20 cm^2	22 (71.0)
20 to <40 cm^2	8 (25.8)
40 to 60 cm^2	1 (3.2)

- **Numbers analysed**

The ITT population included all 31 subjects whose primary wounds were randomised. The safety population included all 31 subjects who were administered either beremagene geperpavec or placebo. The mITT population included 29 subjects whose primary wounds were randomised, received beremagene geperpavec or placebo treatment, and had at least 1 post-baseline primary endpoint assessment. Excluded were 2 subjects who discontinued the study before week 24. The PP population included 24 subjects. Excluded were 3 subjects who discontinued early and 4 subjects who completed the study but had major protocol deviations.

- **Outcomes and estimation**

Among the 31 wound pairs in the primary ITT analysis, 67.4% of beremagene geperpavec-treated wounds *vs* 21.6% of placebo-treated wounds were completely healed at 6 months (p=0.0019; **Table 6, Figure 4**).

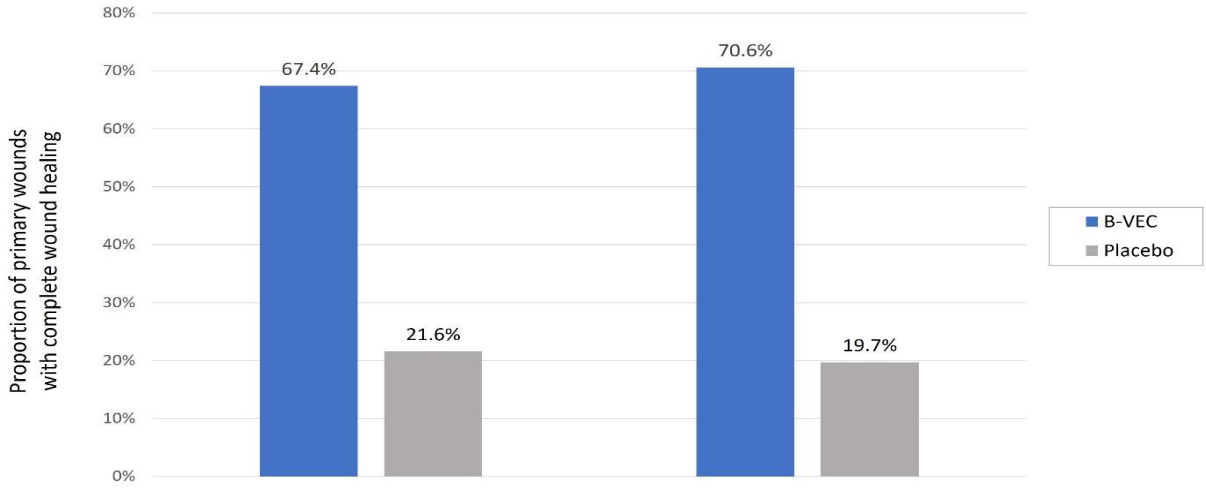
Table 6 Primary Efficacy Endpoint: Wound healing at 6 months (ITT population, imputed data)

Parameter	Responder, n (%)		% Difference (95% CI)[a]	p-value[b]
	B-VEC Wound (n=31)	Placebo Wound (n=31)		
Responder at Weeks 22 & 24 or Weeks 24 & 26 (ITT population)	20.9 (67.4)	6.7 (21.6)	45.8 (23.6, 68.0)	0.0019

Note: Complete wound healing was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin re-epithelialization without drainage. Only wounds that were healed for at least 2 consecutive weeks were counted as positive responses.

a The difference was the treatment/discordance difference in percentage of responders, which was the same as the difference in the percentage of treatment responders and the percentage of placebo responders.

b The p-value was based on exact McNemar's test. Missing endpoint data were imputed assuming the data were missing at random and using multiple imputation methodology.



	Primary endpoint	Key secondary endpoint
Outcome assessment	Weeks 22/24/26	Weeks 8/10/12
Absolute difference	45.8%	51.0%
95% CI	23.6% - 68.0%	29.3% - 72.6%
p value	0.002	<0.001

Figure 4 Complete Wound Healing: Primary and Secondary Endpoints

Sensitivity Analyses of the Primary Efficacy Endpoint

Sensitivity analyses of the primary endpoint are summarised in Table 7 and Figure 5. Forest plots of the primary and sensitivity efficacy responder analyses are shown for imputed data and for observed data (Figure 6).

Table 7 Sensitivity Analyses of the Primary Efficacy Endpoint

Parameter	Responder, n (%)		% Difference (95% CI)[a]	p-value[b]
	B-VEC Wound	Placebo Wound		
Responder at Weeks 22 & 24 or Weeks 24 & 26 (mITT population, n=29, imputed data)	19.6 (67.6)	6.3 (21.7)	45.9 (23.0, 68.7)	0.002[c]
Responder at Weeks 22 & 24 or Weeks 24 & 26 (PP population, n=24, imputed data)	17.0 (70.8)	6.0 (25.0)	45.8 (20.1, 71.6)	0.007[c]
Responder at Weeks 22 & 24 or Weeks 24 & 26 (ITT population, n=31, observed data)	19.0 (61.3)	6.0 (19.4)	41.9 (20.4, 63.4)	0.002
Responder at Weeks 22 & 24 or Weeks 24 & 26 (mITT population, n=29, observed data)	19.0 (65.5)	6.0 (20.7)	44.8 (22.2, 67.4)	0.002
Responder at Weeks 22 & 24 or Weeks 24 & 26 (PP population, n=24, observed data)	17.0 (70.8)	6.0 (25.0)	45.8 (20.1, 71.6)	0.007

Note: Complete wound healing was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin re-epithelialization without drainage. Only wounds that were healed for at least 2 consecutive weeks were counted as positive responses.

a The difference was the treatment/discordance difference in percentage of responders, which was the same as the difference in the percentage of treatment responders and the percentage of placebo responders.

b The p-value was based on exact McNemar's test.

c Missing endpoint data were imputed assuming the data were missing at random and using multiple imputation methodology.

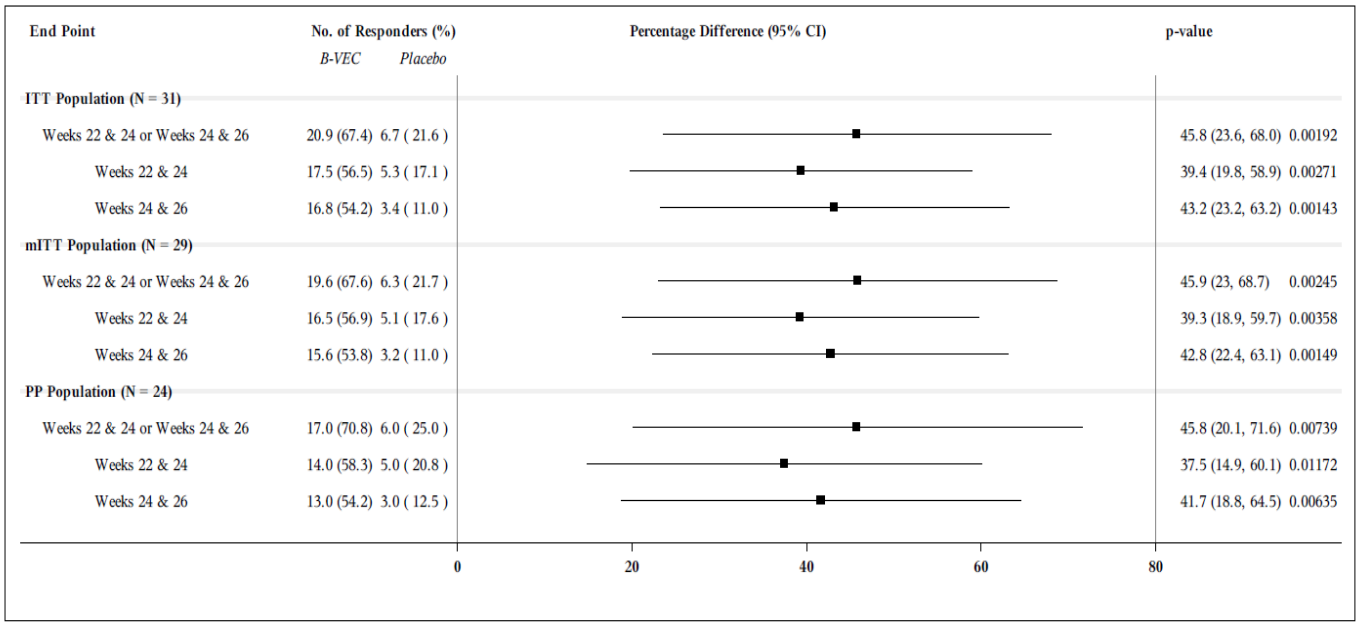


Figure 5 Forest Plot of Primary and Sensitivity Efficacy Responder Analysis (Imputed Data)

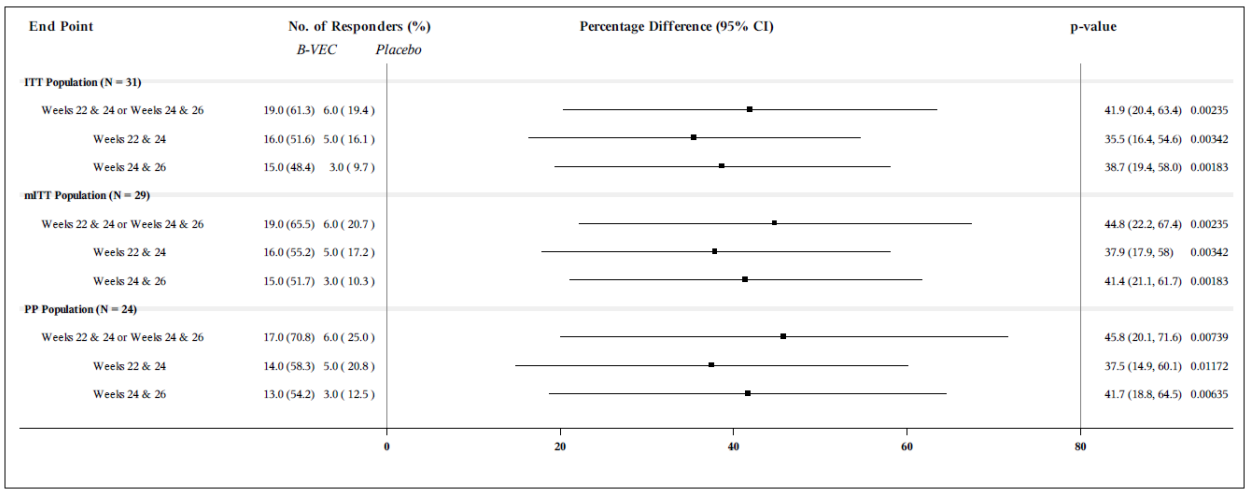


Figure 6 Forest Plot of Sensitivity Efficacy Responder Analysis (Observed Data)

- **Ancillary analyses**

Supplementary primary efficacy endpoint analysis: In this analysis (ITT population, imputed data), the beremagene geperpavec treatment effect using conditional logistic regression model (adjusted for age and gender) yielded an odds ratio (95% CI) of 7.29 (1.68, 31.60); p=0.006. The results were similar for the mITT and PP populations, see Figure 7.

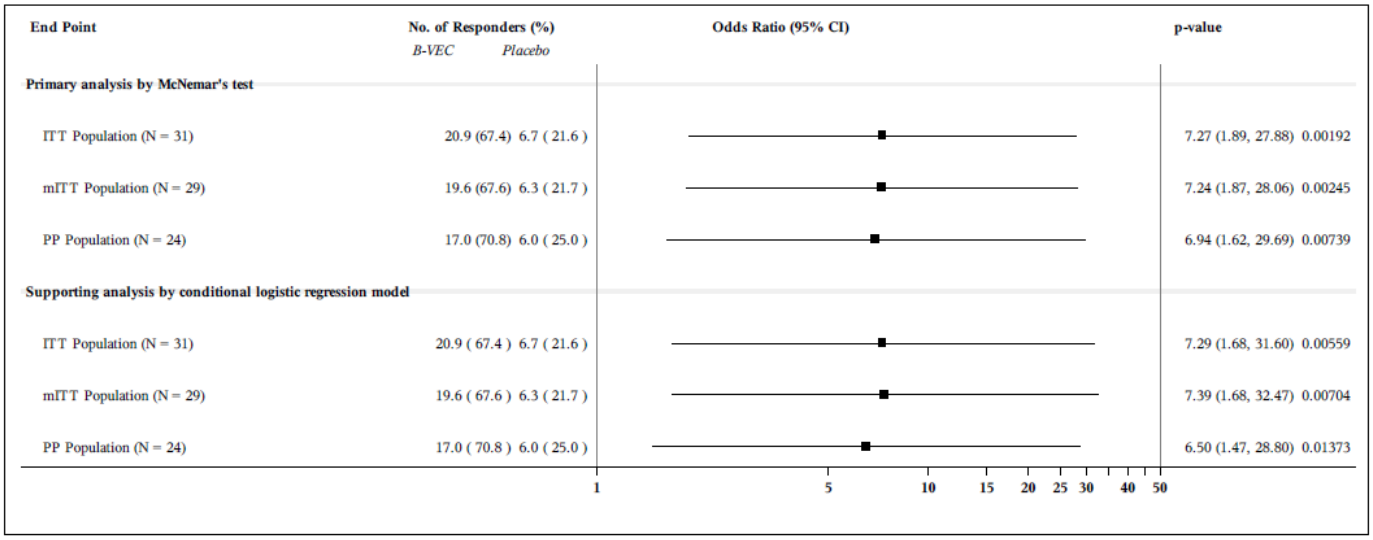


Figure 7 Forest Plot of Primary Efficacy Responder Supplementary Analysis (Imputed Data)

Primary Efficacy Endpoint Subgroup Analyses

By age: Analysis of the primary efficacy endpoint at 6 months by age in the ITT population showed the following responder rates, all in favour of beremagene geperpavec:

- For subjects ≤12 years (n=10), 80.0% of beremagene geperpavec-treated wounds compared to 20.0% of placebo-treated wounds (difference, 60.0 percentage points; 95% CI, 29.6% to 90.4%)

- For subjects >12 and ≤18 years (n=9), 71.1% of beremagene geperpavec-treated wounds compared to 17.8% of placebo-treated wounds (difference, 53.3 percentage points; 95% CI, 17.9% to 88.7%)
- For subjects >18 years (n=12), 54.2% of beremagene geperpavec-treated wounds compared to 25.8% of placebo-treated wounds (difference, 28.3 percentage points; 95% CI, -13.7% to 70.4%)

By gender: Analysis of the primary efficacy endpoint at 6 months by gender in the ITT population showed the following responder rates, both in favour of beremagene geperpavec:

- For males (n=20), 70.0% of beremagene geperpavec-treated wounds compared to 20.0% of placebo-treated wounds (difference, 50.0 percentage points; 95% CI, 20.6% to 79.4%)
- For females (n=11), 62.7% of beremagene geperpavec-treated wounds compared to 24.5% of placebo-treated wounds (difference, 38.2 percentage points; 95% CI, 6.3% to 70.0%)

By race: Analysis of the primary efficacy endpoint at 6 months by race in the ITT population showed no significant difference in responder rate between the beremagene geperpavec- and placebo-treated wounds for non-white subjects: American Indian or Alaska Native (n=5) and Asian (n=6); however, the number of subjects in each of these subgroups was very limited. For white subjects (n=20), responder rates were 70.5% of beremagene geperpavec-treated wounds compared to 7.0% of placebo-treated wounds (difference, 63.5 percentage points; 95% CI, 41.5% to 85.5%)

Key Secondary Efficacy Endpoint Analysis with Sensitivity and Supplementary Analyses

The key secondary endpoint of complete wound healing at 3 months, defined as complete wound closure at weeks 8 and 10 or weeks 10 and 12, was met. Improvement in wound healing was observed at 3 months, with 70.6% of beremagene geperpavec-treated wounds completely healed *vs* 19.7% of placebo-treated wounds in the ITT population with imputed data ($p<0.001$). Results for the key secondary and sensitivity efficacy responder analysis of wounds healed on weeks 8 and 10 or weeks 10 and 12 are summarised in Table 8.

Table 8 Key Secondary and Sensitivity Efficacy Responder Analysis

Parameter	Responder, n (%)		% Difference (95% CI)[a]	p-value[b]
	B-VEC Wound	Placebo Wound		
Responder at Weeks 8 & 10 or Weeks 10 & 12 (ITT population, n=31, imputed data)	21.9 (70.6)	6.1 (19.7)	51.0 (29.3, 72.6)	<0.001[c]
Responder at Weeks 8 & 10 or Weeks 10 & 12 (mITT population, n=29, imputed data)	21.0 (72.4)	5.0 (17.2)	55.2 (34.7, 75.6)	<0.001[c]
Responder at Weeks 8 & 10 or Weeks 10 & 12 (PP population, n=24, imputed data)	18.0 (75.0)	3.0 (12.5)	62.5 (43.1, 81.9)	<0.001[c]
Responder at Weeks 8 & 10 or Weeks 10 & 12 (ITT population, n=31, observed data)	21.0 (67.7)	6.0 (19.4)	48.4 (26.7, 70.1)	<0.001
Responder at Weeks 8 & 10 or Weeks 10 & 12 (mITT population, n=29, observed data)	21.0 (72.4)	5.0 (17.2)	55.2 (34.7, 75.6)	<0.001
Responder at Weeks 8 & 10 or Weeks 10 & 12 (PP population, n=24, observed data)	18.0 (75.0)	3.0 (12.5)	62.5 (43.1, 81.9)	<0.001

Note: Complete wound healing was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin re-epithelialization without drainage. Only wounds that were healed for at least 2 consecutive weeks were counted as positive responses.

a The difference was the treatment/discordance difference in percentage of responders, which was the same as the difference in the percentage of treatment responders and the percentage of placebo responders.

b The p-value was based on exact McNemar's test.

c Missing endpoint data were imputed assuming the data were missing at random and using multiple imputation methodology

By age: Analysis of the key secondary efficacy endpoint at 3 months by age category in the ITT population showed the following responder rates, in favour beremagene geperpavec.

- For subjects ≤12 years (n=10), 80.0% of beremagene geperpavec-treated wounds compared to 20.0% of placebo-treated wounds (difference, 60.0 percentage points; 95% CI, 29.6% to 90.4%)
- For subjects >12 and ≤18 years (n=9), 65.6% of beremagene geperpavec-treated wounds compared to 1.1% of placebo-treated wounds (difference, 64.4 percentage points; 95% CI, 33.2% to 95.7%)
- For subjects >18 years (n=12), 66.7% of beremagene geperpavec-treated wounds compared to 33.3% of placebo-treated wounds (difference, 33.3 percentage points; 95% CI, -8.8% to 75.5%)

By gender: Analysis of the key secondary efficacy endpoint at 3 months by gender in the ITT population showed the following responder rates, in favour beremagene geperpavec:

- For males (n=20), 70.0% of beremagene geperpavec-treated wounds compared to 25.0% of placebo-treated wounds (difference, 45.0 percentage points; 95% CI, 19.2% to 70.8%)
- For females (n=11), 71.8% of beremagene geperpavec-treated wounds compared to 10.0% of placebo-treated wounds (difference, 61.8 percentage points; 95% CI, 23.6% to 100.0%)

By race: Analysis of the key secondary efficacy endpoint at 3 months by race in the ITT population showed a responder rate of 70.0% for beremagene geperpavec-treated wounds compared to 20.0% for placebo-treated wounds (difference, 50.0 percentage points; 95% CI, 24.1% to 75.9%) for white subjects (n=20). The number of subjects in non-white subgroups was very limited: American Indian or Alaska Native (n=5) and Asian subjects (n=6); however, the treatment difference at 3 months was similar to that for white subjects.

Durability of response: Durable response was defined as complete wound closure on at least 2 consecutive visits occurring 2 weeks apart. Durability was assessed by considering the proportion of wounds that met the definition for wound healing at both, 3 and 6 months (simultaneously met primary endpoint and key secondary endpoint). Using this definition, 49.7% of beremagene geperpavec-treated wounds were completely healed compared to only 7.1% of placebo-treated wounds in the ITT population (p=0.002), see Table 9.

Table 9 Supplementary Primary Efficacy Endpoint Analysis: Durability of Response (Imputed Data)

Parameter	Responder, n (%)		% Difference (95% CI)[a]	p-value[b]
	B-VEC Wound	Placebo Wound		
Responder at (Weeks 8 & 10 or Weeks 10 & 12) and (Weeks 22 & 24 or Weeks 24 & 26) (ITT population, n=31)	15.4 (49.7)	2.2 (7.1)	42.6 (22.6, 62.6)	0.002
Responder at (Weeks 8 & 10 or Weeks 10 & 12) and (Weeks 22 & 24 or Weeks 24 & 26) (mITT population, n=29)	14.6 (50.3)	2.0 (6.9)	43.4 (23.0, 63.9)	0.001
Responder at (Weeks 8 & 10 or Weeks 10 & 12) and (Weeks 22 & 24 or Weeks 24 & 26) (PP population, n=24)	13.0 (54.2)	2.0 (8.3)	45.8 (22.8, 68.9)	0.003

CI=confidence interval; ITT=intent-to-treat; mITT=modified ITT; PP=per-protocol.
a: The difference was the discordance difference in percentage of responders between treatments (B-VEC-Placebo), which was the same as the difference in the percentage of marginal treatment responders.
b: The p-value was based on exact McNemar's test. Missing endpoint data were imputed assuming the data were missing at random and using multiple imputation methodology.

Secondary Efficacy Analysis: Change in Pain Severity

Pain severity during wound dressing changes as assessed by VAS in subjects aged ≥6 was evaluated as a secondary endpoint. Consistent trend of decreased pain was observed across weeks 22, 24, and 26. The least square mean differences between beremagene geperpavec and placebo for change in VAS score from baseline were significant at week 22 but not at weeks 24, 26. Although the changes in pain were favourable and consistent with wound healing, the effect sizes were relatively modest, ranging from -0.56 to -0.88.

In the ITT population (observed data) the least square mean difference (95% CI) was -0.61 (-1.10 to -0.13; p=0.016) at week 22; -0.88 (-1.79 to 0.03; p=0.058) at week 24, and -0.56 (-1.17 to 0.05; p=0.072) at week 26. Negative changes reflect a decrease in pain severity.

For children younger than 6 years, pain severity during wound dressing changes was assessed by the FLACC-R scale. In the ITT population, mean change from baseline at weeks 22, 24, and 26 was -0.25, -1.25, and -1.50 for beremagene geperpavec-treated wounds and -1.00, -1.25, and -1.50 for placebo-treated wounds. Negative changes reflect a decrease in pain severity.

PRO: EQ-5D-5L Health Questionnaire

For the change in level of health status from baseline to follow-up for the EQ-5D-5L, a trend toward improvement was observed across multiple domains (anxiety/depression, mobility, pain/discomfort, and self-care), suggestive of an improvement in overall health status (Figure 10).

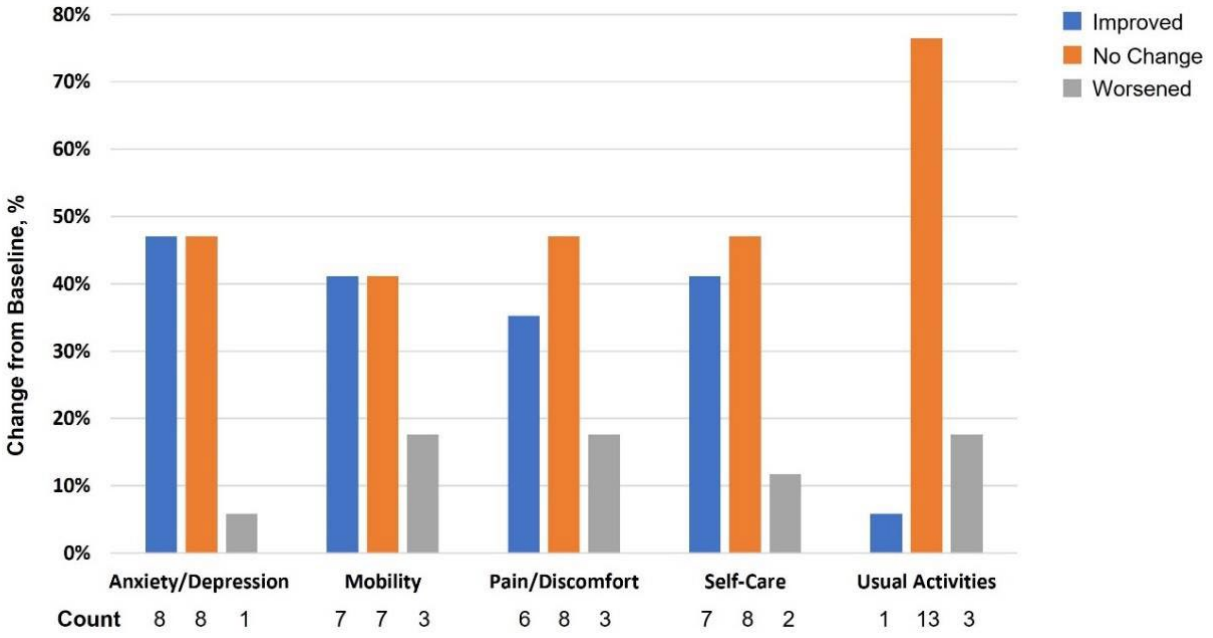


Figure 8 Change from Baseline to Follow-up for EQ-5D-5L Dimensions

PRO: Skindex-29 Questionnaire

Mean Skindex-29 scores at follow-up were numerically lower than at baseline across multiple domains (symptoms, functioning, and emotions), suggestive of improved skin-specific quality of life.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Phase 3 Efficacy and Safety Study of Beremagene Geperpavec (beremagene geperpavec, KB103) for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)		
Study identifier	Protocol ID: beremagene geperpavec-O3, Clinical Trials.gov: NCT04491604	
Design	Phase 3 randomise, multicentre, double-blind,placebo-controlled, intrasubjects comparison of beremagene geperpavec *vs* placebo for the treatment of DEB	
	Duration of main phase:	Start date: 17 August 2020 Stop Date: 29 October 2021
Hypothesis	Exploratory	
Treatments groups Primary matched wounds randomised to treatment with the IP or standard of care	Vyjuvek plus standard of care	31 primary wounds treated with the IMP and SOC for 26 weeks.
	Standard of care (SOC)	31 primary wounds treated with SOC for 26 weeks.

Phase 3 Efficacy and Safety Study of Beremagene Geperpavec (beremagene geperpavec, KB103) for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)			
Study identifier	Protocol ID: beremagene geperpavec-O3, Clinical Trials.gov: NCT04491604		
Endpoints and definitions	Primary endpoint	Wound healing at 6 months	Complete wound healing at 6 months, defined as 100% complete wound closure specified as skin re-epithelialisation without drainage at weeks 22 and 24 or weeks 24 and 26. Only wounds that were healed for at least 2 consecutive weeks were counted as positive responders.
	Key Secondary endpoint	Wound healing at 3 months	Complete wound closure (as defined above) at weeks 8 and 10 or weeks 10 and 12.
	Secondary endpoint	Change in pain severity	Pain severity during wound dressing change measured by the VAS-Visual analogue score
	Secondary endpoint	PRO:EQ-5D-5L	Change in level of health status from baseline to follow-up for each dimension of the EQ-5D-5L
	Secondary endpoint	PRO:Skindex-29	Change in mean Skindex-29 scores from baseline
Database lock	19Nov 2021		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat population (imputed data)			
Descriptive statistics and estimate variability	Treatment group	beremagene geperpavec-treated wound	Placebo treated wound	% Difference
	N	31	31	
	Primary endpoint	20.9	6.7	45.8
		Confidence interval	23.6-68	
		P-value (McNemar's test)	0.0019	
	Key secondary endpoint	beremagene geperpavec	placebo	
		21.9	6.1	
		Percentage difference	51 (29.3-72.6)	
		P-value (McNemar's test)	<0.001	
	Secondary endpoint Pain severity	beremagene geperpavec	placebo	
		Least mean square difference at week 22	-0.61(-1.10—0.13)	
		P-value	0.0016	
		Least mean square difference at week 24	-0.88(-1.79-0.03)	
		P-value	0.058	
		Least mean square difference at week 26	-0.56(-1.17-0.05)	
		P-value	0.072	

Phase 3 Efficacy and Safety Study of Beremagene Geperpavec (beremagene geperpavec, KB103) for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)				
Study identifier	Protocol ID: beremagene geperpavec-O3, Clinical Trials.gov: NCT04491604			
Notes	Supplemental and sensitivity analysis were conducted for the primary and key secondary endpoints for imputed and non-imputed ITT populations. Analysis of durability of response for the primary endpoint at both time points is also presented. The additional analysis revealed similar results. The analysis of the secondary endpoints of pain and health status show modest change to baseline.			
Analysis description	Sensitivity efficacy responder analysis of the primary efficacy endpoint & supplementary primary endpoint analysis: durability of response			
Parameter-responder percentage	**beremagene geperpavec -**	**placebo**	**% difference**	**p-value**
Responder at weeks 22 & 24 or weeks 24 & 26 (mITT population, n=29, imputed data)	19.6 (67.6)	6.3 (21.7)	45.9 (23.0, 68.7)	0.002
Responder at weeks 22 & 24 or weeks 24 & 26 (PP population, n=24, imputed data)	17.0 (70.8)	6.0 (25.0)	45.8 (20.1, 71.6)	0.007c
Responder at weeks 22 & 24 or weeks 24 & 26 (ITT population, n=31, observed data)	19.0 (61.3)	6.0 (19.4)	41.9 (20.4, 63.4)	0.002
Responder at weeks 22 & 24 or weeks 24 & 26 (mITT population, n=29, observed data	19.0 (65.5)	6.0 (20.7)	44.8 (22.2, 67.4)	0.002
Responder at weeks 22 & 24 or weeks 24 & 26 (PP population, n=24, observed data)	17.0 (70.8)	6.0 (25.0)	45.8 (20.1, 71.6)	0.007
Responder at (weeks 8 & 10 or weeks 10 & 12) and (weeks 22 & 24 or weeks 24 & 26) (ITT population, n=31)	15.4 (49.7)	2.2 (7.1)	42.6 (22.6, 62.6)	0.002
Responder at (weeks 8 & 10 or weeks 10 & 12) and (weeks 22 & 24 or weeks 24 & 26) (mITT population, n=29)	14.6 (50.3)	2.0 (6.9)	43.4 (23.0, 63.9)	0.001
Responder at (weeks 8 & 10 or weeks 10 & 12) and (weeks 22 & 24 or weeks 24 & 26) (PP population, n=24)	13.0 (54.2)	2.0 (8.3)	45.8 (22.8, 68.9)	0.003

2.5.5.3. Clinical studies in special populations

There were no dedicated studies in special populations. Paediatric patients were included in the conducted trials in accordance with the agreed PIP and results of outcome in children are discussed in the above

sections. There were no paediatric patients less than one year of age, and no elderly patients treated in the clinical trials. There were no patients with renal or hepatic impairment. As the product is administered topically without absorption, this is acceptable. This is reflected in the SmPC.

2.5.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.5.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.5.5.6. Supportive study

Open-label extension study (OLE; B-VEC-*EX-02)*

After completion of the safety follow-up period for the phase 3 study, subjects were permitted to enrol into an OLE study, which was originally designed with the intention of providing access to continued treatment with beremagene geperpavec, in addition to providing access to study treatment for new patients who were not able to participate in the phase 3 study. Other objectives of the OLE study were to collect long-term safety data with extended use beyond the 26-week treatment (in phase 3), as well as to collect longitudinal assessments of treatment satisfaction, skin-specific quality of life, and general health status. Durability of closure for wounds previously treated with beremagene geperpavec in phase 3 was also assessed at selected time points. Age of inclusion for the OLE study was progressively lowered through protocol amendments to permit collection of data in younger age groups (<6 months). The protocol was designed to give investigators the flexibility to apply beremagene geperpavec to different treatment areas, as needed, to reflect real-world practice. For ease of administration and to minimise dosing errors, the maximum weekly dose was simplified to only 2 age categories (≥3 years or <3 years old).

Disposition: Forty-seven subjects were enrolled in the study, including 24 rollover and 23 naïve subjects. Seven rollover and no naïve subjects completed the last study visit. Rollover subjects were the first subjects enrolled into the OLE study, and therefore were the only subjects to complete the last visit prior to study termination by the Sponsor. The most frequent reason for discontinuation was study termination by the sponsor for commercial reasons, accounting for 34 (72.3%) subjects.

Demographics and baseline characteristics: The mean age of subjects was 16.5 years (range 0.5 to 46) and 26 (55.3%) subjects were 18 years or younger; 2 naïve subjects were below 1 year of age (6 months and 7 months). The majority of subjects were male (63.8%) and white (68.1%); 2 naïve subjects were black or African American. Ethnicity was about equally distributed between Hispanic or Latino (44.7%) and not Hispanic or Latino (55.3%). Two subjects had dominant DEB (1 rollover and 1 naïve subject); the remaining subjects had recessive DEB.

Extent of exposure: The duration of therapy ranged from 1 to 794 days with a median of 642 days for rollover subjects and from 21 to 664 days with a median of 344 days for naïve subjects. Twenty-nine of 47 subjects (62%) had over 1 year of exposure. Duration of exposure was substantially longer among rollover subjects compared to naive subjects, consistent with the fact that they started enrolment earlier and had progressed further in the study before it was terminated. The number of doses received ranged from 1 to 107 with a median of 72.5 doses for rollover subjects and from 3 to 73 with a median of 36.0 doses for naïve

subjects. Consistent with duration of exposure, the number of doses received was higher among rollover subjects compared to naïve subjects.

Efficacy results: Given the open-label, non-randomised design of the OLE study, efficacy measures were collected as exploratory outcomes only. PROs included assessment of treatment satisfaction as measured by the TSQM-9, skin-specific quality-of-life as measured by the Skindex-29, and general health status as measured by the EQ-5D (5L and VAS). In addition, durability of closure for wounds previously treated with beremagene geperpavec in phase 3 was assessed among rollover subjects, where possible.

TSQM-9 questionnaire: For rollover subjects, who received active treatment in phase 3 trial, the TSQM-9 was assessed at baseline of the OLE and at their last study visit. For treatment-naïve subjects, who all started active treatment after enrolling in the OLE study, the TSQM-9 was assessed only at their last study visit. For the rollover subjects, the observed higher score on the TSQM-9 questionnaire and a positive change from baseline, represents greater satisfaction with treatment. Similarly, for the naïve subjects, the high TSQM scores at the last study visit suggest high levels of treatment satisfaction upon completion of the OLE.

Skindex-29 questionnaire: Among subjects 12 years of age or older, Skindex-29 was assessed at baseline and at weeks 26, 39, 52, 78, and 104 (6, 9, 12, 18, and 24 months) and a lower score indicated less impairment, and thus a negative change from baseline represents improvement. Among subjects with non-missing data for Skindex-29, scores in each of the 3 domains (Emotions, Functioning, and Symptoms) and the Total score were lower compared to baseline with the exception of week 78, when 2 subjects had unusually high scores, resulting in a higher mean score among the smaller number of subjects who completed the visit. Due to administrative termination of the study, not all last assessments were done at the scheduled time point, and therefore these assessments were reassigned to the nearest scheduled time point for analysis.

EQ-5D-5L questionnaire: Among subjects 12 years of age or older, EQ-5D-5L and VAS were assessed at weeks 26, 39, 52, 78, and 104 (6, 9, 12, 18, and 24 months). Change in EQ-5D-5L from baseline was assessed as improved, no change, or worsened. In general, EQ-5D-5L responses reflected high levels of impairment, with a high proportion of subjects reporting moderate or greater impairment across multiple dimensions, most notably pain. No consistent pattern of change in EQ-5D-5L was observed; however, interpretation of the data is limited by the low number of subjects with evaluable data, particularly at the latter time points. Not all subjects completed all visits due to variability in follow-up time associated with early termination of the study.

Summary of responders (wound closure): Complete wound closure in the OLE study was determined based on comparison to the exact wound area selected at baseline in the phase 3 study. Out of 24 rollover subjects 19 were evaluated (data was unevaluable for 5 subjects who did not return consistently for follow up visits). The responder rate, based on between 16 and 19 subjects at each visit, ranged from 61.1% to 89.5% in the OLE study, and was comparable to the rates observed at months 3 and 6 in the phase 3 study.

Safety results: Thirty-five subjects (74.5%) experienced at least 1 TEAE during the study. The majority of TEAEs were mild or moderate in severity. The most frequently reported TEAEs (reported for at least 10% of subjects) were COVID-19 for 15 subjects (31.9%), cough for 9 subjects (19.1%), pyrexia for 8 subjects (17.0%), skin infection for 5 subjects (10.6%), and vomiting for 5 subjects (10.6%). Of the TEAEs with relationship to study treatment reported, no events were considered by the investigator to be related to study treatment, 2 as possibly related (both events of wound haemorrhage in the same subject). No SAE was considered related to study treatment; no TEAEs led to treatment/ study discontinuation. There were no deaths.

Real World Evidence (RWE)

The RWE dataset was based on 3 sources: US post-marketing experience, US OLE study (NCT04917874), and 1 patient from the EU early access programme. By the cut-off date (22 Nov 2024), 423 patients received Vyjuvek in the commercial setting, corresponding to 273.9 patient-years of experience. This is over 13 times greater than the number of patients in the pivotal trial (n=31). The age range was 10 days to >92 years. No safety signals were presented by the applicant. Table 14 below shows the details of patients captured in RWE. Certain patients who initiated the treatment during the US OLE and continued to US post-marketing, received >104 weeks of treatment. Cumulatively, these 23 patients contribute to 57.4 patient-years of experience.

In addition, as of November 2024, 12 patients, <1 year of age were exposed to B-VEC, incl. open label access and US post-marketing, or early access real-life experience in Europe, representing 5.2 patient-years' experience.

Table 10 Vyjuvek RWE by age group and diagnosis as of 22 Nov 2024

Age Subgroup* (yrs)	Diagnosis	Patient Count	Total wks (yrs) [Min wks, Max wks]	Age Range (yrs)	Sex Ratio M : F
<1	DDEB	3	50 (1.0) [11, 20]	0.03 to 0.64	1 : 2
<1	RDEB	9	367 (7.1) [3, 112]	0.24 to 0.86	6 : 3
1 to <3	DDEB	7	164 (3.2) [4, 57]	1.01 to 2.89	3 : 4
1 to <3	RDEB	22	1050 (20.2) [4, 131]	1.02 to 2.64	14 : 8
1 to <3	Unknown	1	18 (0.3) [18, 18]	1.24 to 1.24	1 : 0
3 to <46	DDEB	56	1083 (20.8) [1, 84]	3.21 to 45.89	26 : 30
3 to <46	RDEB	245	9931 (191.0) [1, 177]	3.09 to 45.87	129 : 116
3 to <46	Unknown	22	332 (6.4) [1, 55]	3.06 to 37.08	11 : 11
>=46	DDEB	29	550 (10.6) [1, 62]	46.90 to 92.08	13 : 16
>=46	RDEB	23	595 (11.4) [1, 56]	47.70 to 78.37	4 : 19

Age Subgroup* (yrs)	Diagnosis	Patient Count	Total wks (yrs) [Min wks, Max wks]	Age Range (yrs)	Sex Ratio M : F
>=46	Unknown	6	102 (2.0) [2, 41]	51.08 to 82.36	1 : 5

* At the time of first treatment

Human factor study - PRO-HF-02

This study aimed to support removal of the restriction of product preparation in hospital pharmacies only. Of note, home administration by an HCP is approved in the US PI. The main objective was to test the users', HCP and non-HCP, ability to understand and execute multiple defined tasks. The applicant also developed mixing and administration videos, as educational tools to ensure accurate execution of the tasks. The study included 3 different groups, one was a non-HCP (Group C, n=14) who were given access to the PI, disposal and handling information and supplemental educational videos. The other 2 groups were HCPs differentiated by access to the PI alone (Group A, n=17), or, additionally, the supplemental educational videos (Group B, n=18). There were 15 tasks each group had to carry out relating to storage conditions, setting up the space for mixing, thawing, withdrawing with syringe, mixing the suspension and the excipient gels, dispensing the correct dose, assessing wound closure, applying gel to the appropriate wound, cleaning a spill and proper disposal.

Potential anticipated issues and risks were identified and tested in the protocol relating to preparing and administering the medicine. Of note, exposure during preparation and administration, as well as medication errors in clinical or home setting are captured in the RMP safety specification as important potential risks and will be monitored closely in the PASS. The tasks and potential risks identified by the applicant were considered appropriate to ascertain whether the product can be safely and effectively mixed, administered and disposed in the home setting by both a HCP & non-HCP. Examples of the potentials risks include: The shelf-carton or the Vyjuvek gel may be left at the incorrect temperature or beyond the set duration of the proper storage temperature; the incorrect ancillary item may be selected, or an ancillary item may be forgotten; the user may not allow Vyjuvek suspension and the excipient gel proper time to thaw, thus leading to a heterogeneous mixture; the user may attempt to withdraw the excipient gel into the preparation syringe rather than properly withdrawing the Vyjuvek suspension and dispensing it into the excipient gel vial; the user may not mix for the required 10 seconds or may not mix the product vigorously enough; the user may apply Vyjuvek gel to a closed wound, or they could assess an open wound as closed and not apply Vyjuvek gel to that particular wound area; some wounds may receive a lower or higher dose than needed; the dressing may be left too large and cause irritation to the untreated intact skin, the dressing may be cut too small and not completely cover the administration site, or the user does not use a non-absorbent dressing; a spill of product suspension or gel may not be properly cleaned to remove the viral particles; and others. The applicant was requested to capture and monitor all potential risks (part of aRMMs and PASS, see discussion below).

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Vyjuvek programme consisted of a phase 1/2 proof of concept/dose finding study, a phase 3 blinded randomised intra-patient controlled pivotal study and an open label extension study. The total number of new subjects treated in the development programme is limited to 63 different patients: 9 in the phase 1/2, 31 in the pivotal study and 23 in the open label extension study. Some patients from the phase 1/2 were retreated in the phase 2, and some patients form phase 2 were rolled over into the phase 3. All trials were conducted in the USA. The outcome of GCP inspections conducted by FDA at the clinical sites showed no significant deficiencies.

No conventional PK studies were conducted. The product is applied topically to the skin and not absorbed systemically. The applicant performed shedding and immunogenicity studies to detect the virus in the blood and to determine the extent of systemic absorption of the product. Furthermore, immunogenicity studies to detect immune response to the vector and to the transgene were also performed.

Phase 1/2 study KB103-001 was a single-centre, open-label, randomised, intrasubject placebo-controlled study assessing safety and efficacy of topical beremagene geperpavec in DEB treatment. The study was divided into 4 phases: Phases 1, 2a, 2b, and 2c; the inclusion criteria for age and wound size/surface area were:

- Phase 1: ≥18 years old with 2 wounds ≤10 cm^2
- Phase 2a: ≥5 years old with at least 3 wounds ≤20 cm^2
- Phase 2b: ≥2 years old with at least 3 wounds ≤20 cm^2
- Phase 2c: ≥2 years old with at least 2 wounds ≤50 cm^2

Investigational product was applied topically on assigned wounds until the wound closed. Starting dose in phase 1 trial was based on results from the nonclinical toxicity studies: the starting dose of 1×10^8 PFU/day was selected for the first-in-human phase 1 part. Dose escalation in phases 2a (3-6x10^8 PFU/day), 2b (1-1.2x10^9 PFU/day) and 2c (8X10^8 -1.57X10^9 PFU/day) was based on observed safety data and review/approval by the SMC. The dose also varied in the length of administration depending on the size of the wounds and the time the wounds remained open.

Nine subjects were treated. Three subjects were re-treated after a washout period and counted as new patients. The youngest patient was 10 years old. The wound assessments were 30 days apart. Some recurring wounds treated with placebo temporarily closed during treatment. In contrast, recurring wounds treated with active treatment were more likely to close and remain closed. Although the population was small, there was a clinically relevant improvement in wound closure in subjects treated with beremagene geperpavec *vs* placebo. The time to wound closure was shorter and duration of closure a longer with the active product. The phase 1/2 data presented support the proof of concept with some limited histology and electron microscope data.

Phase 3 Study B-VEC-03

Study B-VEC-03 (GEM-3) was a multicentre, intrasubject randomised, placebo-controlled, double-blind, phase 3 study of beremagene geperpavec for the topical treatment of DEB wounds. It consisted of a screening phase, followed by a 26-week treatment phase and a 30-day safety follow-up period (SFU). After the SFU/ early termination, subjects had the option to enrol into an open label extension protocol (B-VEC-EX-

02). If subjects did not participate in the OLE, they were asked to roll over into a long-term follow-up phase in which they are followed for 5 additional years. Each subject served as his/her own control. Two matched wounds were selected in each subject that were similar in size, located similar anatomical regions, and had similar appearance. The matched pair of wounds was randomised, so that one wound received weekly treatment with topical beremagene geperpavec and the other received placebo.

The inclusion criteria were acceptable, and the primary wound sizes varied from approx. 2.3 cm^2 to over 50 cm^2 as the inclusion criteria did not limit the size of the wounds. Most wounds treated with topical beremagene geperpavec (71%) were smaller than 20 cm^2, 19.4% (n=6) ranged from 20 to <40 cm^2 and only 6.5% (n=1) ranged from 40 to 60 cm^2 (i.e. only one subject with a wound > 40 cm^2 received the treatment). It was highlighted that several larger secondary wounds treated with B-VEC showed substantial healing over the course of the phase 3 and OLE studies.

Although the study had a broad age inclusion criterion, there were no subjects below the age of one year or over 44 years. The doses were based on age, wound size and results from the phase 1/2 study, and limited by a maximum weekly exposure. Children aged 0-3 years, 3-6 years and greater than 6 years were put in different dose groups. The dosing regimen was further simplified in the OLE study (B-VEC-EX-02) and this is reflected in the proposed SmPC for ease of administration and to minimise dosing errors. The SmPC was also updated to include instructions on dose *per* wound size i.e. <20 cm^2, 20-40 cm^2 and >60 cm^2.

The primary endpoint was complete wound closure at weeks 22 and 24 or weeks 24 and 26; wound closure between weeks 8 and 12 for the selected wound was considered a key secondary endpoint. Further secondary endpoints included change in pain score as measured using the VAS and change in QOL life score, although difficult to interpret as any change in QOL scores could be the result of treatment with either the active or the placebo. A reduction in VAS score for Vyjuvek treated wounds while changing dressing could be due to improved healing in Vyjuvek treated wounds or due to other factors affecting pain at the time of the dressing change.

Efficacy data and additional analyses

Study 1-phase 1/2 study KB103-001

Three analysis populations were defined:

- Safety – all subjects administered IP (see section on safety below)
- Intent-to-treat (ITT) – all subjects who administered IP and had at least 1 post-dose paired wound assessment
- Per-protocol (PP) population – all subjects who administered IP, had at least 1 post-dose paired wound assessment, and completed the protocol as planned.

The primary endpoints were the proportion of DEB wound sites with complete wound closure from baseline, stratified by the timepoints (weeks 8, 10, and 12). In addition, *p*-values for independence of weekly evaluations (weeks 8, 10, and 12) using the Breslow-Day test were provided. The time to wound closure, defined as the time from the first treatment to complete wound closure (≥90% reduction in wound surface from baseline) was summarised by treatment and compared using log rank test. The duration of wound closure, defined as the time from a complete wound closure to the first reduction in wound surface from baseline to a value below 90%, was given by treatment and compared using log rank test. The study enrolled 9 individual subjects, 3 of whom re-enrolled in a later phase of the study after a washout period. These subjects were counted separately in the different phases, so the total number of subjects enrolled is

considered to be 12. It was clarified that these subjects washed out for approximately three months and contributed with new wounds to the study, except for one chronic dorsal foot wound which continued to treatment in phase 2a and 2b.

All subjects were considered to have completed the study except one, who withdrew after 4 weeks due to an inability to travel. Most subjects (75%) were male, aged 10-35 years (mean 20.3), and all subjects were white.

For the primary endpoint of complete wound closure in beremagene geperpavec -treated wounds compared to placebo-treated wounds at weeks 8, 10, and 12, treatment differences of (n=17) 82.4%, (n=16)41.7%, and (n=14) 71.4% were seen in favour of the active treatment, respectively ($p<0.0001$ based on Cochran-Mantel-Haenszel Test stratified by time points). Since the method of administration, dose, length of treatment and size of wound varied between phase 1, 2a, 2b, and 2c, the numbers in each dose group are small. The median time to wound closure was 13.5 days for actively treated wounds compared to 22.5 days for placebo-treated wounds ($p=0.0216$), and the median duration of wound closure was 103 days for placebo-treated wounds compared to 16.5 days for beremagene geperpavec-treated wounds ($p=0.0009$).

For the secondary efficacy endpoint of IGA scores, active treated wounds had a numerically higher percentage of wound healing compared to placebo-treated wounds over a 3-month period. In PRO pain scale beremagene geperpavec-treated wounds had a numerically lower mean pain score than placebo-treated wounds over a 3-month period. No formal statistical comparison was performed on IGA or PRO pain scales.

The efficacy results of this small study provide sufficient support for a proof-of-concept.

Study 2-Phase 3 Study B-VEC-03

Four population analyses were defined:

- The intent-to-treat (ITT) population included subjects whose primary wounds were randomised regardless of whether they received randomised treatment or not. The ITT population was used for all primary and secondary efficacy analyses and baseline summaries.
- The safety population was defined as all subjects who were administered either beremagene geperpavec or placebo. The safety population was used for all safety analyses.
- The modified intent-to-treat (mITT) population included subjects whose primary wounds were randomised and received beremagene geperpavec or placebo treatment with at least one post-baseline primary endpoint assessment. The mITT population was used for all primary and secondary efficacy sensitivity analyses.
- The per-protocol (PP) population included all safety population subjects who completed the study without major protocol deviations. This population was used for all primary and secondary efficacy sensitivity analyses.

Regarding sample size with 90% power and a 2-sided Type 1 error rate of 5%, 24 subjects (24 wound pairs) were required for a McNemar's test, assuming a response rate of 75% among wounds randomised to beremagene geperpavec and 25% among wounds randomised to placebo. Because the sample size calculation assumed no correlation within subjects, the estimate was conservative. The investigator selected 2 matched wounds (primary wound pair) in each subject that were similar in size, located in similar anatomical regions, and had similar appearance. The matched wound pair was randomised to treatment, so that one wound received weekly treatment with topical beremagene geperpavec and the other received placebo.

Thirty-one subjects were enrolled into the pivotal study, of whom 28 completed it. None of the three withdrawals were for safety or efficacy reasons. Efficacy data from the withdrawn subjects was included in the ITT population. There were 4 subjects excluded from the analysis due to major protocol deviations.

The mean age of subjects was 17.2 years (range 1 to 44) and 19 (61.3%) subjects were paediatric (18 years or younger). The majority of subjects were male (64.5%) and white (64.5%). Ethnicity was equally distributed between Hispanic or Latino (51.6%) and not Hispanic or Latino (48.4%). All subjects had RDEB except 1 who had DDEB. The primary wounds were well matched in size between the treatments with medians of 10.6 cm^2 (mean 14.4) for beremagene geperpavec and 10.4 cm^2 (mean 15.6) for placebo. Primary wound sizes varied in size from approximately 2.3 cm^2 to over 50 cm^2. Based on the mechanism of action of B-VEC (delivery of full length *COL7A1*), genotype is not expected to have an impact on clinical efficacy, which is supported.

The efficacy results for the pivotal trial are compelling. In the ITT population, the number of primary wounds healed at the timepoint of the primary endpoint was 20.9 (67.4%) for the Vyjuvek treated group *vs* 6.7 (21.6%) for the placebo treated group. There was a significant treatment effect observed between treated and untreated groups in the ITT population 45.8% p=0.0019. The primary wound pairs were on the same patient who had the same standard of care, nutrition, trauma to both wounds. Wound closure maintained for at least 2 weeks is a clinically relevant effect. Sensitivity analysis for the mITT, PP populations and analysis of observed and imputed data had a similar outcome with % difference in closure compared to placebo from 41.9% p=0.002-observed data ITT population to 45.9% p=0.007 mITT imputed data population. A similar difference in wound closure compared to treatment with standard of care is observed at other timepoints within the 6 months. Many wounds were closed at both time points i.e. weeks 8/10 and 22/24.

Durability was assessed by considering the proportion of wounds that met the definition of wound healing at both 3 and 6 months (simultaneously met both the primary endpoint and key secondary endpoint). Using this stringent definition, 49.7% of beremagene geperpavec-treated wounds were completely healed compared to only 7.1% of placebo-treated wounds in the ITT population (p=0.002).

Overall, the data supporting efficacy in totality comes from a phase 1/2, pivotal phase 3 trial and an OLE trial. In addition, there are RWE data (in total, n = 423). The primary endpoint of the pivotal trial was met and there was a statistical and clinically relevant difference in wound closure between treatment and placebo groups in all trials. These efficacy data are convincing, although some limitations are noted, e.g. the small size of the pivotal study and the rollover of some patients from phase 1/2 study to the pivotal study. The applicant performed sensitivity analysis excluding 5 subjects who had participated in the phase 1/2 study from the phase 3 analysis. Despite excluding data from these subjects, the primary analysis remains highly significant.

Subgroup analyses for age, gender and race were presented. All age subgroups showed responder rates in favour of beremagene geperpavec; but individual subgroups were not powered to demonstrate statistical significance. Pain severity during wound dressing as assessed by VAS for subjects aged $\geq$6 was a secondary endpoint. A consistent trend of decreased pain was observed across weeks 22, 24, and 26. The applicant also presented the results for PROMs (QoL), which indicate no difference in ED-Q5 parameters and minimal reduction in SKINDEX-29 domain scores. Other potential secondary endpoints to support a treatment benefit would be improvement in pruritis or wound infection. The applicant confirmed that while these aspects were not specifically collected, the AEs/ADRs caused by wound complication or pruritis were collected.

Antibodies against HSV-1 and COL7 were present in a subset of patients after treatment with Vyjuvek; however, their presence was not associated with any observable difference in treatment efficacy or any

specific ADRs. Potential immune related AEs will be monitored as part of routine pharmacovigilance and in the PASS. The sub analysis of vector shedding and immunogenicity from phases 1-3 trials showed no significant systemic dissemination and there were no differences between adults and children except for fewer children being anti-HSV -1 positive at baseline compared to adults. Since Vyjuvek gel is applied to open wounds, the possible age-related differences in skin permeability are unlikely to affect the potential for systemic absorption of the product. Extrapolating the absence of systemic exposure from the older patients is considered reasonable. The product is topically applied with negligible systemic absorption and a negligible risk for integration. Considering that the product will be applied to open wounds, without a robust skin layer present, it is recognised that collecting PK data in children $\leq$6 months would not be feasible.

The indication allows for treatment of children from birth without pivotal data in this population. The applicant provided data to support extrapolation to children from birth to 6 months based on:

- Mechanism of action of the product.
- Clinical manifestations of the disease are similar from birth to children ≥6 months in subjects with the identical underlying genetic, molecular and pathophysiological deficiency.
- Efficacy and safety data from the US OLE study in subjects under 1 year of age. There were 2 subjects treated in this study. One was 186 days old or approx. 6 months. The other patient was 224 days old or approximately 7 months old.
- RWE patients <1 year old treated in the USA /EU. The age ranged from 10 days to 315 days.
- Photographs have been included in the report, which show that treatment with Vyjuvek has resulted in effective timely closure of wounds associated with DEB.

The extrapolation concept to support efficacy in patients less than 1 year is acknowledged given the efficacy demonstrated in older study participants and the issues related to the feasibility of gathering data in the severest subtype of the condition, along with the issues of assessing wound healing in a population suffering incidental wounding through provision of their daily care. The imposed post-authorisation study will have efficacy related variables to ensure consistent approach to data collection relating to wounds and ensuring a specific number of children aged <1 year are enrolled. In the OLE, EU-early access and RWE setting, there were 423 subjects in total exposed to treatment. These data are considered highly supportive but also appropriate to direct the design (choice of variables) of the PASS.

Durability of closure for wounds previously treated in the pivotal study was an exploratory objective in the OLE. In contrast to the pivotal study primary endpoint of complete wound healing, the OLE study focused on a "target area/defined blocks/cluster" as opposed to individual wounds, the rationale being that this reflects real life setting. In addition, the OLE study was safety focused. The location and size of treated target areas be a variable included in the PASS, which is reassuring. The option for administration in the home setting should help minimise issues relating to travel and treatment adherence as these aspects have shown to impact efficacy analysis and how data is collected. The imposed PASS will ensure data is collected and assessed consistently though PSURs, interim report and a 5 year follow up period.

Genetic testing is not explicitly mandated in the PI *prior* to administration but it is implied with the therapeutic indication: *Vyjuvek is indicated for the treatment of wounds in patients with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene, from birth.*

Human factor study - PRO-HF-02

During evaluation, the applicant clarified that while the PRO-HF-02 design included the possible home mixing, this is not a path to pursue for regulatory approval in the initial approval. The CAT supports this approach.

A dedicated questionnaire will be included in the full PASS protocol, covering the product administration in a home setting to assess if accidental exposure occurred, what difficulties patients/caregivers encountered during product administration at home, and if any medication errors occurred. Given the painful nature of the condition, the logistics of wound dressing involved in the pre- and post-administration of this topical treatment and also the fact that this lifelong medicine is to be given on a weekly basis, the rationale for allowing the option of home mixing and administration by a caregiver and patient where appropriate is acknowledged. In principle, there are multiple options relating for mixing and administration:

- Mixing in a hospital pharmacy, and administration and disposal in a hospital/clinic by a HCP;
- Mixing in a hospital pharmacy, and administration and disposal in the home setting by a HCP;
- Mixing in a hospital pharmacy, and administration and disposal in the home setting by a non-HCP;
- Mixing, administration and disposal in the home setting by a HCP;
- Mixing in the home setting by an HCP, and administration/disposal in the home setting by a non-HCP;
- Mixing, administration and disposal in the home setting by a non-HCP.

According to the results obtained in the PRO-HF-02 study, the following conclusions can be made:

Due to the distressful nature of the condition and the unique challenges around wound management, treatment of wounds with a lifelong, weekly topical gel by the caregiver (or patient, if appropriate) is a suitable scenario. The rationale of the HF study based on caregiver and patient feedback was taken into consideration as part of the CAT's assessment and it is the CAT's position that there is insufficient data to support home preparation and mixing by a non-HCP. In summary, based on the entire evidence provided by the applicant and the considerations given to all possible scenarios, the CAT could have considered the following approaches as acceptable:

- Mixing in a hospital pharmacy, and administration and disposal in a hospital/clinic by a HCP;
- Mixing in a hospital pharmacy, and administration and disposal in the home setting by a HCP;
- Mixing in a hospital pharmacy, and administration and disposal in the home setting by a non-HCP;
- Mixing, administration and disposal in the home setting by an HCP;
- Mixing in the home setting by an HCP, and administration/disposal in the home setting by a non-HCP.

The CAT considers that additional data are required in the post-marketing setting to support the following approach: Mixing, administration and disposal in the home setting by a non-HCP.

In line with the proposed SmPC, the applicant clarified that mixing would occur exclusively in a controlled pharmacy setting. In conclusion, the agreed options are:

- Mixing in a pharmacy and application by an HCP in a healthcare setting.
- Mixing in a pharmacy and application by an HCP at home.
- Mixing in a pharmacy and application by a non-HCP at home.

Healthcare setting
Home

Options	Mixing	Application
Mixing in a pharmacy and application by an HCP in a healthcare setting	Pharmacist	HCP
Mixing in a pharmacy and application by an HCP at home	Pharmacist	HCP
Mixing in a pharmacy and application by a non-HCP at home	Pharmacist	Non-HCP

This is supported by the CAT, with clear instructions in the PI and aRMMs reflecting the options captured.

Patient and healthcare provider engagement

In frame of the early dialogue with patient organisations for orphan MAAS, the EMA contacted selected patient and healthcare professional groups with a specific questionnaire. The response of HCPs points to the continuing unmet need in this therapeutic area and the need for gene therapy as a treatment option. Patients and carers note the unmet need and the specific aspects of this disease that affect quality of life, as well as the medicine that could address these issues. Of note, durable wound closure is listed as a desired treatment endpoint. Summary of responses:

HEALTHCARE PROFESSIONAL EXPERIENCE OF: **dystrophic epidermolysis bullosa (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene**
Please include below any aspects that are of particular importance to healthcare professionals, such as standard of care or available treatments and to what extent they cover the intended indication, the treatment duration and if in your view it needs to be optimised, therapeutic/unmet medical needs, what benefits you would hope for in new medicines as well as what level of side effects would consider manageable for patients. Please also mention any aspects about the condition or its treatments that you feel are not well-understood or not sufficiently considered. Please include anything else you feel is important for EMA to know. Please try to keep your main points to 1-2 pages, if necessary, include more details in an appendix. **RESPONSE 1:** Dystrophic epidermolysis bullosa is a rare genetic disorder, which can be severe and have an important impact on the quality of life of the patient and its family. The main challenge are recurrent and chronic wounds for which no specific or curative treatment is available. There is a high therapeutic need. The current possibilities for therapeutic management are symptomatic. Wound dressings, antiseptics are not specifically healing the wounds. Oleogel-S10 (Filsuvez) has been approved by EMA in 2022 and is helpful in healing EB wounds and in reducing symptoms. However, this is not filling the gap. Gene therapy is urgently needed to increase dermal epidermal adhesion on a longer term and avoid

blisters and wounds to recur. On a long term this is the ultimate treatment solution in epidermolysis bullosa.

RESPONSE 2:

RDEB is a monogenic disorder caused by mutations in gene COL7A1, which encodes type VII collagen (C7), a skin structural protein. Its hallmark is a cutaneous and mucosal fragility, leading to a chronic blistering and scarring.

With no curative therapy, nor any effective treatment for secondary severe complications (mainly diffuse chronic non healing wounds, extensive scarring with fibrosis leading to major flexion contractures, pseudo fingers and toes amputation, the risk of septic shocks related to chronic wounds (since birth until adult period) and aggressive skin carcinoma). Pain and pruritus are major and often an untractable symptom. There is a significant burden of wound care (often daily and >60 minutes). RDEB burden is one of the most important burden described in chronic diseases. The burden in all its dimension: physical, psychological but also social and economic burden.

There is an urgent need to explore new strategies.

The current therapeutics are symptomatic and often poorly effective in the most severe forms of RDEB. At present, patient care is centered entirely on wounds dressing, protection from trauma, bandaging and prevention of infection in this devastating group of skin conditions. In fact there is no treatment for healing wounds. Oleogel-S10 (Filsuvez) approved by EMA (2022) is helpful in healing EB wounds in some patients, is a progress but it not a specific treatment and wounds relapse. Gene therapy is the only possibility to correct the specific gene defect with the production of Collagen VII at a level sufficient to cure wounds during a long period avoiding rapid wounds relapse and so, also the secondary complication (pain, itch, infection and fibrosis and perhaps the frequency of carcinoma).

As the skin lesions occur early in the life, and usually at birth in RDEB patients, such treatment is desirable as early as possible in the life of these patients, at best in the first months of life, thereby avoiding complications but also a reduction in stem cells in chronic wounds. A point also to be emphasised in children is the importance of the least traumatic treatment possible in its methods of application.

PATIENT/CARER EXPERIENCE OF:

dystrophic epidermolysis bullosa (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene from birth

Please include below any aspects that are of particular importance to patients/carers, such as quality of life, standard treatments and how acceptable they are, therapeutic/unmet medical needs, what benefits they would hope for in new medicines as well as what level of side effects they would consider acceptable. Highlight if there are large differences between groups of patients/carers about these aspects or if these views are generally similar across the condition. Please also mention any aspects about the condition or its treatments that you feel are not well-understood or not sufficiently considered. Please include anything else you feel is important for EMA to know. Try to keep your main points to 1-2 pages, if necessary, include more details in an appendix.

RESPONSE:

The information below comes primarily from experiences and views of people with or caring for someone with severe recessive dystrophic EB. This is followed by people with or caring for someone with intermediate recessive dystrophic EB or intermediate dominant dystrophic EB. There are many shared experiences and views between these three subtypes. Many of these would not be shared by someone with localised dystrophic EB.

Quality of life including issues and challenges faced daily

Overall, the burden generated by DEB is huge, and quality of life for both a patient and their carer(s) is extremely poor. Asides from managing numerous chronic wounds and the associated pain, pruritus, and infection, patients must navigate the daily challenges of a large number of comorbidities including osteoporosis; anaemia; pseudosyndactyly; oesophageal dysphagia and stenosis; squamous cell carcinoma; fatigue; emotional and psychological distress; severe malnutrition; and gastrointestinal, ophthalmologic, and oral complications among many others that affect every moment of their lives from birth. Incredibly painful wound care procedures can take anywhere from 2-4 hours up to 6-7 hours *per day* resulting in little to no time to commit to education, work, or social activities. Physical limitations from fatigue and deformities can greatly affect opportunities to study or work impeding the ability to make a living and inciting the stress that this situation induces. These limitations can also result in a lack of independence and a great reliance on others to carry out everyday tasks and activities. Emotional and psychological distress is arguably at its pinnacle as a patient transitions through puberty to adulthood when they are forced to contend with the prognosis of their condition and their own mortality.

For carers (usually the parents), their life revolves around managing the condition of their child. It is not uncommon for one parent to stop working in order to become a carer. Even in this case, additional care or nursing support is usually required to help the family. Many carers carry out wound care procedures in the evening when a child is sleeping or has less pain; this usually extends into the night depriving the carer of their own time to rest adequately. Emotionally, it is a huge challenge, from knowing that a dressing change is causing pain to a child, managing a child's expectations and limitations, to being confronted with comments and glances from strangers. Carers often develop bouts of depression and burnout witnessing a person they love suffer every day. There have been known instance of carer suicide.

Standard treatments, their acceptability, and shortcomings

Wound care *Standard treatments*: full body check to look for (a) new blisters to lance and wounds to cover, (b) signs of infection and deterioration, (c) necessity to debride wounds, (d) signs of suspicious areas that might be suggestive of an SCC. Wounds are covered with a contact layer, a secondary layer, and fixtures to keep them in place, such as a tubular bandage. Patients may also use creams, ointments, and gels to either dry or moisturise the skin depending on need, and to manage infection. Suitability and effectiveness of these products vary greatly from patient to patient. Carers have the additional task of spending hours preparing dressings, cutting them to size for different parts of the body, ordering supplies, and arranging them. *Acceptability*: well below par. Wounds either do not heal or, if they do heal, they can easily re-open again. There is never a feeling of any positive achievement in the treatment of wounds. *Shortcomings*: extremely difficult to keep dressings fixed on moveable parts of the body, such as joints. Constant covering of the wound with the wound contact layer and dressings leads to increased skin temperature, which stimulates

bacterial/candida growth and colonisation with biofilm creation. Dressing changes are extremely time consuming and cause an awful lot of pain.

Surgery *Standard treatments*: surgery, which is needed to restore, to the extent that is possible, normal function to the hands and the oesophagus, or the removal of cancerous scar tissue. Outpatient procedure that is required to fit a PEG tube placement. *Shortcomings*: the effect of surgery is brief as repeat surgeries are required both for SCC and function restoration surgeries. For the latter, the processes usually take months of multiple interventions, healing, recovery, and rehab, which patients often skip altogether because of the pain of these processes, which does not compensate for the momentary benefits the surgery brings.

Pain relief *Standard treatments*: A variety of analgesics and psychological therapies. *Shortcomings*: There is a distinct lack of any residual and effective pain relief. In the case of opioids, patients can end up suffering from opioid-induced hyperalgesia (OIH).

Therapeutic/unmet medical needs

Curative therapies Preventive therapies Palliative treatments

There is currently no therapy that prompts permanent wound closure, increased durability of fragile skin, decreased thickening of skin that leads to pseudosyndactyly, and long-lasting pain relief.

There is a distinct lack of preventive care options for EB. Tackling inflammation and fibrosis, which greatly contribute to the lifelong presence of skin blistering and partial-thickness wounds result in pruritus, pain, scarring, deformity, loss of function, and immobility as well as high-risk complications, such as infection and aggressive SCCs.

There are currently no treatments that have an antibacterial effect without containing antibiotic or steroid ingredients, that do not stick to the wound bed when applied (such as gels), or that do not stimulate bacteria/candida growth. There is need for a wound dressing that can be fixed easily on a wound of any type or size, and on any location; stay on the wound for an extended amount of time eliminating daily dressing changes; and that has a cooling effect in high temperatures and a warming effect in low temperatures.

Other

There is little focus on psychological support for patients and carers, and treatments/research into target areas of the body, such as the oral cavity and internal organs that go beyond the current ones available.

Benefits hoped for in new medicines

A systemic therapy that treats the internal as well as external issues of EB. Curative therapies to break the cycle of "blister, wound, heal, repeat". Permanent healing of external (skin) and internal (mucosa) wounds coupled with strengthened skin would eliminate chronic symptoms and triggered comorbidities, and potentially lead to a halt and/or reversal of physical deformities leading to a profoundly improved quality of life.

Level of side effects considered acceptable

This is highly subjective and difficult for patients/carers to answer without knowing the intended benefit of a therapy or device, and how much this benefit will ultimately outweigh any side effects potentially experienced. Commonly tolerated side effects for *noticeable* and *endured improvement*

include slight increase in temperature, mild additional pain (from headaches to local pain, pruritus, numbness), some gastrointestinal effects, and some fatigue, weakness, cough, colds, etc. A side effect that would adversely affect the skin would not be tolerated.

Aspects about the condition or its treatments that are not well-understood or not sufficiently considered.

Expression of the condition, internal effects of the condition, pain and pruritus, high temperature phenomenon, antibiotics, chronicity of wounds and risk of infection, comorbidities, the financial burden

CAT comments:

The response of HCPs points to the continuing unmet need in this therapeutic area and the need for gene therapy as another treatment option. Patients and carers reflect the unmet need and to specific aspects of the disease that affect quality of life and the ideal medicine that could address all of these issues. Of note, durable wound closure is listed as a desired endpoint for a treatment.

2.5.7. Conclusions on the clinical efficacy

Based on the efficacy data obtained in the clinical development programme of beremagene geperpavec support its use in the following indication:

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

The topical suspension gel is to be applied weekly to open surface wounds with specific mixing, administration and disposal instructions to support the administration. Upon CAT's request for further data from the RWE and OLE study, the provided data were considered relevant to conclude on the totality of the efficacy data and furthermore, to support the appropriate design of the category 1 PASS (see section on clinical safety), which will include efficacy variables as secondary objectives.

The CHMP endorses the CAT conclusion on clinical efficacy as described above.

2.5.8. Clinical safety

2.5.8.1. Patient exposure

Safety data were collected from 2 completed randomised placebo-controlled studies and from the OLE study (see Table 15). One integrated database was created to combine these data at the individual subject level from phase 1/2 (KB103-001) and pivotal phase 3 study (B-VEC-03). In the pooled safety data, the subject numbers were kept the same as in KB103-001 and B-VEC-03. Subjects who participated in more than one phase/protocol were analysed as separate subjects because they were treated for different wounds on different treatment schedules with adequate washout(s) to separate their exposures. For the pooled safety analysis from the two controlled studies, the population was 43 subjects, 12 in the phase 1/2 study and 31 in the phase 3 study.

Table 11 Patient exposure (cut off)

Study ID Report No. & Country of Sites Dates Status	Study Design	Key Inclusion Criteria	Enrollment Gender Age (Years)	Treatment	Safety Variables
KB103-001 KB103-001 CSR 1 US site 06 May 2018 to 01 Nov 2019 Completed	Single-center, open-label, intrasubject randomized, placebo-controlled	≥2 years of age; diagnosis of RDEB confirmed by genetic testing, IF, IEM, and confirmed *COL7A1* mutations; wounds Phase 1: ≤10 cm^2; Phase 2a and 2b: ≤20 cm^2; and Phase 2c: ≤50 cm^2	12 subjects[a] enrolled/ 11 completed 9 M/3 F 10 to 35 years (mean 20.3)	Topical treatment with B-VEC or placebo (vehicle) gel Unit dose varied by study phase, ranging from 1×10^8 to 6×10^8 PFU per ≤20 cm^2 wound area	• AEs • clinical laboratory evaluations • vital signs • physical examinations
B-VEC-03 (also GEM-3) B-VEC-03 CSR 3 US sites 17 Aug 2020 to 29 Oct 2021 Completed	Multicenter, double-blind, intrasubject randomized, placebo-controlled	≥6 months of age; diagnosis of DDEB or RDEB confirmed by genetic testing including COL7A1; 2 cutaneous wounds similar in location and appearance	31 subjects[b] enrolled/ 28 completed 20 M/11 F 1 to 44 years (mean 17.2), including 19 subjects ≤18 years	Topical treatment with B-VEC or placebo (vehicle) gel Dose/wound varied by wound area: 4×10^8 PFU for <20 cm^2 8×10^8 PFU for 20 to 40 cm^2 1.2×10^9 PFU for 40 to 60 cm^2 Maximum weekly dose varied by age: 1.6×10^9 PFU for ≥6 mo to <3 years 2.4×10^9 PFU for ≥3 yrs to <6 years 3.2×10^9 PFU for ≥6 years Treatment duration: once weekly for 26 weeks	• AEs • clinical laboratory evaluations • vital signs • physical examinations

Study ID Report No. & Country of Sites Dates Status	Study Design	Key Inclusion Criteria	Enrollment Gender Age (Years)	Treatment	Safety Variables
B-VEC-EX-02 B-VEC-EX-02 CSR 5 US sites 25 May 2021 to 31 July 2023 Complete	Open-label treatment extension for subjects who completed B-VEC-03 and for newly enrolling subjects with DEB	From birth; diagnosis of DDEB or RDEB confirmed by genetic testing including *COL7A1*	47 subjects enrolled (24 rollover, 23 naïve) 0.5-45.9 years (mean 16.5), including 26 subjects ≤18 years	Topical treatment with B-VEC gel Maximum weekly dose per subject =10^9 PFU/mL Subjects <3 years received half the volume of subjects ≥3 years Treatment duration: Up to 112 weeks	• AEs

AE=adverse event; COL7=collagen VII; CSR=clinical study report; DEB=dystrophic epidermolysis bullosa; DDEB=dominant DEB; M=male; SAE=serious adverse event

a: Includes 3 subjects who were re-enrolled in a later phase for treatment of different wounds after approximately 3-month washout (Table 2).

b: Includes 5 subjects who also participated in KB103-001 (Table 2).

Doses evaluated: A range of unit doses and dose frequencies were initially explored in the phase 1/2 study. Wounds measuring ≤20 cm^2 were given a unit dose between 1×10^8 (the first-in-human starting dose) to 1.2×10^9 PFU. The single subject who participated in phase 2c and had a 65.3 cm^2 wound received unit doses up to 1.57×10^9 PFU. Depending on wound size, number of wounds treated, and frequency of treatment, the maximum weekly dose *per* subject in phase 2 ranged from 1.2×10^9 PFU/week to 6.0×10^9 PFU/week (median 4.2×10^9 PFU/week). The estimated maximum weekly topical dose received in each phase of the phase 1/2 study were: phase 1: ~2×10^8 PFU/week; phase 2a: ~6×10^9 PFU/week; phase 2b: ~6×10^9 PFU/week; phase 2c: ~9×10^9 PFU/week.

The doses selected for phase 3 study were based on phase 1/2 study, and subjects were administered a unit dose of 4.0×10^8 PFU *per* 20 cm^2 of wound area, well within the range of 1.0×10^8 to 1.2×10^9 PFU administered in phase 2. Since the phase 3 study enrolled younger patients than in the phase 1/2 study, the maximum weekly dose was reduced for younger age groups to account for lower average body surface area; the maximum weekly doses used in phase 3 based on the subject's age were: ≥6 months to <3 years dosed

at 1.6 $\times 10^9$ PFU/week; ≥3 years to <6 years dosed at 2.4 $\times 10^9$ PFU/week; ≥6 years dosed at 3.2 $\times 10^9$ PFU/week.

2.5.8.2. Adverse events

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 for the phase 1/2 study and version 24.1 for the phase 3 study. All AEs were treatment-emergent (newly appeared, increased in frequency, or worsened in severity on or after the initiation of active treatment).

An overview of AEs by study and pooled is provided in Table 12 (A, B, C).

Table 12 A -Overview of AEs (Safety Population): Study KB103-001 (N=12)

Total number of adverse events (AEs)	35
Subjects with at least one: n (%)	
AE	9 (75.0)
Drug-related AE	4 (33.3)
Severe AE	0
Serious adverse event (SAE)	0
Drug-related SAE	0
SAE leading to death	0
AE leading to premature discontinuation of treatment	0
AE leading to premature discontinuation of study	0
Deaths	0

Table 12 B -Overview of AEs (safety population): Study B-VEC-03 (N=31)

Total number of adverse events (AEs)	45
Subjects with at least one: n (%)	
AE	18 (58.1)
Drug-related AE	1 (3.2)
Severe AE	2 (6.5)
Serious adverse event (SAE)	3 (9.7)
Drug-related SAE	0
SAE leading to death	0
AE leading to premature discontinuation of treatment	0
AE leading to premature discontinuation of study	0
Deaths	0

Table 12 C -Overview of AEs (safety population): pooled (N=43)

Total number of adverse events (AEs)	80
Subjects with at least one: n (%)	
AE	27 (62.8)
Drug-related AE	5 (11.6)
Severe AE	2 (4.7)
Serious adverse event (SAE)	3 (7.0)
Drug-related SAE	0
SAE leading to death	0
AE leading to premature discontinuation of treatment	0
AE leading to premature discontinuation of study	0
Deaths	0

Common AEs: The most frequently reported TEAEs across both studies were Pruritus for 4 subjects (9.3%) and erythema, rash, chills, and squamous cell carcinoma (SCC), each reported for 3 subjects (7.0%).

All AEs in both studies were mild or moderate in severity, except for 4 AEs in the phase 3 study that were considered to be severe. The severe events were all SAEs and involved hospitalisation: Cellulitis, anaemia (2 events) and diarrhoea. All of these SAEs resolved. In the phase 1/2 study, 4 subjects had AEs that the investigator considered to be at least possibly related to IP. Among 4 subjects in the phase 1/2 study, the 19 drug-related AEs were injection site pain, purulent discharge (at wound), swelling, application site pruritus, erythema, rash, fatigue, feeling cold, injection site erythema, product taste abnormal, pyrexia, throat irritation, and wound complication (itch on arm wounds). Twelve of the 19 events were associated with intradermal injections. All of these events were reported as mild and resolved. In the phase 3 study, 1 subject had 1 AE reported as possibly related to IP. Erythema in one subject was reported as mild and resolved; the subject was 1 year old and heavily wrapped. The study centre reported intermittent erythema beneath the wound dressings on the intact and untreated skin, and considered it to be a general observation, not target area specific.

Selected AEs: These were identified primarily on the basis of the safety experience among the 31 subjects who participated in the phase 3 study. Phase 1/2 data were not taken into consideration because of the open-label nature of the study design, different dosing regimens used, and the fact that most drug-related events observed were associated with the intradermal route of administration, which was only used to establish evidence of molecular correction, was not included in phase 3, and is not intended for commercial use.

The AEs included in the SmPC (sec. 4.8) are listed by MedDRA system organ class and preferred term. The frequency of adverse reactions is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data:

System organ class	Common
Skin and subcutaneous tissue disorders	Pruritus Erythema Rash
General disorders and administration site conditions	Chills
Respiratory, thoracic, and mediastinal disorders	Cough Rhinorrhea

2.5.8.3. Serious adverse event/deaths/other significant events

No SAEs occurred in the phase 1/2 study. Three subjects in the phase 3 study experienced 5 SAEs. No deaths were reported during either study.

Squamous cell carcinoma (SCC) of the skin was reported in 3 subjects in the phase 3 study. SCC is frequently diagnosed in patients with DEB, who are known to be at increased risk for skin cancer due to chronic wound healing. The timing and location of the reported cases of SCC in this phase 3 study are not consistent with causality. In all 3 subjects, SCC occurred at sites that were not directly exposed to the treatment.

The System Organ Class (SOC) with the most frequent AEs were Skin and subcutaneous tissue disorders and General disorders and administration site conditions. Local application site and injection site AEs were more commonly reported in the phase 1/2 study where intradermal injections were performed into intact skin to establish evidence of molecular correction. In the phase 3 study, which involved topical administration only, the only AEs in General disorders and administration site conditions reported were fatigue, pyrexia, and chills, none of which were considered by the investigator to be drug related.

2.5.8.4. Laboratory findings

Haematology and serum chemistry: In the phase 1/2 study, there were no clinically significant changes in laboratory parameters, including liver enzymes. Changes from baseline were usually less than 10%, showed no distinct shifts over time, and were consistent with medical history findings or were associated with AEs deemed unrelated to treatment by the investigator. In the phase 3 study, among hematology parameters, low hemoglobin consistent with mild anemia was common at baseline. Mild leukocytosis was also common at baseline consistent with the treatment population. Three subjects had significant leukocytosis (~20K) at baseline. Three subjects had low glucose values related to laboratory artifact (possibly due to prolonged exposure of serum to cells). There were no clinically meaningful changes in haematology and serum chemistry values associated with treatment.

Vital signs: Vital signs were unremarkable except for a few cases of mild tachycardia at baseline in B-VEC-03. There were no clinically meaningful changes in vital signs related to treatment in either study.

Physical examination findings: In both studies, abnormal findings on physical examinations were related to DEB and included scarring, blistering, oral erosions, eye erosions, and infection. There were no new notable findings during study treatment.

2.5.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.5.8.6. Safety in special populations

Overviews of AEs for subgroups based on age category, gender, and race are provided in Table 13, Table 14, and Table 15, respectively. There were no apparent clinically relevant differences in the occurrence of AEs by these subgroups, although the number of subjects in many of these subgroups was very limited. The demographic characteristics of the 3 subjects who experienced SAEs varied: 1 was a 19-year-old American Indian or Alaska native male, 1 was a 10-year-old Asian male, and 1 was a 23-year-old white male.

Table 13 Overview of Adverse Events by Age Category (Safety Population)

	≤12 Years			>12 and ≤18 Years			>18 Years		
Parameter	KB103-001 (N=1)	B-VEC-03 (N=10)	Pooled (N=11)	KB103-001 (N=5)	B-VEC-03 (N=9)	Pooled (N=14)	KB103-001 (N=6)	B-VEC-03 (N=12)	Pooled (N=18)
Total number of adverse events (AEs)	2	12	14	15	9	24	18	24	42
Subjects with at least one: n (%)									
AE	1 (100)	6 (60.0)	7 (63.6)	4 (80.0)	4 (44.4)	8 (57.1)	4 (66.7)	8 (66.7)	12 (66.7)
Drug-related AE	0	1 (10.0)	1 (9.1)	1 (20.0)	0	1 (7.1)	3 (50.0)	0	3 (16.7)
Severe AE	0	1 (10.0)	1 (9.1)	0	0	0	0	1 (8.3)	1 (5.6)
Serious adverse event (SAE)	0	1 (10.0)	1 (9.1)	0	0	0	0	2 (16.7)	2 (11.1)

Table 14 Overview of Adverse Events by Gender (Safety Population)

	Male			Female		
Parameter	KB103-001 (N=9)	B-VEC-03 (N=20)	Pooled (N=29)	KB103-001 (N=3)	B-VEC-03 (N=11)	Pooled (N=14)
Total number of adverse events (AEs)	15	28	43	20	17	37
Subjects with at least one: n (%)						
AE	6 (66.7)	13 (65.0)	19 (65.5)	3 (100)	5 (45.5)	8 (57.1)
Drug-related AE	2 (22.2)	1 (5.0)	3 (10.3)	2 (66.7)	0	2 (14.3)
Severe AE	0	2 (10.0)	2 (6.9)	0	0	0
Serious adverse event (SAE)	0	3 (15.0)	3 (10.3)	0	0	0

Table 15 Overview of Adverse Events by Race (Safety Population)

	White			American Indian or Alaska Native			Asian		
	KB103-001 (N=12)	B-VEC-03 (N=20)	Pooled (N=32)	KB103-001 (N=0)	B-VEC-03 (N=5)	Pooled (N=5)	KB103-001 (N=0)	B-VEC-03 (N=6)	Pooled (N=6)
Total number of adverse events (AEs)	35	24	59	0	8	8	0	13	13
Subjects with at least one: n (%)									
AE	9 (75.0)	10 (50.0)	19 (59.4)	0	3 (60.0)	3 (60.0)	0	5 (83.0)	5 (83.0)
Drug-related AE	4 (33.3)	1 (5.0)	5 (16.0)	0	0	0	0	0	0
Severe AE	0	0	0	0	1 (20.0)	1 (20.0)	0	1 (16.7)	1 (16.7)
Serious adverse event (SAE)	0	1 (5.0)	1 (3.1)	0	1 (20.0)	1 (20.0)	0	1 (16.7)	1 (16.7)

Pregnancy: No data are available about beremagene geperpavec use in pregnant women and there is no information on its presence in human milk, or its effects on the breastfed infant. No nonclinical reproductive or developmental toxicity studies were conducted. The use of Vyjuvek is not recommended in pregnancy.

2.5.8.7. Safety related to drug-drug interactions and other interactions

Studies on potential drug-drug interactions with B-VEC have not been conducted. The applicant discussed potential interactions with Filsuvez (authorised for the treatment of DEB). Whilst there is no biological reason to expect an interaction with Filsuvez, no study has been conducted. Therefore, concurrent administration should be avoided. The SmPC limits the use of concomitant topical medications at the wound site when Vyjuvek is administered.

2.5.8.8. Discontinuation due to adverse events

In the pooled analysis, most subjects completed the planned treatment period. In study KB103-001, 5 subjects were discontinued by sponsor due to administrative purposes; they were considered to have completed the study. Overall, 4 subjects withdrew from the studies (1 in KB103-001 and 3 in phase 3), see Table 16.

Table 16 Summary of Disposition and Reasons for Discontinuation During the Treatment Period (Safety Population): Pooled

	(N=43) n (%)
Completed	34 (79.1)
Discontinued	9 (20.9)
Reason for Discontinuation	
Other (Sponsor's Decision)	5 (11.6)
Withdrawal by subject	4 (9.3)

2.5.8.9. Post marketing experience

There is no information on the use of Vyjuvek in the applied indication in the EU. The applicant provided update on the AE reports in the US to FDA, and their analysis did not identify new safety issues with beremagene geperpavec that required any regulatory action.

2.5.9. Discussion on clinical safety

The safety population in the clinical trials with beremagene geperpavec is limited, mainly due to the rarity of the condition. The median length of treatment in the phase 3 trial was 24 weeks, ranging from 1 to over 26 weeks. In the OLE study, the exposure duration was a median of 642 for rollover subjects and 344 days for treatment naïve subjects. Twenty-nine of 47 subjects (62%) had over 1 year of exposure. All subjects had a genetically confirmed diagnosis of DEB which was recessive in all cases except one. The dominant phenotype in this case was severe. The mean age of subjects treated was 18 and most patients were male Caucasians. The mean size of the primary wound area treated was 11.5cm^2.

In the integrated safety database (phase 1/2 and phase 3 studies), subjects who participated in more than one phase were analysed separately as they were treated for different wounds, on different treatment schedules with adequate washout periods. Thus, the pooled safety data for B-VEC are based on the outcomes of 43 patients from both studies, KB103-001 (n=12 patients) and B-VEC-03 (n=31 patients). From a safety aspect, the CAT debated if a new wound, in a previously enrolled patient, is equivalent to a new patient. Overall, 8 patients were re-enrolled, but it cannot be completely excluded that if 8 new patients were enrolled, their safety profile might be distinctive. However, in this specific setting and considering the nature of the disease, and the proposed topical administration *per* wound, the applied scenario reflects real life and clinical picture of patients.

In the OLE study, half of enrolled patients were naïve, the other half has rolled over from the pivotal study. In this safety focused study, there were no differences in safety profiles reported for the 2 groups, despite the difference in treatment exposure. As of data cut off Nov 2024, there were no safety signals reported.

Extrapolation exercise was conducted for efficacy, safety, and dosing from the source population (DEB subjects >1 year) to the target population (DEB subjects from birth to 1 year of age). This was considered acceptable for indication granting, nevertheless, further data will be gathered in the post-marketing phase. In addition, as of July 2024, 10 patients >1 of age were exposed to B-VEC, including open label access and post-marketing in the US or early access real-life experience in Europe representing 5.2 patient-years' experience.

Eighty AEs were reported for 9 (75.0%) subjects in the phase 1/2 study and 18 (58.1%) in the phase 3 study. AEs considered by the investigator to be at least possibly related to B-VEC were reported for 5 (11.6%) subjects. Three subjects experienced SAEs (all in the phase 3 study); none was drug related. There were no deaths, and no AE led to premature treatment discontinuation. The most frequently reported TEAEs across both studies were pruritus for 4 subjects (9.3%) and erythema, rash, chills, and squamous cell carcinoma (SCC), each reported for 3 subjects (7.0%). SCC is associated with the disease, and for some patients was a reason to pause the treatment to focus on managing this diagnosis. The applicant considered that it is unfeasible to conduct a prospective study to assess the potential impact of B-VEC on SCC occurrence. SCC is not underdiagnosed in these patients; the potential signal will be detected through standard pharmacovigilance practice, which is acceptable. The PI also states that treatment should not be applied to wounds with a confirmed or suspicious diagnosis of SCC. While wound infection or non-closure, were reported as AEs, wound complications as such were not specifically collected. Hence, wound specific data will be gathered in the PASS.

The presence of anti-HSV-1 or anti-COL7 antibodies did not have an obvious impact on efficacy or safety of the tested product. However, the number of subjects was limited. Repeated dosage could theoretically over time impact efficacy due to the antibody mediated immune response. Further monitoring of immune related AEs will occur as part of routine pharmacovigilance practice and if any immune related AEs are reported, blood samples might be collected to detect antibodies against HSV-1 and COL7, if feasible. Given the nature of this dermatological condition, assessment of wound response and closure should mitigate the theoretical risk on durability of effect due anti-drug antibodies. Wound related variables are being assessed in the PASS and as part of routine PV if any immune related adverse events are reported, the treating physician will be asked to collect blood samples to evaluate antibodies against HSV-1 and COL7 to evaluate its impact. It is important to consider that additional or routine blood testing is challenging due to the nature of the condition.

No discontinuation related to AEs was reported, but 85% of the patients in OLE study discontinued for other reasons: 1% lost in follow-up, 72.3% for study termination by sponsor and 10.6% in withdrawal by subject. The main reasons were the lack of safety signals, the median follow-up of patients in the study had reached 1

year, the number of newly treated patients in the OLE extension matched the number rolled over form the phase 3 and the product became commercially available in the USA. Furthermore, it was clarified by the applicant that the study closure date mainly related to logistical reasons (travel and administration) emphasising the need for the option of local treatment administration. The were no safety reasons identified.

The proposed indication allows for treatment of children from birth. Children less than 6 months old were not enrolled in the pivotal study. The applicant provided real world data to support extrapolation to children from birth to 6 months, including data with 12 patients <1 year old treated as of November 2024. Further information will be collected in the imposed PASS. All safety concerns are captured in the PASS as objectives, which is agreed by the CAT.

The OLE and RWE data presented were uncontrolled and the collected photographs considered supportive. The missed doses or missed visits in the OLE study were clarified to be mainly due to logistics and not safety. Although discontinued early due to commercial reasons, the OLE does provide further data concerning long term safety and exposure as patients were able to continue treatment and data were captured as RWE (n=44).

Long term follow-up of patients (especially children <6 months) is required as this is currently captured as missing information in the RMP. The requested CAT/CHMP category 1, imposed PASS was accepted by the applicant, and included as an Annex II condition of the MA. The study primary objective includes monitoring of concerns captured in the safety specification which is supported by the CAT. This involves long term safety in patients less than 6 months old. Secondary objectives are: monitoring of medication errors in the clinical/home setting, occurrence of accidental exposure of Vyjuvek to HCPs, caregivers and close contacts, effectiveness of defined aRMMs, effectiveness of Vyjuvek in real-life clinical practice. The following variables will be subject to collection in the PASS: baseline demographics, DEB diagnosis (incl. subtype), medical history, concomitant medications and comorbidities, location and size of treated wounds, exposure to Vyjuvek, (incl. reasons for discontinuation), AEs, medication errors, effectiveness of the aRMM, response to patient-reported outcome (PRO) questionnaires. Specific variables are set for paediatric patients less than 3 years (relevant to safety of dosing larger body surface area in children).

Duration of the PASS is supported by the CAT: 2-year enrolment period (approx. 143 patients in US, France and Germany), followed by a 5-year follow-up period. It is noted that a 2-year period between end of data collection and final study report availability will need to be considered further when the final PASS protocol is submitted to for agreement to the PRAC. Further PASS details are discussed in the section on RMP (see below).

Furthermore, the applicant provided reports on quarterly Periodic Adverse Drug Experience Report (PADER) submitted to FDA covering the period from for period 20 Aug 2023-18 Aug 2024. No new safety issues with Vyjuvek were found that required regulatory action.

The CAT considered the totality of the safety data provided (clinical development programme, OLE, RWE, FDA reports) and the lack of major safety concerns, the commitment to conduct the imposed PASS where long-term safety data will be gathered enabling for better safety profiling of Vyjuvek, are sufficient at this stage.

The ADRs captured in the PI are cough, rhinorrhoea, pruritus, erythema, rash and chills. From the safety database all the adverse reactions reported in clinical trials have been included in the SmPC.

2.5.10. Conclusions on the clinical safety

In the clinical development programme, Vyjuvek was well tolerated, with few AEs and ADRs, mainly limited to skin disorders (pruritus, erythema and rash), chills, cough and rhinorrhoea. Some concerns were raised to better characterise the products tolerance and safe use in the context of the clinical setting, notably the home setting. The first Human factor study submitted (PRO-HF-01) study focused on B-VEC administration by an HCP (notably a nurse) but could not support safe administration to be made by the patient or the caregiver. Upon CAT's request, the final human factor validation report (PRO-HF-02) was provided, to support administration, and safe disposal of the product by both an HCP or a non-HCP in the home setting, provided that the preparation/mixing step is performed in a controlled pharmacy. Hence, following the mixing and preparation of the product in the controlled pharmacy environment, there is the option for home administration by a non-HCP with appropriate training as outlined in the RMP and PI.

As additional safety information, quarterly PADERs submitted to FDA were also provided to the CAT. The analysis of the spontaneously reported safety data did not identify new safety issues with beremagene geperpavec requiring regulatory action. Therefore, the CAT concluded that based on these reports, the safety profile of beremagene geperpavec remains unchanged from that observed in the clinical development.

The applicant confirmed that as of data cut off (November 2024), there was no safety signals reported for the 423 patients treated to date in the real-world setting, which includes patients enrolled into the OLE study and EU-early access. Of these, 408 were treated in the home setting.

Lack of long-term safety, and safety in patients less than 6 months of age are captured as missing safety information in the RMP. The CAT concluded that it is this information should be investigated in a post-marketing period. Therefore, the applicant committed to conduct a PASS as a condition to the MA. The primary objective of the study will be long-term evaluation of the occurrence of treatment related AEs in DEB patients treated with Vyjuvek. This will include the assessment of the safety of Vyjuvek in less than 6 months old DEB patients, the follow up of AEs with delayed manifestation, and treatment discontinuations/interruptions due to safety reasons.

The CAT considers the following measures necessary to address the missing safety data:

Description	***Due date***
Non-interventional post-authorisation safety study (PASS): In order to further characterise the long-term safety of Vyjuvek in patients with dystrophic epidermolysis bullosa with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene, including patients less than 6 months of age, the MAH should conduct and submit the results of a prospective, non-interventional, multi-country study in patients treated with Vyjuvek in a real-life clinical setting.	*Final report: 31 December 2034*

The CHMP endorses the CAT conclusion on clinical safety as described above.

2.6. Risk Management Plan

2.6.1. Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Exposure of HCP and caregivers to Vyjuvek during preparation or administration Accidental exposure of Vyjuvek from patient to close contacts or HCP via direct contact with administered wounds or body fluids Medication errors in the clinical and home setting
Missing information	Long-term safety Safety in patients less than 6 months of age

2.6.2. Pharmacovigilance plan

Post surveillance safety study (PASS) synopsis:

PASS-01 is a prospective, non-interventional, multi-country study to confirm the long-term safety profile, including in paediatric patients less than 6 months of age, receiving Vyjuvek for the treatment of DEB wounds, in a real-life clinical setting.

Research question and Study Objectives

The **primary research question** of the study is:
What is the long-term safety profile, including in paediatric patients less than 6 months of age, receiving Vyjuvek for the treatment of DEB wounds, in a real-life clinical setting?

The **primary objective** of the study is to evaluate the occurrence of treatment related adverse events in patients with DEB treated with Vyjuvek as ascertained by the treating healthcare professional. The study primary objective will include the monitoring of:

- Long term safety (including occurrence of adverse events with delayed manifestation, treatment discontinuations/interruptions due to safety reasons)
- Safety in patients less than 6 months

As **secondary objectives**, this study will evaluate:

- the occurrence of medication errors;
- the occurrence of accidental exposure of Vyjuvek to HCPs, caregivers and close contacts;
- the effectiveness of the additional Risk Minimization Measures (aRMM), as defined in the Risk Management Plan, aimed at reducing accidental exposure and medication errors, particularly in the home setting.
- the effectiveness of Vyjuvek in real-life clinical practice.

Study design

This PASS is a prospective, non-interventional, multi-country and multi-centre study, based on primary data collection, to be conducted in US, Germany and France (additional countries may be added if needed to achieve the projected sample size). The study will have a 2-year enrolment period, followed by a 5-year follow-up period.

All patients with DEB receiving treatment with Vyjuvek and meeting the inclusion/exclusion criteria will be documented in the study. The prescribing physician's decision that Vyjuvek treatment is in the patient's best interest is to be made before and independently of his/her decision to invite the patient to participate in the study. At all times during the study, patients will be treated and monitored according to the approved Vyjuvek label (Summary of Product Characteristics in EU and Prescribing Information in US), the prescribing physician's routine clinical practice and no additional clinical visits or invasive tests will be performed.

To fulfil the primary and secondary objectives of the study, data will be collected on the variables listed below when patients attend their standard of care visits, which are expected to occur approximately every 3 to 6 months.

Population

Patients with DEB receiving treatment with Vyjuvek and close contacts such as treating HCPs and caregivers.

Inclusion criteria

Patients have to meet all of the following criteria to be included:

1. According to the prescribing physician, it is in the patient's best interest to receive Vyjuvek for the treatment of DEB
2. The decision to start treatment with Vyjuvek has been made before and independently of the decision to include the patient in this study
3. Written informed consent is obtained from the patient (or legally acceptable representative, if the subject is unable to provide informed consent)

Exclusion criteria

The patient's treatment is not in accordance with the approved Vyjuvek label (Summary of Product Characteristics in EU and Prescribing Information in US).

Variables

The following variables will be documented during the follow-up period:

- Baseline Demographics: date of birth, sex, race/ethnicity, country of treatment
- DEB diagnosis: date of diagnosis and subtype (recessive or dominant)
- Relevant medical history, concomitant medications and comorbidities (at baseline and at follow-up visits)

- Exposure to Vyjuvek, including start and stop dates, and reasons for discontinuation (temporary or definitive, including adverse events and lack of effectiveness)
- Location and size of treated Target Areas (defined blocks of the body) (at baseline and at follow-up visits)
- Two Patient-Reported Outcomes (PRO) questionnaires will be included (at baseline and at yearly follow-up visits):
    - Treatment Satisfaction Questionnaire for Medication (TSQM-9)
    - Visual Analog Scale (VAS) 1-10 for pain and itch (at baseline and at follow-up visits)
- Treatment related adverse events, as ascertained by the treating health care professional.
    - If medication errors are reported, the setting in which treatment administration occurs (clinical or home setting) and who administers the product (HCP or patient/caregiver) will be determined.
- Effectiveness of the aRMM defined in the RMP and aimed at reducing accidental exposure and medication errors, particularly in the home setting
    - This will measured through a dedicated questionnaire covering the administration of the product in the home setting to assess if accidental exposure has taken place, which difficulties the patients/caregivers may have encountered during administration of the product at home and if any medication errors have occurred.
- In pediatric patients less than 3 years, the following additional variables will be collected:
    - % of body surface area (BSA) treated with B-VEC (at baseline and at follow-up visits)
    - Weight and height (at baseline and at follow-up visits)
    - Attainment of gross motor developmental milestones (at baseline and at follow-up visits)

Data sources

During the follow-up period, the prescribing physicians will be responsible for the correct documentation of all variables.

Study size

It is planned to include approximately 143 patients. The patient number is based on an estimate of the number of patients with DEB to be treated by the physicians in the participating countries, over the 24 months enrolment period, who are eligible and accept to participate in the study. The prevalence of DEB has been estimated at 6 cases per million inhabitants. Considering that the population of the U.S. is about 346 million, in Germany is about 84 million, and in France is about 68 million, the number of prevalent DEB cases in those three countries is estimated to be approximately 3000. It is assumed that during the 24-month enrolment period 2.5% to 10% of the patients with DEB will be treated with Vyjuvek, are eligible and will also accept to participate in the study. Considering that most patients are treated in reference centres in Germany and France, whereas in the U.S. the treatment is less centralized (which makes it more challenging to recruit patients into a study), a higher likelihood of enrolment in the European countries (10%) than in the U.S

(2.5%) is assumed. This leads to an expected enrolment of 50 patients in Germany, 41 patients in France, and of 52 patients in the U.S. Of the total numbers of patients to be enrolled, a minimum of 10 patients below 6 months of age is expected to be included. If the enrolment does not meet this projected sample size, additional countries may be added to the study.

Data analysis

Data will be summarized by descriptive statistics as applicable (number of observations, mean, standard error, median, minimum and maximum for most continuous data; frequencies and percentages of categorical data, as appropriate). Additionally, confidence intervals or graphical presentations may be provided as appropriate.

Analyses of all parameters will be described in more detail in the Statistical Analysis Plan (SAP) and will comprise all methods applied for analysis of the corresponding data.

Results will be presented for the overall population and by age groups (including a separate analysis for patients with less than 6 months), genotype (recessive RDEB/dominant DEB) and geographic area of treatment (EU/US).

Milestones

- Protocol submission within 3 months after the Marketing Authorisation
- Registration in the European (EU) PAS register: Within 30 days after protocol endorsement by European Medicines Agency (EMA)
- Anticipated start of data collection: Q4 2025
- Anticipated end of data collection: Q4 2032
- An interim report will be generated when at least 50 patients have completed a 1-year of follow-up
- Final report of study results: Q4 2034

The study synopsis for a non-interventional Category 1 PASS in several EU countries is acceptable. However, final assessment of all elements of PASS-01 will take place with submission of the full study protocol, post-authorisation. Below, some comments to be taken into account by the Applicant for the full protocol:

Feasibility to reach the study size: It is expected that from Germany, at least the key EB expert centers in Hanover and Freiburg, and from France, at least *Hôpital Necker, Hôpital Saint Louis* in Paris, and the *Centre Hospitalier Universitaire in Nice* will participate. Additional EB centers from Germany and France as well as from U.S. and potentially from other countries may however be needed to reach the study size, given that the number of DEB patients in the mentioned key EB expert centers may be lower than the suggested number which has been based on overall number of EB patients including all EB subtypes. Inclusion of additional sites and countries is needed if the patient enrolment does not meet this projected sample size.

Final justification of the study size including the number of patients below 6 months should be provided with the full protocol.

The inclusion of a comparator group (e.g. patients not treated with Vyjuvek or inclusion of historical comparator cohort) is strongly recommended, to enable evaluation of any association between exposure and outcomes and to increase the clinical relevance of the data collected.

As part of the objectives, PASS-01 will evaluate the effectiveness of the aRMM, which should include quantitative measurements of dissemination of aRMM to all relevant parties (next to evaluation of health outcomes such as medication errors) for the following reasons: For pharmacists, access to the preparation video is granted via the QR code on the outer carton (only pharmacies will receive the carton; section 6 package leaflet); however, the prescribing physicians/nurses and patient/caregivers, who do not receive the carton and may not always get the package leaflet, have to rely on the QR code included in the HCP guide and/or patient/caregiver guide, to access the aRMM tools in form of administration video, and (if applicable) preparation video. Proper dissemination of the aRMM to all involved parties is therefore important for safe and effective use of the product. Coverage of dissemination of aRMM to involved parties should be part of the evaluation of the effectiveness of aRMM, and should be addressed in the full protocol of PASS-01.

Study/Status	Summary of objectives	Safety concerns addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit-risk)				
PASS-01 A prospective, non-interventional, multi-country study to confirm the long-term safety profile, including in paediatric patients less than 6 months of age, receiving Vyjuvek for the treatment of DEB wounds, in a real-life clinical setting. Planned	The study primary objective will include the monitoring of: • long-term safety • safety in patients less than 6 months The secondary objectives of the study are to assess: • the occurrence of medication errors; • the occurrence of accidental exposure of Vyjuvek to HCPs, caregivers and close contacts; • the effectiveness of the aRMM • the effectiveness of Vyjuvek in real-life clinical practice.	Long-term safety Safety in patients less than 6 months of age Exposure of HCP and caregivers to Vyjuvek during preparation or administration Accidental exposure of Vyjuvek from patient to close contacts or HCP via direct contact with administered wounds or body fluids Medication errors in the clinical and home setting	Registration in the European (EU) PAS register	Within 30 days after protocol endorsement by European Medicines Agency (EMA)
			Anticipated start of data collection	31-DEC-2025
			Anticipated end of data collection	31-DEC-2032
			Progress reports	With every PSUR
			Interim report(s)	Once when approximately 50 patients have completed a 1-year follow-up
			Final Study Report	31-DEC-2034

2.6.3. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk		
None	NA	NA
Important Potential Risks		

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Exposure of HCP and caregivers to Vyjuvek during preparation or administration	**Routine risk minimization measures:** SmPC Sections 4.2, 4.6, and 6.6 • Section 4.2 describes the precautions to be taken before manipulating or administering Vyjuvek • Further details on precautions, handling and disposal of Vyjuvek are listed in Section 4.6 in the SmPC • Section 6.6 provides details on appropriate PPE that should be worn and the measures to take if there is accidental exposure and precautions with waste disposal PL Sections 2 and 6 • PL Section 2 and 6 provides information on accidental contact with Vyjuvek B-VEC handling and administration should be conducted by a trained HCP/patient/caregiver. **Additional risk minimization measures:** • Guide for HCPs • Guide for patients and caregivers • Vyjuvek dose preparation video • Vyjuvek administration video	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:** • None **Additional Pharmacovigilance activities:** • PASS-01 Study Progress Report: With every PSUR Interim Report: Once approximately 50 patients have completed a 1-year follow-up Final Report: 31-DEC-2034
Accidental exposure of VYJUVEK from patient to close contacts or HCP via direct contact with administered wounds or body fluid	**Routine risk minimization measures:** SmPC Sections 4.2, 4.6, and 6.6 • Section 4.2 describes the precautions to be taken before manipulating or administering Vyjuvek • Further details on precautions, handling and disposal of Vyjuvek are listed in Section 4.6 in the SmPC • Section 6.6 provides details on appropriate PPE that should be worn and the measures to take if there is accidental exposure and precautions with waste disposal PL Sections 2 and 6 • PL Section 2 and 6 provides information on accidental contact with Vyjuvek B-VEC handling and administration should be conducted by a trained HCP/patient/caregiver. **Additional risk minimization measures:** • Guide for HCPs • Guide for patients and caregivers • Vyjuvek dose preparation video • Vyjuvek administration video	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:** • None **Additional Pharmacovigilance activities:** • PASS-01 Study Progress Report: With every PSUR Interim Report: Once approximately 50 patients have completed a 1-year follow-up Final Report: 31-DEC-2034
Medication Errors in the clinical and home setting	**Routine risk minimization measures:** SmPC Sections 4.2 and 4.6 • Section 4.2 describes the precautions to be taken before manipulating or administering Vyjuvek • Further details on precautions, handling and disposal of Vyjuvek are listed in Section 4.6 in the SmPC PL Sections 3 and 5	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:** • None **Additional Pharmacovigilance activities:** • PASS-01 Study

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• Section 3 in the PL describes how Vyjuvek is given to the patient • Section 5 in the PL describes how Vyjuvek is stored B-VEC handling and administration should be conducted by a trained HCP/patient/caregiver. **Additional risk minimization measures:** • Guide for HCPs • Guide for patients and caregivers • Vyjuvek dose preparation video • Vyjuvek administration video	Progress Report: With every PSUR Interim Report: Once approximately 50 patients have completed a 1-year follow-up Final Report: 31-DEC-2034
Missing Information		
Safety in patients <6 months of age	**Routine risk minimization measures:** SmPC Section 4.8 • As Vyjuvek has not been studied in patients <6 months in the clinical studies, recommendation to consider the benefits of treatment against the risks provided in SmPC Section 4.8. B-VEC handling and administration should be conducted by a trained HCP/patient/caregiver. **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:** • None **Additional Pharmacovigilance activities:** • PASS-01 Study Progress Report: With every PSUR Interim Report: Once approximately 50 patients have completed a 1-year follow-up Final Report: 31-DEC-2034
Long-term safety	**Routine risk minimization measures:** SmPC Sections 4.4 • Recommendation for long-term follow up is provided in SmPC Section 4.4 PL Section 2 • Expectation for long-term monitoring are described in PL Section 2 **Additional risk minimization measures:** • Guide for HCPs • Guide for patients and caregivers • Vyjuvek dose preparation video • Vyjuvek administration video	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:** • None **Additional Pharmacovigilance activities:** • PASS-01 Study Progress Report: With every PSUR Interim Report: Once approximately 50 patients have completed a 1-year follow-up Final Report: 31-DEC-2034

2.6.4. Conclusion

The CAT considers that the risk management plan version 5 is acceptable.

The CHMP endorses the CAT conclusion on the RMP as described above.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP and CAT considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 19 May 2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8.2. Labelling exemptions

A request of translation exemption of the labelling as *per* Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD group for the following reasons:

The QRD group accepted the use of English only for inner and outer labels after considering that patients will not be involved in the preparation of the medicinal product and will be handed over the syringes ready to use.

The labelling subject to translation exemption as *per* the QRD group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD group.

2.8.3. Quick Response (QR) code

A request to include a QR code in the labelling and package leaflet for the purpose of providing access to the Vyjuvek dose preparation and administration videos, and to electronic copies of the guides for HCPs and patients/caregivers has been submitted by the applicant and has been found acceptable.

2.8.4. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Vyjuvek (beremagene geperpavec) is included in the additional monitoring list as it contains a new active substance which was not contained in any medicinal

product authorised in the EU. Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

3.1. Therapeutic context

3.1.1. Disease or condition

Dystrophic epidermolysis bullosa, a condition caused by mutations of the collagen VII gene (*COL7A1)* encoding type VII collagen (COL7), is a group of heritable skin diseases characterised by skin fragility, blister formation, milia, and scarring of the skin and mucosal membranes, including certain mucosa exposed to disruptive external environments, oropharynx, oesophagus, rectum, genitourinary system, and eyes. Healing of erosions results in debilitating scarring. Damage to the mouth and oesophagus can make it difficult to chew and swallow food, leading to chronic malnutrition and slow growth. Complications from extensive scarring can include fusion of the fingers and toes, joint deformities, and vision impairment.

As *per* the 16-year analysis of registry data from the National Epidermolysis Bullosa Registry, a cross-sectional and longitudinal epidemiological study of 3,300 patients with confirmed EB across the entire continental United States from 1986 to 2002, the prevalence of recessive DEB was estimated to be 1.35 persons *per* million inhabitants and the prevalence of dominant DEB 1.49 persons *per* million inhabitants. Similar rates were reported elsewhere in the world, suggesting no significant global differences. There is no sex or ethnic predilection for any EB type or sub-type.

3.1.2. Available therapies and unmet medical need

There are no approved corrective treatment options for DEB patients. For most DEB patients, management remains supportive in nature and is mainly limited to palliative care. Current standard of care is focused on reducing trauma and infections while managing the symptoms associated with multiple wounds of varying duration, size, and healing stage. Regimented personal hygiene and skincare are necessary to promote wound healing and prevent infection and wound growth. Pain medications are common. Surgery is indicated for co-morbidities such as pseudosyndactyly, oesophageal strictures, and skin cancer. The burden of wound care for RDEB is substantial, requiring multiple daily changes of wound dressings that can take several hours. Thirteen to 54% of patients report daily dressing changes and 15% to 40% report spending up to 3 hours *per* change.

In 2022, Filsuvez, topical birch bark extract, received marketing authorisation in the EU for the treatment of partial thickness wounds associated with dystrophic and junctional EB in patients 6 months and older. Filsuvez, was shown to accelerate wound healing in patients with EB, see (Filsuvez EPAR).

Given the severity of this disorder and the limited treatment options, there is a clear need for therapies preferably focusing on the root cause of the disease, which could be administered in a minimally invasive way.

3.1.3. Main clinical studies

Results of two controlled clinical studies, KB103-001 (GEM-1) and B-VEC-03 (GEM-3), and of an uncontrolled, open-label extension study (B-VEC-EX-02), were submitted. The main study was a phase 3 blinded randomised intra-patient controlled pivotal study with an open label extension study. All trials were conducted in the USA. A single-centre, open-label, randomised, intrasubject placebo-controlled phase 1/2 proof of concept and dose finding study was also conducted with topical beremagene geperpavec in DEB. The study was divided into 4 phases and there are 4 groups defined in the inclusion criteria with different age ranges, wound sizes and doses. Nine subjects were treated; three subjects were re-treated after a washout period and counted as new patients. The youngest patient was 10 years old.

No conventional PK studies were conducted, as the product is applied to the skin and not absorbed systemically. Shedding studies to detect the virus in blood and to determine the extent of systemic absorption of the product were performed. Furthermore, immunogenicity studies to identify immune response to the vector and to the transgene were also conducted.

The population in the phase 3 trial (GEM-3) included subjects with a genetic diagnosis of DEB. Both dominant and recessive forms of DEB were part of the inclusion criteria; however, there was only one subject with dominant DEB recruited in the trial. There were 10 children under 12 years of age treated in the programme with no children of 1 year or less. There were no patients aged 65 or older; the oldest patient being 44 years. The primary wounds in the GEM-03 pivotal study were well matched in size between the treatment arms with medians of 10.6 cm^2 (mean 14.4) for the active treatment and 10.4 (mean 15.6) cm^2 for placebo. Primary wound sizes varied in size from approx. 3 cm^2 to over 50 cm^2. Twenty-three (23 or 74.2 %) of beremagene geperpavec-treated wounds were less than 20 cm^2 in size, with 6 wounds between 20-40cm^2 and 2 between 40-60cm^2. Twenty-two (22 or 71%) of placebo treated wounds were less than 20 cm^2, with 8 between 20-40 cm^2 and 1 between 40-60 cm^2. The primary endpoint for the pivotal phase 3 trial was the complete wound closure at 26 weeks. Wound closure between weeks 8 and 12 for a selected wound was a key secondary endpoint. Assessment of wound closure was performed by a blinded central assessor. A sensitivity analysis and durability of response analysis for wound closure at both timepoints was performed.

3.2. Favourable effects

Among the 31 wound pairs in the primary ITT analysis of the phase 3 trial, 67.4% of beremagene geperpavec-treated wounds compared to 21.6% of placebo-treated wounds were completely healed at 6 months ($p=0.0019$). In all of the sensitivity analyses, significantly greater wound healing was seen in the beremagene geperpavec-treated wounds compared to the placebo. Effect sizes were similar across the sensitivity analyses. Complete wound closure is summarised in the effects table below at weeks 22, 24, and 26 for the ITT, mITT, and PP populations (see below).

The primary endpoint of complete closure of wounds at 22 or 24 weeks sustained for at least 2 weeks was met. There is a significant difference in healing between treated and untreated wounds. The key secondary endpoint of complete wound healing at 3 months, defined as complete wound closure at weeks 8 and 10 or weeks 10 and 12, was also met, i.e. 70.6% of beremagene geperpavec-treated wounds completely healed *vs* 19.7% of placebo-treated wounds in the ITT population with imputed data ($p<0.001$). A durable response in the phase 3 study was defined as complete wound closure on at least 2 consecutive study visits occurring 2 weeks apart. Durability was also assessed by considering the proportion of wounds that met the definition for wound healing at both 3 months and 6 months. Using this stringent definition, 49.7% of beremagene

geperpavec-treated wounds were completely healed *vs* 7.1% of placebo-treated wounds in the ITT population (p=0.002).

For rollover subjects in the OLE, the proportion of primary wounds demonstrating complete wound closure rates were similar to those observed the pivotal study, suggesting persistent closure, consistent with the observed changes in the PRO measures. Out of 24 rollover subjects, 19 were evaluated (data was unevaluable for 5 subjects who did not return for follow up visits due to logistical reasons). The responder rate ranged from 61.1% to 89.5% in the OLE study and was comparable to the rates observed in the phase 3 study.

Pain severity during wound dressing changes was a secondary endpoint. Consistent trend of decreased pain was observed across weeks 22, 24, and 26. In the ITT population (observed data) the least square mean difference (95% CI) was -0.61 (-1.10 to -0.13; p=0.016) at week 22 -0.88 (-1.79 to 0.03; p=0.058) at week 24, and -0.56 (-1.17 to 0.05; p=0.072) at week 26. There was a trend towards improvement of anxiety/depression, mobility, pain/discomfort, self-care, as *per* the PRO:EDQ-5D-5L, suggesting a progress in overall health status. Similarly for PRO:Skindex-29 mean scores at follow-up were numerically lower than at baseline across multiple domains (symptoms, functioning, and emotions), suggestive of improved skin-specific quality of life.

Overall, a solid demonstration of clinical efficacy was provided as reflected by the clinically relevant effect size and the reliability of the results (consistency of results, *p*-value). Despite the study population of >1 year of age patients (with a small number of younger children treated in the OLE study), the extrapolation of efficacy to children from initial diagnosis at birth is agreed (see below), considering also the young patients' vulnerability and difficulties to collect clinical data.

3.3. Uncertainties and limitations about favourable effects

Uncertainties related to the age of the target population as no children below 1year of age were treated in the clinical trials. The applicant provided data to support extrapolation from 1year old children and older to children from birth to 1 year of age based on mechanism of action of the product. Clinical manifestations of the disease are similar from birth to children ≥6 months in subjects with the identical underlying genetic, molecular and pathophysiological deficiency; efficacy and safety data from the OLE study in subjects under 1 year of age; RWE patients below 1 year old treated. Photographs showed that treatment has resulted in effective timely closure of wounds associated with DEB.

Altogether, in the clinical programme, the OLE and the RWE setting, there were over 400 subjects exposed to Vyjuvek treatment. This number is reassuring in both, the efficacy outcomes, and overall safety, as no signals were detected to date. Forty-two children less than 3 years have received treatment of which 12 patients are less than 1 year old. Additional data with 12 patients less than 1 year treated as of Nov 2024 were provided; efficacy, safety and photographs of wound healing were submitted for 2 of these children aged 6 and 7 months. RWE is from the US, where 9 subjects less than one year have also been treated in the commercial setting, 2 patients from the OLE study and one subject in the EU aged 9 months who was treated with Vyjuvek. The data of the 12 children <1 year old treated with Vyjuvek (incl. a 10-day old baby) is particularly supportive.

Overall, the extrapolation concept to support efficacy in patients from birth is considered acceptable given the efficacy demonstrated in older study participants and the issues related to the feasibility of gathering efficacy data in terms of the rarity of the severest subtype of the condition, present at birth and diagnosed by genetic

testing, along with the issues of assessing wound healing in a population who suffer incidental wounding through provision of their daily care. In the imposed PASS, the applicant will endeavour to recruit patients <1 year (n =10). This will be thoroughly assessed when the final PASS protocol is submitted.

All patients will have a diagnosis confirmed by genetic testing *prior* to receiving treatment as *per* the inclusion criteria of the clinical trial. In addition, further information will be collected in the post-authorisation safety study, capturing specific variables in relation to wounds and infants aged <6 months, in particular: location and size of treated wounds/target areas at baseline and at subsequent standard of care visits, %BSA treated wounds/target areas, weight & height baseline and subsequent standard of care visits, and attainment of gross motor developmental milestones. The effectiveness of Vyjuvek in real-life clinical practice will also be assessed as a secondary objective. There was one subject with the dominant DEB genotype treated in the trials and whilst the dominant phenotype tends to be a milder disease and therefore providing confidence in the extrapolation, it remains that clinical data are also expected in this subgroup of DEB to further substantiate the efficacy and safety.

Skin permeability and the impact of this on systemic absorption was considered for newborn baby's skin, which is thinner and more permeable compared to the skin of a 6-month-old baby and hence, possibly more susceptible to absorbing substances. However, this relates primarily to intact skin barrier. Vyjuvek gel is applied to open wounds, and in that instance, the age-related differences in skin permeability may not affect the potential for systemic absorption. Extrapolation from older patients is therefore considered reasonable.

Furthermore, the applicant argued that there is little, or no absorption based on the phase 1/2 study and while this data is limited (sparse sampling frequency), non-clinical data demonstrated that with topical treatment applied to mouse wound, there was no detectable vector within the blood. Some low levels were seen in bone marrow of a single animal ($9.36x10^2$ copies/µg DNA) and a couple of animals were below LLoQ. From a clinical perspective, all blood samples and all but one urine sample collected throughout the study were below the limit of detection/quantification for all subjects and this was unaffected by the number of wounds treated. Considering that Vyjuvek will be applied to open wounds, without a robust skin layer present, collecting PK data in participants less than 6 months would not be feasible.

The posology outlined in the PI includes dosing instructions relating to the area of the wound to be treated as *per* the pivotal study, and the maximum dose is also specified, i.e. the recommended total maximum weekly dosing for children from birth up to 3 years old is 1 mL (2×10^9 PFU). The recommended total maximum weekly dosing for children above 3 years of age, adolescents, and adults is 2 mL (4×10^9 PFU). The clinical trials used wound size to determine the recommended maximum dose. There was limited data on dose and response in larger wounds, i.e. greater than 40 cm^2, and hence, the SmPC includes a table where the dose *per* wound size is outlined. In the OLE study, and the patients treated in the RWE setting, where subjects received the dose as *per* the SmPC, five children between birth and three years of age were treated with the dose outlined in the SmPC with no AEs reported. As a post marketing measure, in patients less than 3 years, % BSA treated with B-VEC at baseline and at follow up visits will be collected as a variable in the imposed category 1 PASS.

3.4. Unfavourable effects

Overall, the product was well tolerated with few AEs and ADRs. The reported AEs remain limited to skin disorders (pruritus, erythema and rash), chills, cough and rhinorrhoea. The integrated safety analysis included 43 subjects, 12 in the phase 1/2 and 31 in the phase 3 study. Eighty AEs were reported across both studies, by 9 (75.0%) subjects in the phase 1/2 and 18 (58.1%) in the phase 3 study. ADRs were reported

for 5 (11.6%) subjects. Three subjects experienced SAEs, all in the phase 3 study; no SAE was assessed as drug-related. There were no deaths during the study and no AE led to premature discontinuation of treatment or study. Common adverse reactions (≥1/100 to <1/10) included pruritus, chills, erythema, rash, cough, and rhinorrhoea. Pruritus was reported in 4 subjects (9.3%) and Erythema, Rash, Chills, and Squamous cell carcinoma, each reported for 3 subjects (7.0%). Adverse reactions were mild or moderate in nature and did not result in discontinuation of treatment. Treatment with B beremagene geperpavec led to detectable antibodies to HSV-1 and COL7 but was not associated with any safety events or clinically relevant immunologic reactions. In the clinical programme, the OLE and RWE setting, there were 423 subjects exposed to Vyjuvek treatment. This number of treated subjects is supportive in nature and reassuring of the overall safety profile as no safety signals were detected to date.

3.5. Uncertainties and limitations about unfavourable effects

The safety population is small due to the orphan nature of the condition. There is no safety data for children < 1 year of age or in adults > 44 years of age in the pivotal study. Safety data from the OLE and RWE for subjects less than one year of age and those greater than 45 years of age are also supportive. Data for patients < 6 months old are captured in the RMP as missing information.

There are no data on potential drug interactions with other topical agents. The SmPC states that concomitant medication should not be administered with Vyjuvek.

The safety profile in subjects with milder or dominant disease is not described, however it is not anticipated to be worse. There are limited long term safety data, captured as missing information in the RMP and these will be collected in the imposed PASS. There is limited safety information for treatment of larger wounds, but the PI provides guidance on a maximum weekly doses and administration instructions, depending on the wound size. As the pivotal clinical trial was conducted in a hospital setting, there was no data on potential risks such as infection or medication error from use in a home setting, but this was addressed in the human factor study. The product will only be mixed in a controlled environment, namely the pharmacy and the option for home administration will be available to enable flexibility and adherence to treatment. The RMP addresses these aspects and management of potential risks in the safety specification and in the educational materials.

The applicant agreed to conduct a category 1 PASS. The study will have a 2-year enrolment period, followed by a 5-year follow-up period and it will aim to address mainly the long-term safety profile of Vyjuvek, incl. in very young patient population.

3.6. Effects table

Table 17 Effects table for efficacy and safety of beremagene geperpavec, cut-off date 29th October 2021

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Responder defined as - complete wound closure at 22 & 24 weeks or 24 & 26 weeks	Responder at weeks 22 & 24 or weeks 24 & 26 (mITT population, n=29, imputed data)	Number (%)	19.6 (67.6)	6.3 (21.7)	45.9 (23.0, 68.7) P =0.002	Data from the pivotal phase 3 trial ID B-VEC-03
	Responder at weeks 22 & 24 or weeks 24 & 26 (PP population, n=24, imputed data)		17.0(70.8)	6.0(25.0)	45.8 (20.1, 71.6) P=0.007	
	Responder at weeks 22 & 24 or weeks 24 & 26 (ITT population, n=31, observed data)		19.0 (61.3)	6.0 (19.4)	41.9 (20.4, 63.4) P=0.002	
	Responder at weeks 22 & 24 or weeks 24 & 26 (mITT population, n=29, observed data		19.0 (65.5)	6.0 (20.7)	44.8 (22.2, 67.4) P=0.002	
	Responder at weeks 22 & 24 or weeks 24 & 26 (PP population, n=24, observed data)		17.0 (70.8)	6.0 (25.0)	45.8 (20.1, 71.6) P=0.007	
	Responder at (weeks 8 & 10 or weeks 10 & 12) and (weeks 22 & 24 or weeks 24 & 26) (ITT population, n=31)		15.4 (49.7)	2.2 (7.1)	42.6 (22.6, 62.6) P=0.002	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
	Responder at (weeks 8 & 10 or weeks 10 & 12) and (weeks 22 & 24 or weeks 24 & 26) (mITT population, n=29) Responder at (weeks 8 & 10 or weeks 10 & 12) and (weeks 22 & 24 or weeks 24 & 26) (PP population, n=24)		14.6 (50.3) 13.0 (54.2)	2.0 (6.9) 2.0 (8.3)	43.4 (23.0, 63.9) P=0.001 45.8 (22.8, 68.9) P=0.003	
Change in Pain severity on dressing change	Change in VAS score for subjects aged 6 and over At week 22 (ITT)	ITT population least mean squares difference	-0.61 (-1.10 to 0.13) P=0.016		Significant difference at week 22. Patients acted as own controls difficult to interpret	
Unfavourable Effects						
Skin and subcutaneous tissue disorders	Pruritis Erythema Rash	incidence	common (≥1/100 to <1/10);		Patients acted as their own controls therefore all patients received treatment therefore comparison to placebo was not possible. Only adverse events that occurred with a frequency of > 5 % in the pivotal trial were considered	
General disorders and administrative site conditions	Chills		common (≥1/100 to <1/10);			
Respiratory, thoracic and mediastinal conditions	Cough Rhinorrhoea		common (≥1/100 to <1/10);			

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

There is an unmet medical need in the treatment of DEB. The data from the pivotal trial presented supports a clinically relevant benefit to patients. Wound closure is maintained for at least 2 weeks, with a greater than 40% difference in response rate for treated wounds compared to matched wounds treated with standard of care. Wound closure was also measured at an earlier time point, i.e. 8 weeks and many wounds were closed and maintained closure for at least 2 weeks at this time point and at the later time point of 24 weeks. When wounds are closed patients need less painful wound dressings and are at fewer risks of infection. Compared to current available standard of care, treatment with Vyjuvek results in a clinically significant treatment benefit. Overall, a comprehensive clinical demonstration of efficacy was provided as reflected by the clinically relevant effect size and the reliability of the results. The extrapolation concept to support efficacy in patients less than 1 year is considered acceptable given the efficacy demonstrated in older study participants and the issues related to the feasibility of gathering efficacy data in young children. Whilst the unmet need in younger children and neonates is acknowledged, this need is most relevant for wounds that form *in utero* or are present from birth. These wounds tend to become chronic and debilitating. This along with an assurance that accurate diagnosis is made, will contribute to the benefit in the youngest patients. Therefore, the extrapolation of efficacy to children from initial diagnosis at birth is agreed, subject to further follow up in the PASS.

The data supporting efficacy and safety originates from a phase 1/2 trial a phase 3 pivotal trial and an open label extension trial along with RWE in the commercial setting in the US. The primary endpoint was complete wound healing and there was a statistical and clinically relevant difference in wound closure between treatment and placebo groups in all trials. The RWE of Vyjuvek includes 423 treated patients and 273.9 patient-years of experience. This is over 13 times greater than the number of patients enrolled in the GEM-3 trial (n=31). This RWE data is considered relevant and supportive in nature acknowledging the limitations of such data.

The safety profile is reassuring with most side effects of mild intensity, tolerable and related to topical application. There were only three serious AEs reported, none of which were considered causally related to the active. There is limited data on long-term safety and the risk of medication error with home application is not known. These are captured in the RMP as missing information and potential risks respectively. Further safety data collection will be the key aim of the imposed PASS.

Vector shedding was minimal and non-infectious indicating a low risk to carers. Treatment with beremagene geperpavec led to detectable antibodies to HSV-1 and COL7 but was not associated with any safety events or clinically relevant immunologic reactions. Further study with repeated use of beremagene geperpavec beyond 2 years showed no additional safety concerns or development of tolerance.

In addition to the administration in a healthcare setting, Vyjuvek can be administered by HCP or caregivers/patients in the home setting provided that mixing will occur in a controlled sterile environment i.e., a controlled pharmacy. This is supported by the CAT, as flexibility to where the product is administered is needed given the frequency of treatment, painful wound dressings involved. These aspects will also be monitored in the PASS.

3.7.2. Balance of benefits and risks

The primary and secondary endpoints were clinically meaningful and statistically significant. Persistent skin lesions in DEB are a great physical, emotional, psychological and for patients. Sustained closure is a clinically meaningful effect. Pain VAS score and the patient-reported outcome measures (PROMs) are also relevant tools but interpretation of reduction of pain compared to control can be somewhat limited as patients have both, the treatment and pain measurement at the time of on dressing changes. However, results point to a downward trend in pain, consistently with wound closure. The trend in PROMs was also positive but it is not clear what the exact contribution of the active treatment compared to SOC was, since patients acted as their own controls. The primary endpoint of the pivotal trial was measured after 24 weeks when patients could continue in an OLE. The results demonstrated durability of response. Patients were followed up in the OLE which equally showed durable effects. However, there are limitations to the results of the OLE study as previously outlined.

As requested by the CAT as an Annex II condition, the applicant will conduct a PASS, to address the long-term safety in the indicated population, including children less than 6 months of age. The RMP captures safety in patients less than 6 months of age as missing information in the summary of safety concerns and specifies the PASS as additional pharmacovigilance activities to monitor the safety concerns. Data from the RWE and OLE study up to the cut-off date (Nov 2024) were submitted as well, which were considered supportive, especially data on 10 babies treated in the real-world setting.

Overall, the benefits of treatment with beremagene geperpavec are considered to outweigh the risks described in the risk management plan.

3.7.3. Additional considerations on the benefit-risk balance

This is an application for a standard marketing authorisation of Vyjuvek. There is a strong pharmacological rationale for this approach and the mechanism of action of this product being a gene therapy is supported by histology of skin biopsies in treated patients. The presented pivotal trial was limited to 31 subjects, 18 of whom were <18 years old. The trial was a RCT where patients acted as their own controls and matched wounds were treated on similar sites on the body. Given the rarity of this condition, the population size is small and does not include the very young patients. However, this is balanced by the effect size and adequate power of the study. Therefore, the trial design is appropriate even if the external validity of the findings is limited by the number of patients treated. To support the comprehensiveness of the clinical data, further information derived from over 400 patients treated in the OLE and RWE (cut-off Nov 2024) was provided. There were 12 patients <1 year of age treated and 44 patients $\geq$46 years of age. Whilst the number treated to date could be considered comprehensive, the applicant did not submit the efficacy or effectiveness data from these subjects as OLE was primarily a safety study. This limits the collection of efficacy data in the real-world setting. However, based on the totality of evidence, including these additional data, a standard MA with an imposed category 1 PASS to further investigate the long-term safety is supported.

The CHMP endorses the CAT conclusion on the marketing authorisation as described above.

3.8. Conclusions

The overall benefit/risk balance of Vyjuvek is positive, subject to the conditions stated in section

'Recommendations'.

The CHMP endorses the CAT conclusion on benefit-risk balance as described above.

4. Recommendations

Similarity with authorised orphan medicinal products

The CAT by consensus is of the opinion that Vyjuvek is not similar to Filsuvez within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on similarity.

The CHMP endorses the CAT conclusion on similarity as described above.

Outcome

Based on the CAT review of data on quality, safety and efficacy, the CAT considers by majority decision that the benefit- risk balance of Vyjuvek is favourable in the following indication:

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

The CAT therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Based on the draft CHMP opinion adopted by the CAT and the review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit- risk balance of Vyjuvek in 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,* is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Vyjuvek in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Vyjuvek is marketed, all HCPs (pharmacists, prescribing physicians, and/or nurses) and patients/carers who are expected to prescribe, use, or oversee the administration of Vyjuvek have access to/are provided with the following educational packages aimed at highlighting the important potential risks of Vyjuvek. These packages will be translated into the local language to ensure understanding of proposed mitigation measures by all users.

HCP educational materials consist of

- Guide for HCPs
- Vyjuvek dose preparation video
- Vyjuvek administration video

Patient/Caregiver educational materials consist of

- Guide for patients and caregivers
- Vyjuvek administration video

Guide for HCP

<u>The guide will explain the following</u>

Preparation and administration

- Training on how to prepare and administer Vyjuvek, including a QR code with access to a preparation and administration video.
- Ability for the HCP to order a demonstration kit to facilitate the training of the HCP, patient, or caregiver.

Storage and Transport

- Appropriate storage conditions prior to and after mixing of Vyjuvek and handling of the drug
- Requirements for transport of prepared syringes to the setting of administration (including surveillance of temperature and timeline)

Administration objectives and patient/caregiver counselling

- The appropriate dosing and treatment plan
- Detailed information on treated wound dressing
- Steps to consider to prevent further accidental exposure

- Actions to take in the event of an accidental exposure and in case of emergency
- Appropriate biological waste management
- The HCP should provide and discuss the patient and caregiver guide with the patient/caregiver
- HCPs should encourage patients to participate in the long-term study PASS-01

Home setting

- Requirements for home administration, including availability and timely administration
- In case of in-home administration, the prescribing physician should establish a treatment plan, indicating the appropriate dose and prioritizing wounds to treat initially and sequential wounds to treat afterwards
- Suitability of the patient for home administration by HCP:
    - Training of HCP who will administer the product in home setting
    - Educating / counselling of patient and caregiver on home administration and discuss and provide the patient and caregiver guide
- Suitability of the patient for home administration by care giver or patient:
    - Requirement for at least one application of Vyjuvek to be administered by patient/caregiver under the supervision of a HCP in a healthcare setting (or as many times as needed to be compliant with all steps)

Guide for patients and caregivers

<u>The guide will explain the following</u>

- Training administration video (QR code with access to administration video)
- How the administration of Vyjuvek is performed
- Steps to consider to prevent accidental exposure
- Actions to take in the event of an accidental exposure and in case of emergency
- Detailed information on treated wound dressing, including changing and disposing of wound dressings
- Appropriate biological waste management
- Encourage the patient to participate in the long-term study PASS-01

Home setting

- Requirements for home administration, including availability and timely administration
- Requirements for transport of prepared syringes to the setting of administration (including storage conditions and timeline)
- Appropriate storage conditions of Vyjuvek and handling of the drug
- In the case of home administration by a caregiver or patient, there will be a requirement for at least one application of Vyjuvek to be administered by patient/caregiver to take place under the

supervision of a HCP in a healthcare setting(or as many times as needed to be compliant with all steps)

- The prescribing physician has established a treatment plan, indicating the appropriate dose and prioritizing wounds to treat initially and sequential wounds to treat afterwards

Vyjuvek dose preparation video

The video will explain: all steps necessary for mixing and preparing the Vyjuvek syringes for administration, including transport conditions of the prepared syringes to the setting for administration in accordance with the EU SmPC and package leaflet.

Vyjuvek administration video

The video will explain: all steps of administration including wound dressing and waste disposal in accordance with the EU SmPC and package leaflet and national guidelines on genetically modified and biological material.

The CHMP does endorse the CAT conclusion on the additional risk minimisation measures.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Non-interventional post-authorisation safety study (PASS): In order to further characterise the long-term safety of Vyjuvek in patients with dystrophic epidermolysis bullosa with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene, including patients less than 6 months of age, the MAH should conduct and submit the results of a prospective, non-interventional, multi-country study in patients treated with Vyjuvek in a real-life clinical setting.	Final report: 31 December 2034

The CHMP endorses the CAT conclusion on the obligation to conduct post-authorisation measures as described above.

New active substance status

Based on the review of available data on the active substance, the CAT considers that beremagene geperpavec is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on NAS.

The CHMP endorses the CAT conclusion on the new active substance status claim.

Paediatric data

Furthermore, the CAT reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0024/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

The CHMP endorses the CAT conclusion on the paediatric data.