BLA Clinical Review Memorandum

Application Type	Original Application
STN	125774/0
CBER Received Date	Original submission: June 20, 2022 Major amendment submission: December 20, 2022
PDUFA Goal Date	May 19, 2023
Division / Office	DCEGM/OCE
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Ning Hu, MD, MS Office of Therapeutic Products (OTP)/Division of Clinical Evaluation (DCE)/ Division of Clinical Evaluation General Medicine (DCEGM)/ General Medicine Branch 2 (GBM2)
Review Completion Date / Stamped Date	May 18, 2023
Supervisory Concurrence	Rosa Sherafat-Kazemzadeh, MD, Clinical team lead OTP/OCE/DCEGM/GMB2 Lei Xu, MD, PhD, Branch Chief OTP/OCE/DCEGM/GMB2
Applicant	Krystal Biotech, Inc.
Established Name	Beremagene geperpavec-svdt
(Proposed) Trade Name	VYJUVEK™
Pharmacologic Class	Herpes-simplex virus type 1 (HSV-1) vector-based gene therapy
Formulation(s), including Adjuvants, etc.	VYJUVEK biological suspension is supplied as a 1.0 mL extractable volume in a single dose vial at a nominal concentration of 5×10^9 PFU/mL. The excipient gel is supplied as a 1.5 mL fill volume in a separate single use vial.
Dosage Form(s) and Route(s) of Administration	VYJUVEK biological suspension (1 mL) is mixed into the excipient gel vial prior to administration as VYJUVEK gel.
Dosing Regimen	Weekly dose of approximately $4x10^8$ PFU per 20 cm^2
Indication(s) and Intended Population(s)	For the treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa with mutation(s) in *the collagen type VII alpha 1 chain* (*COL7A1*) gene
Orphan Designated	Yes

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GLOSSARY

AE	adverse event
AF	anchoring fibril
BLA	biologics license application
BMZ	basement membrane zone
B-VEC	beremagene geperpavec-svdt
(b) (4)	
CFR	Code of Federal Regulations
CI	confidence interval
COL7	human type VII collagen
COL7A1	collagen type VII alpha 1 chain
DDEB	dominant dystrophic epidermolysis bullosa
DEB	dystrophic epidermolysis bullosa
DEBRA	Dystrophic Epidermolysis Bullosa Research Association of America
EB	epidermolysis bullosa
FDA	U.S. Food and Drug Administration
FIH	first-in-human
FLACC-R	Face, Legs, Activity, Cry, Consolability-Revised
HD	hemodialysis
HSV-1	herpes-simplex virus type 1
IEM	immunoelectron microscopy
IF	immunofluorescence
IND	Investigational New Drug
IP	investigational product
IR	information request
ITT	intent-to-treat
LTFU	long-term follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
NC1/NC2	noncollagenous domain 1/2
OLE	open-label extension
PC	pachyonychia congenita
PD	pharmacodynamic
PK	pharmacokinetic
PFU	plaque forming units
PI	prescribing information
PMR	postmarketing requirement
RDEB	recessive dystrophic epidermolysis bullosa
REMS	Risk Evaluation and Mitigation Strategies
SAE	serious adverse event
SCC	squamous cell carcinoma
TEAE	treatment-emergent adverse event
USPI	United States Prescribing Information
VAS	visual analog scale

1. EXECUTIVE SUMMARY

Beremagene geperpavec-svdt (proprietary name: VYJUVEK; also known as B-VEC or KB103) is a suspension of a herpes simplex virus type 1 (HSV-1) vector-based gene therapy, mixed with the supplied sterile excipient gel for topical application on wounds. B-VEC is a replication deficient HSV-1-based vector that has been genetically modified to express the human type VII collagen (COL7) protein.

The proposed indication for B-VEC is for the treatment of wounds in patients six (6) months of age and older with dystrophic epidermolysis bullosa (DEB), with mutation(s) in the *collagen type VII alpha 1 chain* (*COL7A1*) gene.

DEB is a rare genetic disorder with significant unmet medical need. DEB is clinically and genetically heterogeneous and is characterized by fragile and blistering skin and mucosal membranes that heal with scarring. The onset of symptoms is usually at birth or in early childhood. There may be associated complications, including malnutrition, anemia, infection, and skin cancer. Death may occur prematurely due to multiple causes, including infection, progression of disease, organ failure, and malignancy.

DEB is caused by mutations in the *COL7A1* gene, which results in reduced or absent levels of biologically active COL7 protein. COL7 is a structural component of anchoring fibrils (AFs) which hold the epidermis and dermis together and are essential for maintaining the integrity of the skin. DEB can be inherited in an autosomal dominant or recessive fashion. Patients with dominant DEB (DDEB) has lower than normal functional AFs. Patients with recessive DEB (RDEB) has no functional AFs, and therefore, more severe clinical manifestations. In the United States (US), the prevalence of RDEB and DDEB is estimated to be 1.35 and 1.49 persons per million inhabitants, respectively (Fine 2016). There is no U.S. Food and Drug Administration (FDA)-approved treatment for DEB.

The Biologics License Application (BLA) is supported by two clinical studies: a Phase 3 study (Study B-VEC-03) and a Phase 1/2 study (Study KB103-001).

The Phase 3 study was a multicenter, intra-subject randomized, placebo-controlled, double-blind efficacy and safety study of B-VEC for the topical treatment of DEB wounds. The Phase 3 study provides the primary evidence of safety and effectiveness of B-VEC for the treatment of DEB wounds.

The Phase 3 study enrolled 31 subjects (20 males and 11 females), in which five were re-enrolled from the Phase 1/2 study by contributing different wounds with adequate washout periods. Among the 31 subjects, 30 have RDEB and one has DDEB. All subjects had clinical manifestations consistent with DEB and genetically confirmed mutations in the *COL7A1* gene. The mean age of the subjects was 17 years (one year to 44 years), including 61% pediatric subjects (n=19, age from one year to <17 years). Sixty-four percent (64%) of subjects were White; 19% were Asian, and the remainder were American Indian or Alaska Native. Two matched wounds (the primary pair) in each subject were selected and randomized to receive either topical application of B-VEC or the placebo (i.e., excipient gel) weekly for 26 weeks. The size of the B-VEC treated wounds ranged from 2.3 to 57.3 cm^2, with 74.2% of wounds measuring <20 cm^2 and 19.4% ranging from 20 to <40 cm^2. The size of placebo-treated wounds ranged from 2.3 to 51.5 cm^2, with 71.0% of wounds measuring <20 cm^2 and 25.8% ranging from 20 to <40 cm^2. Each subject also contributed a few unmatched secondary wounds (the number

of secondary wounds varied in each subject) to receive open-label B-VEC treatment. The unmatched secondary wounds contribute to the safety evaluation.

Efficacy was demonstrated based on the primary endpoint of the difference in the proportion of complete wound closure (defined as 100% wound closure as indicated by skin re-epithelialization without drainage), at 24 Weeks confirmed at two consecutive study visits 2 weeks apart, assessed at Weeks 22 and 24 or at Weeks 24 and 26, between the B-VEC and the placebo-treated DEB wounds in the primary wound pairs. Twenty (20) of the 31 (64.5%) B-VEC treated wounds achieved complete closure. Eight of the 31 (25.8%) placebo-treated wounds achieve complete closure. The treatment difference was 38.7% (95% confidence interval [CI]: 13.9, 63.5; p= 0.012). Efficacy was supported by the key secondary endpoint of the difference in proportion of complete wound closure (defined as 100% closure) at Weeks 8 and 10 or at Weeks 10 and 12 between the B-VEC and the placebo-treated DEB wounds in the primary wound pairs. Twenty-one of the 31 (67.7%) B-VEC treated wounds achieved complete closure. Seven of the 31 (22.6%) placebo-treated wounds achieve complete closure. The treatment difference was 45.1% (95% CI: 21.8, 68.5; p= 0.003).

There were no deaths in the Phase 3 study. Three subjects experienced five serious adverse events (SAEs). None of the SAEs was considered related to B-VEC treatment. The most frequent adverse reactions (incidence >5%) include pruritis, chills, erythema, rash, cough, and rhinorrhea. The overall safety profile did not raise any concern.

The Phase 3 study intended to enroll subjects with DEB aged 6 months or older based on study enrollment criteria. However, the youngest subject enrolled in the Phase 3 study was 1 year old. The safety profile of two subjects with autosomal recessive DEB of six and seven months old, respectively in an open-label study (Study B-VEC-EX-02) supports the safety of B-VEC in patients aged between 6 months and less than 12 months.

The Phase 1/2 study (Study KB103-001) was a first-in-human (FIH), single-center, open-label, randomized, intra-subject placebo-controlled study to assess safety and molecular correction [pharmacodynamic (PD) activity], and to explore preliminary efficacy of B-VEC for the treatment of DEB. The study comprised of four phases: Phase 1, Phase 2a, Phase 2b, and Phase 2c. Nine unique subjects were enrolled and three of the nine subjects were enrolled in both Phase 2a and Phase 2b with adequate washout period (the total number of subjects is considered as 12). All subjects received topical administration of B-VEC on selected wounds. In addition, subjects in Phase 1 and Phase 2b received intradermal injection of B-VEC to intact skin for the evaluation of PD.

The PD activity (expression, secretion, and localization of COL7 transgene in B-VEC) of B-VEC was demonstrated in six subjects (9 biopsy sites) in the Phase 1/2 study. The noncollagenous domain 1 (NC1) and domain 2 (NC2) of COL7, and linear deposition at the dermal-epidermal junction was demonstrated in skin biopsies harvested after the B-VEC treatment. These data provide mechanistic support and serve as confirmatory evidence of effectiveness of B-VEC for the treatment of DEB wounds.

The efficacy and safety findings of the Phase 1/2 study are not integrated with the Phase 3 study because each subject received varying doses and dosing regimens, which were significantly different from the weekly topical dose used in the Phase 3 study. The route of intradermal injection of B-VEC to intact skin incorporated in Phases 1 and 2b was for evaluation of PD activity only. The preliminary clinical efficacy evaluation in the Phase 1/2 study was limited due to multiple design and analyses issues. The efficacy assessment in the Phase 1/2

study is considered exploratory. The efficacy findings suggested clinical benefit of B-VEC on DEB wounds. The overall safety evaluation in the Phase 1/2 study did not raise any concern.

In conclusion, B-VEC demonstrated substantial evidence of effectiveness for the treatment of DEB based on primary evidence of effectiveness from an adequate and well controlled Phase 3 study, plus confirmatory evidence of the PD activity (expression and localization of COL7 transgene) demonstrated in the Phase 1/2 study. The risks of B-VEC are characterized based on a safety database of 31 subjects aged one year to 44 years in the Phase 3 study. Although the safety database is small, it is acceptable considering the seriousness of the rare disease, the significant unmet medical need, the substantial evidence of effectiveness and acceptable safety profile of B-VEC. The safety profile of two subjects with RDEB aged six and seven months, respectively, in an open-label study (Study B-VEC-EX-02) supports the safety of B-VEC in patients aged between 6 months and less than 12 months. The reviewed safety data do not warrant Risk Evaluation and Mitigation Strategies (REMS), or a safety postmarketing requirement (PMR) clinical study.

B-VEC demonstrated a favorable benefit/risk profile for the treatment of wounds in patients six months of age and older with DEB, with mutation(s) in the *COL7A1* gene. This reviewer recommends approval of this BLA.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Demographic information for 31 subjects in the Phase 3 study (Study B-VEC-03) is shown in Table 1.

Table 1. Demographic and Baseline Characteristics for the Phase 3 Study (B-VEC-03)

Characteristic	**Subjects (ITT Population) (N=31)**
Age, year	-
Mean (SD)	17.2 (10.70)
Median (minimum, maximum)	16.1 (1, 44)
Age range, year	-
≤12 years, n (%)	10 (32.3)
>12 and <17 years, n (%)	8 (25.8)
≥17 years, n (%)	13 (41.9)
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)
Non-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)

Characteristic	Subjects (ITT Population) (N=31)
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)

Source: The reviewer adapted from the summary of clinical efficacy (module 2.7.3) Table 8, page 22, submitted in BLA 125774/0.
Abbreviations: B-VEC, beremagene geperpavec-svdt; DEB, dystrophic epidermolysis bullosa; ITT, intent-to-treat; SD, standard deviation.

1.2 Patient Experience Data

Patient experience data relevant to this submission are summarized in Table 2.

Table 2. Patient Experience Data Relevant to This Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	6.1.8, Endpoints and Criteria for Study Success
☒	Observer-reported outcome	6.1.2, Design overview 6.1.8, Endpoints and Criteria for Study Success
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	

☐	FDA Patient Listening Session	
☒	Other stakeholder meeting summary report	2.1, Disease or Health-Related Condition(s) Studied
☐	Observational survey studies	
☐	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

DEB is a rare and clinically and genetically heterogeneous skin fragility disorder characterized by blistering of the skin and mucosal membranes that heal with scarring. The onset of symptoms is usually at birth or in early childhood. There may be associated complications, including malnutrition, anemia, infection, and skin cancer. Death may occur prematurely due to multiple causes, including infection, progression of disease, organ failure, and malignancy.

DEB is caused by mutations in the *COL7A1* gene, which results in reduced or absent levels of biologically active COL7. COL7 is a structural component of AFs, which hold the epidermis and dermis together and are essential for maintaining the integrity of the skin.

DEB can be inherited in an autosomal dominant (DDEB) or recessive (RDEB) fashion. In DDEB, the predominant type of mutation is a missense mutation in one of the two alleles of the *COL7A1* gene resulting in a glycine substitution within the triple helical domain of the pro-alpha-chain COL7. Both the mutant and the wild-type alleles are expressed in DDEB and result in some AFs that are functionally intact. RDEB is a more severe form, in which nonsense mutations, deletions, insertions, or splice-site mutations with frame shift of translation typically result in premature termination codons in both alleles of the *COL7A1* gene. Homozygosity or compound heterozygosity for premature termination codon mutations in the *COL7A1* gene result in null alleles and complete absence of AFs.

RDEB severe generalized is the most severe form of the condition. Affected infants are typically born with widespread blistering and areas of missing skin, often caused by trauma that occurs during birth. Most often, blisters are present over the whole body and affect mucous membranes such as the moist lining of the mouth and digestive tract. As the blisters heal, they result in severe scarring. Scarring in the mouth and esophagus can make it difficult to chew and swallow food, leading to chronic malnutrition and slow growth.

Additional complications of ongoing scarring may include fusion of the skin between the fingers and toes, loss of fingernails and toenails, joint deformities (contractures) that restrict movement, and eye inflammation leading to vision loss. Additionally, patients with RDEB severe generalized have a very high risk of developing squamous cell carcinoma (SCC) in young adulthood.

Based on the National Epidermolysis Bullosa Registry in US from 1986 to 2002 (Fine 2016), the prevalence of RDEB in the US was estimated to be 1.35 persons per million inhabitants and DDEB was estimated to be 1.49 persons per million inhabitants.

As part of the FDA Externally Led Patient-Focused Drug Development initiative, on April 6, 2018, a joint public meeting led by Pachyonychia Congenita (PC) Project and the Dystrophic Epidermolysis Bullosa Research Association of America (DEBRA) (Pachyonychia Congenita Project 2018) was held.

The following pertinent questions were asked during the meeting with the responses gathered from the attendants (in person and online):

- Would you consider participating in a clinical trial?
  - Yes, I have participated in a trial, and I would do so again. 54%
  - Yes, I have participated in a trial, and I would not do so again. 0%
  - No, I have not participated in a trial, because I didn't know about the opportunity. 31%
  - No, I chose not to participate after being offered to. 6%
  - Not sure 9%
- Which outcome below would you rate as MOST important for a possible drug or to treat EB? (Select only 1)?
  - Would decrease frequency of blistering or wounding 67%
  - Would stop or slow down the progression of EB but might have some potential side effects 27%
  - Would increase the speed at which a wound would heal 3%
  - Would lessen, but not totally relieve, symptoms with few side effects 3%

On June 15, 2022, DEBRA held a listening session with FDA. Patients with DEB and their caregivers shared their perspectives of the disease that mattered most to them. The representatives from DEBRA stated that any wound area reduction or pain reduction would be considered important to them.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

There are no FDA-approved treatments for DEB. Management of DEB is supportive and includes wound care, pain management, control of infection, nutritional support, and prevention and treatment of complications.

FDA approved a Humanitarian Devices Exemption device, Composite Cultured Skin to be used as a wound dressing in patients with mitten hand deformity due to RDEB as an adjunct to standard autograft procedures [i.e., skin grafts and flaps for covering wounds and donor sites created after the surgical release of hand contractions (i.e., "mitten" hand deformities)].

2.3 Safety and Efficacy of Pharmacologically Related Products

This is a novel HSV-1 vector-based gene therapy product. There are no pharmacologically related products currently available.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

The product is not approved in any country. No foreign clinical data were submitted in the BLA.

2.5 Summary of Pre- and Post-Submission Regulatory Activity Related to the Submission

FDA engaged and corresponded with the Applicant on multiple occasions before and after the Investigational New Drug (IND) application and BLA submission. Major regulatory milestones are summarized in Table 3.

Table 3. Major Regulatory Milestones

Correspondence	Pertinent Comments/Information
October 13, 2016	Pre-IND Meeting (PS 003039)
November 2, 2017	Granted Orphan Drug designation
March 26, 2018	BB IND 18100 submission with the Phase 1/2 study
May 23, 2018	Granted Fast Track designation
June 21, 2019	Granted RMAT designation
November 21, 2019	RMAT initial comprehensive teleconference
February 20, 2020	End of Phase 2 meeting
March 22, 2022	Pre-BLA meeting
August 18, 2022	BLA filed, granted Priority Review designation
August 22, 2022	Granted Rare Pediatric Disease designation (RPD-2016-95) for RDEB and DDEB
October 25, 2022	BLA 120-Day Safety and Efficacy Update received
January 5, 2022	Add three months to the review cycle due to CMC major amendment
May 19, 2023	PDUFA Action goal date

Source: The reviewer.
Abbreviations: BLA, Biologics License Application; CMC, Chemistry, Manufacturing, and Controls; DEB, Dystrophic Epidermolysis Bullosa; IND, Investigational New Drug application; PDUFA, Prescription Drug User Fee Act; RDEB, Recessive Dystrophic Epidermolysis Bullosa; RMAT, Regenerative Medicine Advanced Therapy.

End-of-Phase 2 meeting: February 20, 2020

- FDA expressed the concern that the study design based on an intra-subject comparison would compromise the evaluation of systemic toxicity.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. The BLA was filed on August 19, 2022.

3.2 Compliance With Good Clinical Practices And Submission Integrity

Both the Phase 1/2 study and Phase 3 study enrolled only subjects in the US and were conducted under IND 018100, in accordance with the regulations specified in 21 CFR 312 and were compliant with Good Clinical Practice international ethical and scientific quality standards for the design, conduct, recording, and reporting of clinical trials involving human subjects. The clinical trials included provisions for informed consent by parents or guardians of all study subjects and for ethical treatment of study subjects.

During the BLA review, routine Bioresearch Monitoring inspections were conducted at three domestic CI sites (Table 4) participating in the conduct of study Protocol B-VEC-03. The inspections did not reveal significant problems impacting the data submitted in support of this BLA. Table 4 below summarizes the BIMO inspections.

Table 4. Summary of BIMO Inspections at Three Clinical Investigator Sites

Site ID	Number of Subjects Randomized	Location	483 Issued	Final Inspection Classification
01	14	M. Peter Marinkovich, MD Redwood City, CA	No	No Action Indicated (NAI)
02	8	Mercedes Gonzalez, MD. Coral Gables, FL	No	NAI
03	9	Shireen V. Guide, MD Rancho Santa Margarita, CA	Yes	Voluntary Action Indicated (VAI)

Abbreviations: BIMO, Bioresearch Monitoring Program Information
Source: From BIMO review

3.3 Financial Disclosures

No significant issues with financial disclosures were identified that could lead to undue bias in the data submitted in support of this BLA.

Covered clinical study (name and/or number): KB103-001 B-VEC-03
Was a list of clinical investigators provided? ☒Yes ☐No (Request list from applicant)
Total number of investigators identified: 4
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0 Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☐ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? ☐ Yes ☐ No (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0

Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

All of the studies included in this application were conducted in accordance with FDA regulations, the International Council for Harmonisation (ICH) E6 Guideline for Good Clinical Practice, Declaration of Helsinki, and applicable local, state, and federal laws. Each study was reviewed and approved by the appropriate institutional review boards and biosafety committees, as required.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

B-VEC is a biological suspension of an HSV-1 vector-based gene therapy that expresses two copies of a (b) (4) transgene encoding COL7, mixed with excipient gel, for topical application. B-VEC is supplied in a 1.0 mL extractable volume in a single dose (b) (4) mL vial at a nominal concentration of 5×109 plaque forming units (PFU)/mL per vial. The excipient gel is supplied in a 1.5 mL extractable volume in a single use 2 mL vial. B-VEC (1 mL) is combined with 1.5mL of excipient gel prior to administration.

Please refer to Chemistry, Manufacturing, and Controls review for further details.

4.2 Assay Validation

Please refer to Chemistry, Manufacturing, and Controls review for details.

4.3 Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review team recommends approving the application from their perspective with the recommended labeling revisions. The Pharmacology/Toxicology program to support the BLA is summarized below. Please refer to Dr. Theresa Chen's Pharmacology/Toxicology review for further details.

4.4 Clinical Pharmacology

PD activity was evaluated in the Phase 1/2 study (KB103-001). Biopsies of skin following B-VEC treatment were evaluated for expression and localization of both COL7's NC1 and NC2 domains at the basement membrane zone (BMZ; i.e., the dermal-epidermal junction) via immunofluorescence (IF). Further, biopsies were evaluated for the presence of AFs after B-VEC treatment via immunoelectron microscopy (IEM).

Pharmacokinetics (PK) was assessed by viral vector biodistribution and shedding. Traditional PK studies based on absorption, distribution, metabolism, and excretion were not performed for B-VEC, as they were not deemed relevant given the product's physicochemical properties, route of administration, and mechanism of action (MOA).

Immunogenicity to HSV-1 and COL7 were also assessed as part of the Phase 1/2 and Phase 3 (Study B-VEC-03) studies.

Please refer to the Clinical Pharmacology review for further details.

4.4.1 Mechanism of Action

DEB is associated with loss-of-function mutations in the *COL7A1* gene encoding COL7, which is a major component of AFs that are responsible for adhering the epidermal layer of the skin onto the underlying dermis via a basement membrane (Tidman and Eady 1985; Burgeson 1993; Dunnill et al. 1996).

Following topical administration of B-VEC, the proposed MOA involves the following sequential events:

- Entry into cells (e.g., keratinocytes and fibroblasts)
- Transport to nucleus and expression of *COL7A1* transgenes
- Secretion of COL7
- Assembly of secreted COL7 into AFs.

As B-VEC is nonintegrating (i.e., its genetic material remains physically separate from the host cell chromosome), it is not anticipated to carry the potential risk of insertional mutagenesis to trigger oncogenesis.

4.4.2 Human Pharmacodynamics

PD activity was evaluated in the Phase 1/2 study. The expression, secretion, and localization of COL7 transgene in skin biopsies was evaluated based on IF detection of NC1 and NC2 of COL7, and IEM methods.

The Phase 1/2 study was divided into 4 phases: Phase 1, Phase 2a, Phase 2b, and Phase 2c. Nine (9) unique subjects participated in the study. Three of the 9 subjects enrolled in both Phase 2a and Phase 2b with adequate washout period. These three subjects contributed different wounds for treatment and evaluation in Phase 2a and Phase 2b, except for one chronic dorsal foot wound from a subject who achieved partial closure and was selected to continue treatment in Phase 2b. The rollover subjects from Phase 2a had different identification numbers in Phase 2b, hence the study has 12 unique identification numbers. Please refer to Section 6.1 of this review for further details of the Phase 1/2 study (Study KB103-001).

The PD endpoints include the detection of the NC1 and NC2 of COL7 and linear deposition of both domains at the dermal-epidermal junction or BMZ.

Reviewer Comment:
The PD endpoints were considered reasonable because the NC1 and NC2 constitute main functional domains of COL7.

The following is a summary of the PD results from the Phase 1/2 study:

- At baseline (pretreatment), skin biopsies from the 12 subjects (9 unique and 3 re-enrolled) were negative for NC2 domain of COL7. A lower expression of NC1 domain of COL7 (<20% of normal skin) was noted in all 12 subjects.

Reviewer Comment:
The expression of NC1 and NC2 domains of COL7 does not appear to sustain for the three re-enrolled subjects after a washout period, which indicates repeated (e.g., weekly) application of B-VEC on DEB wounds is likely necessary to maintain the biological effect.

- Following B-VEC application, nine skin biopsies were collected from six unique and three re-enrolled subjects (three subjects did not provide post-treatment skin biopsies). B-VEC florescence intensity for NC1 domain was increased in 8 out of 9 skin biopsies (fluorescence intensity of 30-100% of normal skin), and the NC2 domain is expressed in 8 out of 9 biopsies (30-100% of normal skin). In one treated subject with baseline anti-COL7 antibodies, no detection of NC2 domain and a small increase in expression of NC1 domain (30% of normal skin) were observed.
- For the 3 subjects whose biopsies were analyzed by IEM, <25% of normal skin NC1 and NC2 staining was observed at baseline. Following topical application of B-VEC, IEM analysis revealed detectable (>25-100% of normal skin) and appropriately localized AFs at the BMZ.

In conclusion, the PD activity (expression, secretion, and localization of COL7 transgene) was demonstrated in nine skin biopsies (n=6 unique subjects) in the Phase 1/2 study.

Reviewer comment:
The PD data provided confirmatory evidence of effectiveness of B-VEC for the treatment of DEB wounds.

4.4.3 Human Pharmacokinetics

Vector Biodistribution (Within the Body) and Vector Shedding (Excretion/Secretion and Infectivity)

In the Phase 1/2 study, viral vector DNA was detected in skin swab samples in all nine treated subjects with maximum levels ranging from 5.1×10^4 to 4.1×10^8 vector genomes. In 6 out of 9 subjects (67%), negative shedding was confirmed with three measurements below limit of detection within 8 weeks of treatment with B-VEC. No viral vector DNA was detected in blood or urine.

In the Phase 3 study, systemic and potential environmental exposure assessments were conducted at weekly clinical site visits via quantification of B-VEC genomes in blood, urine, skin swabs, and bandage samples (vector shedding) using a validated quantitative polymerase chain reaction assay, and detection of infectious viral particles in skin swabs (infectivity) using a validated plaque titer assay.

All blood samples and all but one urine sample collected throughout the study were below the limit of detection/quantification for all subjects. Skin swabs from 19 of the 31 subjects (61.3%) were positive for viral vector following treatment with B-VEC. Negative shedding from skin swabs was achieved in 16 of the 19 subjects (84.2%) within six weeks following treatment with B-VEC. Most wound dressings (93.5%, 29/31) contained a range of detectable vector genomes. However, no extracellular infectious particles were detected on the skin surface of any subject at any timepoint tested after topical B-VEC application.

The Clinical Pharmacology reviewer concluded that the viral vector kinetic analysis demonstrates no systemic exposure (blood and urine) following topical application of B-VEC.

Reviewer comment:
The lack of systemic exposure following topical application of B-VEC on DEB wounds indicates that the observed systemic adverse events (AEs) in the clinical studies were unlikely related to the B-VEC treatment.

Immunogenicity

Antibodies against viral vector (HSV-1) and transgene protein (COL7) were evaluated in the Phase 2 and Phase 3 studies. A total of 63.6% of evaluated subjects (14/22) were anti-HSV-1 antibody positive at baseline. Six of the 8 anti-HSV-1 seronegative subjects seroconverted by Week 26 following treatment with B-VEC. For subjects with available matched baseline and end-of-study serum samples, antidrug antibodies to COL7 were detected in 72.2% (13/18) of subjects treated with B-VEC for up to 26 weeks.

The Clinical Pharmacology reviewer concluded that although the sample size is limited, PD activity is demonstrated in subjects with baseline anti-HSV-1 antibodies. It appears that pre-existing anti-COL7 antibodies did not impact PD activity. The data suggest that serum antibodies against HSV-1 and COL7 do not affect local transduction and transgene expression following topical application of B-VEC.

4.5 Statistical

The Statistical reviewer verified that the primary study endpoint analyses cited by the Applicant were supported by the submitted data. Please see Dr. Qianmiao (Ann) Gao's the statistical review for further details.

4.6 Pharmacovigilance

There have been two ongoing studies to continuously collect safety and efficacy information of B-VEC on patients with DEB:

- An open-label extension (OLE) study (B-VEC-EX-02) provides continued access to B-VEC for subjects who participated in the Phase 3 study, as well as new DEB subjects who were unable to participate in the Phase 3 study.

- A 5-year long-term follow-up (LTFU) prospective study (KRYS-LTFU-01) for subjects who have completed the Phase 3 study (B-VEC-03) or completed the OLE study (B-VEC-EX-02) consists of annual assessments for collection of SAEs for five years and annual safety reports will be submitted to the FDA per regulatory regulations.

In addition, the Applicant proposes routine pharmacovigilance for post-approval safety monitoring.

Based on review of available data, the safety concerns from the Phase 1 and Phase 3 clinical trials can be monitored through routine medical practice, adequate prescribing information, and the voluntary postmarketing plans proposed by the Applicant. The reviewed safety data do not substantiate the need for a Risk Evaluation and Mitigation Strategy, a safety postmarketing requirement study, or a safety postmarketing commitment study from a clinical perspective.

Please see the Pharmacovigilance review for further details.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The clinical program of B-VEC consists of the following studies:

- Completed studies
  - A Phase 3 study: Study B-VEC-03
  - A Phase 1/2 study: Study KB103-001
- Ongoing studies
  - An OLE study: Study B-VEC-EX-02
  - An observational LTFU study: Study KRYS-LTFU-01

The safety and efficacy evaluations of B-VEC were primarily focused on data from the Phase 3 study (Study B-VEC-03). The efficacy and safety findings will be included in the United States Prescribing Information (USPI).

The review of the Phase 1/2 Study (Study KB103-001) was focus on the PD activity of the product on B-VEC-treated skin. Such data provide mechanistic evidence of PD activity of the product on the target skin and serve as confirmative evidence of effectiveness to support the BLA. This assessment is described in Section 4.4.2 of this review. Further details can be found in the Clinical Pharmacology review.

The efficacy and safety findings of the Phase 1/2 study are not integrated with the Phase 3 study because each subject in the Phase 1/2 study received variable doses and dosing regimens, which were significantly different from the weekly dose and dosing regimen used in the Phase 3 study. Additionally, most frequently reported drug-related AEs were associated with the intradermal route of administration, which was only used to establish evidence of PD activity. The doses and dosing regimens and the route of intradermal injection were not used in the Phase 3 study or proposed for commercial use. The efficacy and safety findings of Phase 1/2 study (Study KB103-001) are briefly described and discussed in Section 6.2.

The objectives of the OLE study (Study B-VEC-EX-02) were to provide continued use of B-VEC and collect safety information in patients who completed Phase 3 study and naïve patients who did not participate in the Phase 3 study. The Applicant submitted safety updates from the ongoing OLE study (Study B-VEC-EX-02) in the 120-day BLA safety update. During the USPI negotiation, the Applicant submitted additional information of two subjects aged six and seven months, respectively, to support the inclusion of patients with DEB as young as six months of age in the proposed indication. A summary of the OLE study and the safety information of the two young subjects can be found in

Appendix 1.

No data from the observational LTFU study were submitted to the BLA.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The sources for this review are the clinically relevant modules in the BLA submission:

- The administrative and prescribing information in module 1
- Summary clinical information in module 2.5 and 2.7
- Clinical study reports in module 5 including the narrative clinical study reports, appendices, tabulation and analysis datasets, case report forms, and literature references submitted by the Applicant.

In addition, the reviewer used publicly available resources, including UpToDate and PubMed, to understand the disease of the interest.

5.3 Table of Studies/Clinical Trials

Table 5. Summary of Clinical Studies

Study ID/Phase/ Status	Objectives	Study Design	Number of Subjects/ Sex/Age Range, Year	Treatment/Duration
KB103-001 Phase 1/2 Completed	Safety, molecular correction, and preliminary efficacy	Single-center, open-label, intra-subject randomized, vehicle-controlled, 4 phase (1, 2a, 2b, 2c) study.	12 subjects[1] 9 M/3 F 10 to 35 years (Mean 20.3)	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
B-VEC-03 Phase 3 Completed	Safety and Efficacy	Multicenter, intra-subject randomized, vehicle-controlled, double-blind study	31 subjects[2] 20 M/11 F 1 to 44 years (Mean 17.2),	Topical treatment with B-VEC or placebo (vehicle) gel <u>Dose/wound varied by wound area:</u> 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 <u>Maximum weekly dose varied by age:</u> 1.6×10^9 PFU for ≥6 months (mos) to <3 years (yrs) 2.4×10^9 PFU for ≥3 yrs to <6 yrs 3.2×10^9 PFU for ≥6 yrs <u>Treatment duration:</u> Once weekly for 26 weeks

Study ID/Phase/ Status	**Objectives**	**Study Design**	**Number of Subjects/ Sex/Age Range, Year**	**Treatment/Duration**
B-VEC-EX-02 OLE of the Phase 3 study Ongoing	To provide continued access to B-VEC for subjects who completed B-VEC-03 and naïve subjects with DEB.	Cohort 1: Subjects who completed B-VEC-03 and naïve subjects with DEB Cohort 2: Subjects who completed B-VEC-03 (no further B-VEC treatment)	Planned: Cohort 1: ~40 Cohort 2: ~10	Topical treatment with B-VEC gel Maximum weekly dose per subject = 10^9 PFU/mL Subjects <3 yrs receive half the volume of subjects ≥3 yrs Treatment duration: once weekly for 78 weeks
KRYSLTFU-01 Long-term safety follow-up study Ongoing	Long-term safety evaluation of the gene therapy products that have a shared backbone of HSV-1	Multicenter, prospective, observational, cohort study	Determined by parent protocol	None (observational only)

Source: The reviewer adapted from the summary of the clinical overview (module 2.5) Table 1, page 22, submitted in BLA 125774/0.
[1.] Includes 3 subjects who were re-enrolled in a later phase for treatment of different wounds after approximately a 3-month washout.
[2.] Includes 5 subjects who were treated in Study KB103-001 for different wounds at least a year prior to Study B-VEC-03.
Abbreviations: B-VEC, beremagene geperpavec-svdt; DEB, dystrophic epidermolysis bullosa; DDEB, dominant DEB; F, female; M, male; mos. months; OLE, open-label extension; PFU, plaque forming units; RDEB, recessive DEB; yrs, years.

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

No advisory committee meeting was held because initial review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

5.4.2 External Consults/Collaborations

Not applicable.

5.5 Literature Reviewed (if applicable)

During review of the BLA, this reviewer consulted FDA regulatory guidance documents, as well as academic literature for background and context regarding the targeted disease and the MOA of the product. The literature consulted is listed in References.

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1: B-VEC-03

Study Title: A Phase 3 Efficacy and Safety Study of Beremagene Geperpavec (B-VEC, Previously KB103) for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)

Clinical Trial Registry Identifiers: ClinicalTrials.gov: NCT04491604

6.1.1 Objectives (Primary, Secondary, etc.)

The primary objective was to determine whether topical administration of B-VEC in addition to the standard of care improved wound healing as compared with placebo in children, adolescents, and adults with DEB.

Reviewer Comment:
The language of the study objective was taken verbatim from the clinical study report of the B-VEC-03 trial (Module 5.3.5.1) under the study objective. The protocol did not specify the secondary objectives.

6.1.2 Design Overview

The study was a multicenter, intra-subject randomized, placebo-controlled, double-blind, Phase 3 study of B-VEC for topical application on DEB wounds. Each subject serves as his/her own control by contributing a primary wound pair to be randomized to receive weekly topical application of either B-VEC or the placebo (excipient gel). The primary wound pair was selected to evaluate the primary and key secondary endpoints and the wounds in the pair were matched in size and anatomical locations. The duration of the study includes a 26-week treatment duration followed by an additional month of safety follow-up.

In addition to the primary wound pair, the investigators selected a few unmatched secondary wounds (the number of secondary wounds varied in each subject) in each subject to receive open-label B-VEC treatment. The total dose applied to the primary and secondary wounds each week did not exceed the maximum weekly dose.

Study visits occurred at screening and weekly for 26 weeks, followed by a safety follow-up visit 30 days (±4 days) from the last B-VEC application. Wound areas for primary and secondary wounds at baseline were determined by the investigator using Canfield photography quantitation. The primary endpoint was assessed at weeks 22 and 24, or 24 and 26 and the key secondary endpoint was assessed at weeks 8 and 10, or 10 and 12, for wound closure by the blinded investigator.

After the safety follow-up / early termination visit, subjects had the option to enroll into the OLE study (B-VEC-EX-02). If subjects did not participate in the OLE study, they were asked to roll over into the five-year LTFU study (KRYS-LTFU-01).

Reviewer Comment:
1. The intra-subject randomization and comparison of DEB wounds have their strength and limitation in assessing the efficacy and safety.

    a. The comparisons of local effects (e.g., wound closure and local AEs) between different treatment groups can be facilitated by eliminating inter-subject variation.

    b. Such design (i.e., absence of a concurrent control group consisting of subjects receiving only placebo) may confound the interpretation of systemic effects (e.g., systemic AEs), considering the complicated clinical manifestations of DEB and multiple concomitant treatments used in this population. This concern was conveyed to the Applicant during the clinical development under IND 18100 and communicated with the Applicant via information requests (IRs) during the BLA review cycle. The issue is further discussed in Section 6.1.12 (safety analysis).

2. The intra-subject control design also raises concerns on adequacy of blinding given that one subject may contribute multiple wounds including, one blinded primary wound pair to receive either B-VEC or placebo, and several unblinded secondary wounds to receive B-VEC. The concerns were discussed with the Applicant via IRs. The Applicant responded adequately with the following justification on September 29, 2022.

    a. The principal investigator at each site was the sole individual who assessed each subject's primary wound pair at all timepoints for primary and secondary endpoints assessment. The principal investigators were blinded for the entire duration of the study.

    b. The same excipient gel was mixed with isotonic saline and B-VEC at the same ratio to be used as placebo and active treatment, respectively, and were dispensed at the same volume (i.e., 0.2mL in each syringe). The placebo gel and the B-VEC gel had the same viscosity and were similar in appearance.

3. The primary endpoint and the key secondary endpoint were assessed at two sets of time (e.g., primary endpoint: Weeks 22 & 24 or Weeks 24 & 26), which subjected the data to bias because the Applicant was given an option to choose the better result of the two results that would lead to an overall better outcome. This issue is further analyzed and discussed in Section 6.1.11 (Efficacy Analysis).

6.1.3 Population

Key enrollment criteria were as follows:

Inclusion Criteria:

- Age ≥6 months at the time of informed consent
- Confirmation of DEB diagnosis (either DDEB or RDEB) by genetic testing, including *COL7A1*
- Two cutaneous wounds meeting the following criteria:
  - Location: similar in size, located in similar anatomical regions, and similar in appearance
  - Appearance: clean with adequate granulation tissue, excellent vascularization, and did not appear infected
- Male or female subjects 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 B-VEC
- Negative pregnancy test at Visit 1 (Week 1), if applicable

Reviewer Comment:
The Applicant confirmed that genetic testing to identify mutations in the *COL7A1* gene was conducted in all subjects to confirm the diagnosis of DEB. The genetic testing results were reviewed and confirmed by a certified geneticist.

Exclusion Criteria

- Diseases or conditions that could have interfered with the assessment of safety and efficacy of the study treatment and compliance of the subject with study visits/procedures, as determined by the investigator
- Current evidence or a history of SCC in the area that would undergo treatment
- Subjects who were actively receiving chemotherapy or immunotherapy at Visit 1 (Week 1)
- Active drug or alcohol addiction as determined by the investigator

- Hypersensitivity to local anesthesia (lidocaine/prilocaine cream)
- Participation in an interventional clinical trial within the last 3 months (not including B-VEC application)
- Receipt of a skin graft in the last 3 months

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects were treated weekly by topical application of B-VEC or placebo for up to 26 weeks or until wound closure. The dose was calculated based on the subject's age and the wound size. The wounds were measured at Visit 1 by an investigator using a Canfield photography quantitation system. The unit dose (Table 6) were determined based on this initial measurement.

Each primary wound pair was treated with either B-VEC or placebo based on the randomization schedule. Secondary wounds were treated with B-VEC until the maximum weekly dose (Table 7) was used.

Table 6. Unit Dose Based on Wound Area

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

Source: The reviewer adapted from the clinical study report for Study B-VEC-03 (module 5.3.5.1) page 21, submitted in BLA 125774/0.
Abbreviations: PFU, plaque-forming unit.
*For wound area over 60 cm^2, recommend calculating the total dose based on this table until the maximum weekly dose is reached.

Table 7. Maximum Weekly Dose Based on Age at the Visit

Age Range	Maximum Weekly Dose (PFU)	Maximum Weekly Volume (mL)*
6 months to <3 years old	1.6×10^9	0.8
(b) (4)	(b) (4)	(b) (4)
≥ 3 years old	3.2×10^9	1.6

Source: The reviewer adapted from the clinical study report for Study B-VEC-03 (module 5.3.5.1) page 21, submitted in BLA 125774/0.
Abbreviations: PFU, plaque-forming unit.
*Maximum weekly volume after mixing VYJUVEK biological suspension with excipient gel.

Reviewer comment:
The maximum weekly dose in each age groups (Table 7) reflected the dose and dosing regimen used in the Phase 3 study. Based on the following justification, the Applicant proposed a simplified maximum weekly dose as illustrated in the table below in the USPI.

1. (b) (4) PFU to 3.2×10^9 PFU are within the release specification range of (b) (4) PFU for B-VEC, with no discernable difference between the two doses.

2. The simplified dose calculation is more straightforward for prescribing health care providers after B-VEC approval.

Table 8. Simplified Maximum Weekly Dose Based on Ag

Age Range	Maximum Weekly Dose (PFU)	Maximum Weekly Volume (mL)*
6 months to <3 years old	1.6×10^9	0.8
≥ 3 years old	3.2×10^9	1.6

Source: The reviewer adapted from the clinical study report for Study B-VEC-03 (module 5.3.5.1) page 21, submitted in BLA 125774/0.
Abbreviations: PFU, plaque-forming unit.
*Maximum weekly volume after mixing VYJUVEK biological suspension with excipient gel.

Per communication with the CMC reviewer, Dr. Bo Liang and the BLA committee chair, Dr. Anna Kwilas, the viral titers of (b) (4)) and 3.2 x 10^9 PFU (1.6 mL of B-VEC) are considered equivalent.

Therefore, the reviewer agrees with the Applicant's proposal of including the table with simplified maximum weekly dose based on the two age groups in USPI.

6.1.5 Directions for Use

Topically applied B-VEC gel consisted of thawed cryopreserved drug product, B-VEC, mixed with the excipient gel, Methocel. Placebo consisted of excipient gel, mixed with isotonic saline, without the active drug product.

B-VEC gel was prepared in 1 mL syringes each containing either 4×10^8 PFUs of B-VEC gel or an equivalent matching volume of placebo gel at the study site.

6.1.6 Sites and Centers

Study B-VEC-03 is being conducted at the locations listed in Table 9.

Table 9. List of Investigators and Study Sites

Site #	Principal Investigator/Site Address	Sub-Investigators
01	M. Peter Marinkovich, MD Stanford Dermatology Clinic 455 Broadway St., 1st Floor, D126 Redwood City, CA 94063	Isin Sinem Bagci, MD
02	Mercedes Gonzalez, MD Pediatric Skin Research 4425 Ponce de Leon Blvd., Suite 115 Coral Gables, FL 33146	Not applicable
03	Shireen Guide, MD Mission Dermatology Center 29829 Santa Margarita Parkway Rancho Santa Margarita, CA 92688	Kendra Michelle Higgins, PA-C

6.1.7 Surveillance/Monitoring

The assessment schedule for Study B-VEC-03 is detailed in Table 10.

Table 10. Schedule of Events for Study B-VEC-03

Visit week (Window)	Screening[1] (-60 to 0)	Week 1	Week 2-21 (± 3 Days)	Week 22 (± 3 Days)	Week 32 (± 3 Days)	Week 24 (± 3 Days)	Week 25 (± 3 Days)	Week 26 (± 3 Days)	Safety Follow-up/ET (30 Days After Last Dose)
Physical exam[10]	X	X[2]							
Inclusion/exclusion criteria		X							
Demographics	X	X[2]							
Medical history	X	X[2]							
Genetic testing	X[1]								
Wound selection		X							
Wound randomization[3]		X							
Pain assessment- wound pair[4]		X		X		X		X	
Quality of Life Questionnaire (EQ-5D)[5]		X						X	
Skindex-29 questionnaire[5]		X						X	
Imaging[6]		X	X	X	X	X	X	X	X
Assessment of wound closure[7]		X	X	X	X	X	X	X	
Swabs for viral shedding/infectivity[8]		X	X	X	X	X	X	X	
Swabs for viral shedding on dressing returned[9]			X						
Physical exam[10]		Complete						Abbrev	Abbrev
Treatment and procedure review[11]	X	X	X	X	X	X	X	X	X
Medication review[11]	X	X	X	X	X	X	X	X	X
AE and SAE review		X	X	X	X	X	X	X	X
Vital signs[12]		X	X				X		X
Urine pregnancy test[13,14]		X						X	
Urine for viral shedding[15]	X	X[2]						X	
CMP w/ direct bilirubin[15]	X	X[2]						X	
CBC/Diff[15]	X	X[2]						X	

Visit week (Window)	**Screening[1] (-60 to 0)**	**Week 1**	**Week 2-21 (± 3 Days)**	**Week 22 (± 3 Days)**	**Week 32 (± 3 Days)**	**Week 24 (± 3 Days)**	**Week 25 (± 3 Days)**	**Week 26 (± 3 Days)**	**Safety Follow-up/ET (30 Days After Last Dose)**
COL7 & HSV serum ADA[15]	X	X[2]		X		X		X	
Whole blood viral shedding[15]	X	X[2]						X	
IP application[16]		X	X	X	X	X	X	X	
Roll-over to LTFU or OLE protocol[17]									X

Source: The reviewer adapted from Study Report for B-VEC-03s, submitted in BLA 125774/0 on June 20, 2022.
1. If genetic testing is required, this test may occur up to 60 days prior to the other screening procedures, following subject consent/assent. Genetic testing may take 6-8 weeks to obtain results.
2. Informed consent/assent, demographics, medical/procedural history, urine (if male), and blood specimens will not be recollected if collected at a screening visit.
3. The matched primary wound pair will be randomized.
4. Pain questionnaires are to be completed during the dressing change of the individual matched wounds. If subject is 6 years of age or older, they will be asked to complete the VAS questionnaire for matched wounds during the dressing change. If younger than 6 years of age, their parent/caregiver will be administered the FLACC-R questionnaire for the matched wounds during the dressing change (refer to Section 9.6.2).
5. Both the Quality of Life (EQ-5D) and Skindex-29 Questionnaires will be administered to subjects 12 years of age and older at the time of consent. Questionnaires may be administered for the subject to complete after the visit and bring back at the next scheduled visit.
6. Images will be collected on both closed and open wounds. Image in the same order and orientation at each visit prior to IP application.
7. Primary wound closure assessments will be evaluated by the investigator only at Weeks 8, 10-12, 22-24, and 26. Secondary wound closure is assessed weekly to determine if a new wound may be selected to receive treatment if the originally selected area and its neighboring wound/s have closed, as applicable.
8. Viral shedding and infectivity swabs will be collected from the primary matched wounds only and will be collected whether the wound is open or closed.
9. Subjects are required to bring the study visit wound dressing back to the site. Primary wound dressings will be separately bagged. Secondary wound dressings may be bagged together. Once returned to the site, viral shedding swabs will be collected for all primary wound dressings that came into contact with the subject's skin. Attempt collection of 4 consecutive VS dressing returns; if unable, collect at least 4 dressing VS samples per subject. Once 4 VS samples have been collected from the primary wound pair, all dressings may be bagged together and returned to the site for disposal and specimen collection will be discontinued.
10. The physical examination is described in Section 9.6.5.1.
11. All medication taken 3 months prior to Screening/Visit 1 through the end of the study will be recorded as well as all applicable procedures and treatments within the last 3 months prior to Screening/Visit 1.
12. On days on which both vital signs and blood draws occur, attempt to take vital signs prior to the blood draw. Vital signs are collected every 5 visits (Visits 1, 5, 9, 13, 17, 21, 25, and at SFU/ET). Vital signs may be obtained more frequently as determined by the investigator.
13. A urine pregnancy test will be completed on all women of childbearing potential prior to blood collection and drug administration, as determined by the investigator.
14. Subjects with history of genitourinary involvement, including painful urination due to the underlying disease, and subjects who are 4 years of age and younger are not required to provide a urine sample, as determined by the investigator. Documentation must be recorded on the CRF and listed in medical history.
15. Labs will be attempted unless, per the discretion of the investigator, it is not in the best interest of the subject. If labs are attempted and not obtained, documentation will be noted in the study visit. Furthermore, if labs are not attempted, justification must be recorded in the study visit. The investigator must determine clinical significance for out-of-range values.
16.Conduct all other study visit procedures prior to B-VEC and placebo administration. Matched Wounds: IP will be applied to wounds that are open. If a matched wound and neighboring wound are closed, no IP will be applied and application will be re-initiated once the wound reopens at a scheduled visit, as determined by the investigator. Secondary Wounds: IP will only be applied to open wounds as determined by the investigator, not to exceed the remaining weekly dose. IP may be applied to immediate neighboring wounds. Up to 4 unmatched Secondary Wounds may be selected to receive open-label B-VEC during the study treatment. Trace the area that is receiving treatment (including the neighboring wounds). Neighboring wounds are defined as wounds approximately 2-3 cm away from the original matched and unmatched (Primary and Secondary) wound.
17. At the SFU (30 days ± 4 days) following the last dose of B-VEC, subjects may roll over into an OLE protocol or will be asked to roll over into an LTFU protocol.
Abbreviations: ADA, antidrug antibodies; AE, adverse event; CBC/Diff, complete blood count with differential; CMP, comprehensive metabolic panel; COL7, human type VII collagen; ET, early termination; FLACC-R, Face, Legs, Activity, Cry, Consolability-Revised; HSV, herpes simplex virus; IP, investigational product; LTFU, long-term follow-up; OLE, open-label extension; SFU, safety follow-up; SAE, serious adverse event; VAS, visual analog scale; VS, viral shedding.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint:

The difference in proportion of complete wound closures (responders) in B-VEC-treated and placebo-treated intra-subject primary wound sites at Weeks 22 and 24 or Weeks 24 and 26.

- A responder was defined as having wounds that were closed for at least 2 consecutive weeks at defined timepoints.
- Complete wound closure was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin re-epithelialization without drainage.

Key Secondary Endpoint:

The difference in proportion of complete wound closure in B-VEC-treated and placebo-treated intra-subject primary wound sites at Weeks 8 and 10 or Weeks 10 and 12.

Other Secondary Efficacy Endpoint:

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

Reviewer Comment:

For this review, the wound closure assessments as defined in the primary endpoint and key secondary endpoint were emphasized as they are prespecified and controlled for multiplicity. The analysis was conducted based on the intent-to-treat (ITT) analysis set. The results of the analyses based on these endpoints will be included in USPI.

The efficacy assessment based on the VAS or FLACC-R pain score would have been a clinically meaningful outcome measure to capture the B-VEC's effect on a different important clinical domain of the disease (e.g., pain with wound dressing change) to support the efficacy. However, several issues were identified that limited the interpretation of this endpoint:

1. This endpoint was not prespecified in the statistical analysis plan.
2. The rescue pain medications used around the time of the wound dressing change were not pre-defined or recorded.
3. No imputation strategy was prespecified. No missing pain scores were imputed.

The change in pain severity based on the observed pain scores would subject the analyses to significant bias and is therefore not interpretable. The efficacy assessment based on pain score will not be included in the USPI.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Design Features:

Two matched primary wounds from each subject were randomized at a 1:1 ratio to B-VEC and placebo treatment arms without stratification.

Statistical Hypothesis:

The null hypothesis for the primary efficacy endpoint was the absence of a treatment effect on wound healing against the alternative hypothesis of the presence of a treatment effect on wound healing.

Analysis Populations:

ITT: Analysis set included subjects whose primary wounds were randomized, regardless of whether they received randomized treatment or not.

Statistical Methods:
Analyses of the primary and key secondary efficacy endpoints were conducted on the ITT (n=31) analysis set.

- Primary efficacy endpoint
  - The responder rate at Week 22 and 24 or Week 24 and 26 was analyzed by exact McNemar test with a two-sided Type I error rate of 0.05.
- Key secondary efficacy endpoint
  - The responder rate at Week 8 and 10 or Week 10 and 12 was analyzed by exact McNemar test. The Type I error rate was controlled by fixed-sequence method, i.e., the key secondary endpoint would only be tested if the primary efficacy endpoint was significant and will be subject to the same Type I error rate of 0.05.

Subgroup Analyses:

In the ITT analysis set, subgroup analyses for the primary efficacy endpoint were performed on the following baseline variables:

- Wound surface area:
  - <20 cm^2
  - ≥20 cm^2
- Age of the subjects:
  - ≤12 years
  - >12 and ≤18 years
  - >18 years

Missing Data and Imputation:

The missing primary efficacy endpoint values were imputed with a worst-case scenario imputation strategy as below:

- All the wounds that missed the primary efficacy endpoint value in the B-VEC group were categorized non-responders.
- All the wounds that missed the primary efficacy endpoint value in the placebo group were treated as responders.

Reviewer Comment:
The Applicant originally used the multiple imputation method assuming a missing at random to impute the missing primary efficacy endpoint values with a set of 10 plausible datasets based on a logistic regression model with covariates: treatment, sex, age, race, and primary wound area.

The clinical and statistical team had concerns that the missing data may not be properly imputed for the following reasons:

- The complete wound closure endpoint may be associated with covariates not included in the model or even not measured in the study.
- The association between the endpoint and the covariates may not be properly constructed if the model is inappropriately specified.

The concerns were conveyed to the Applicant via IR communication on September 22, 2022. The Applicant performed primary analysis using the worst-case scenario imputation strategy as we recommended for the primary efficacy and the key secondary endpoints analyses.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The ITT population included all 31 subjects whose primary wounds were randomized. The safety population included all 31 subjects.

6.1.10.2 Demographics

Demographic characteristics for the ITT/safety population are summarized in Table 11.

Table 11. Summary of Demographic Characteristics

Demographic Characteristics	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)

Source: The reviewer adapted from BLA 125774/0; Study Report for B-VEC-03, page 45.
Abbreviations: SD: standard deviation

6.1.10.2 Medical/Behavioral Characterization of the Enrolled Population

The baseline characteristics for the ITT/safety population are summarized in Table 12.

Table 12. Summary of Baseline Characteristics

Baseline Characteristic	All Subjects (N=31)
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)

Baseline Characteristic	All Subjects (N=31)
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)

Source: The reviewer adapted from BLA 125774/0; Study Report for B-VEC-03, page 45
Abbreviations: DEB: dystrophic epidermolysis bullosa; SD: standard deviation

6.1.10.3 Subject Disposition

Thirty-one subjects were randomized and 28 completed the study. Three subjects discontinued the study:

1. Subject (b) (6) was terminated from the study after Week 6 based on the investigator's opinion that it was not in the subject's best interest to continue due to difficulty scheduling and missed appointments.
2. Subject (b) (6) withdrew consent at Week 26 visit due to challenges arranging air transportation to the study site in the setting of the COVID-19 pandemic. This subject missed physical visits for Weeks 22, 23, 25 and 26. The last physical visit to the site was on Week 24. However, the wound closure assessment was conducted remotely at Weeks 22 and 26.
3. Subject (b) (6) chose early termination after Week 12 due to the need to relocate for college.

Among the 31 subjects, five subjects were enrolled in the Phase 1/2 study using different wounds and rolled over to the Phase 3 study with a washout period of over one year (Table 13). Each row in Table 13 represents a unique subject (different subject IDs).

Table 13. Wash Out Period on Subjects Who Rolled Over Between the Phase 1/2 and Phase 3 Studies

Subject ID Phase 1 and 2a in Phase 1/2 Study	Subject ID Phase 2b in Phase 1/2 Study	Last Dose in Phase 1/2 Study	Subject ID in Phase 3 Study	First Dose in Phase 3 Study	Wash Out (Days)
KB103-001(b) (6)	N/A	(b) (6)	B-VEC-03-(b) (6)	(b) (6)	873
KB103-001	KB103-001(b) (6)		B-VEC-03-		623
KB103-001	KB103-001		B-VEC-03-		416
N/A	KB103-001		B-VEC-03-		405
N/A	KB103-001		B-VEC-03-		402

Source: The reviewer adapted from the Applicant's response to clinical information request, submitted to BLA 125774/3 (module 1.11.3) on August 1, 2022.

Reviewer Comment:

1. The Applicant considered the three subjects that discontinued the study had efficacy data missing for primary efficacy assessment. The imputation strategy for efficacy analyses is discussed in section 6.1.11.1.

2. This reviewer considers enrollment rollover of subjects who contributed different wounds acceptable for this rare disease. The washout periods of more than one year appear adequate and unlikely impact the safety or efficacy assessments considering the need for weekly dosing of B-VEC.

3. The protocol deviations were reviewed and were deemed unlikely to affect the efficacy and safety analyses.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Primary Endpoint: The difference in proportion of DEB wound closure in B-VEC-treated and placebo-treated intra-subject primary wound sites at Weeks 22 and 24 or Weeks 24 and 26.

Table 14 summarizes the primary efficacy endpoint analysis. Among the 31 randomized wound pairs, 20 of the 31 (64.5%) B-VEC treated wounds achieved complete closure. Eight of the 31 (25.8%) placebo-treated wounds achieve complete closure. The treatment difference was 38.7% [95% CI: 13.9, 63.5; p= 0.012].

Table 14. McNemar Test Primary Efficacy Endpoint Analysis (Primary): Primary Wound Pairs at Weeks 22 & 24 or Weeks 24 & 26 – ITT Population (N=31)

Responder/Non-Responder Group	B-VEC Responder	B-VEC Non-Responder	Overall	Treatment Difference (95% CI)	P-value[1]
Placebo responder	4 (12.9)	4 (12.9)	8 (25.8)	38.7 (13.9, 63.5)	0.012
Placebo non-responder	16 (51.6)	7 (22.6)	23 (74.2)	-	-
Overall	20 (64.5)	11 (35.5)	-	-	-

Source: The reviewer adapted from the Applicant's response to clinical information request, submitted to BLA 125774/11 (module 1.11.3) on September 30, 2022.
1. p-value is based on exact McNemar test. The missing primary efficacy endpoints from two subjects are imputed by worst-case scenario: for the missing endpoints in B-VEC group, imputed as non-responder; for the missing endpoints in placebo group, imputed as responders. The assessments for Subject (b) (6) were not set to missing.
Abbreviations: B-VEC, beremagene geperpavec-svdt; CI, confidence interval, ITT, intent-to-treat.

Reviewer Comment:
For subject (b) (6) , the B-VEC treated wound (P1) was assessed as Closed at Weeks 22 and 24 and Open at Week 26. The placebo treated wound (P2) was assessed as Open at Weeks 22, 24, and 26. The Applicant originally treated the wound closure data for Weeks 22, 24, and 26 as missing because the wound closure assessment was conducted remotely at Weeks 22 and 26.

The subject traveled from a different state for weekly visits to the study site by flight. The subject was able to make all the weekly visits except for the Weeks 22, 23, 25 and 26 visits, which were missed because of flight cancellations due to the COVID-19 pandemic. The wound closure assessment was performed by a blinded evaluator onsite at Week 24. For Weeks 22 and 26, the principal investigator conducted the evaluation remotely via a zoom video call. The principal investigator visually assessed the exact regions of the body in which the primary wounds were located at the Week 1 Visit (P1: posterior right thigh; P2: lateral right forearm). During the remote assessment, the principal investigator used the Canfield baseline images to locate the exact region, following the same procedure they would have followed at an on-site visit.

According to the FDA Guidance to Industry, Investigators, and Institutional Review Boards titled "Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency", a study-wide change in protocol conduct under the IND regulations protocol amendments that are necessary to prevent imminent hazards to trial participants can generally be immediately implemented with subsequent submission and formal approval by the institutional review board and notification to FDA through filing a protocol amendment to the IND. Because the time of this amendment (virtual assessment of wound closure for subject (b) (6) was close to the time of the BLA submission, the Applicant documented virtual assessment for subject (b) (6) in the BLA application, however, treated this subject as data missing and imputed the data with originally proposed multiple imputation method.

While we request the Applicant to use the worst-case scenario imputation strategy for primary efficacy and the key secondary analyses, a sensitivity analysis was conducted by either treating Subject (b) (6) as data missing or counting the efficacy data obtained through the virtual assessment. Neither sensitivity analysis reached the tipping point of leading to a different efficacy outcome.

In accordance with the FDA guidance, the clinical team determined to include the efficacy data obtained through the virtual assessments in the primary efficacy analyses for Subject (b) (6) . The missing efficacy data from two other discontinued subjects were imputed by the worst-case scenario imputation strategy.

The primary endpoint as defined at two sets of timepoint would allow the Applicant to choose one of two outcomes that shows a favorable result. To better understand the durability of the efficacy, the following additional data were analyzed:

- Five B-VEC-treated wounds that closed at Weeks 22 and 24 had the wounds re-opened at Week 26. All five subjects received B-VEC treatment at Weeks 22, 24, and 26, but not at Weeks 23 and 25.
- Four (4) placebo-treated wounds that closed at Weeks 22 and 24 had wounds re-opened at Week 26.

Reviewer Comment:
The analyses of the five B-VEC-treated wounds that closed at Weeks 22 and 24 but re-opened at Week 26 indicate that repeated weekly application of B-VEC is needed to maintain its effect on the DEB wounds. The finding in the placebo group is consistent with the waxing and waning features of the DEB wounds. The reviewer considers that the numbers of reopened wounds between the B-VEC (5) and placebo (4) groups comparable.

In conclusion, efficacy was demonstrated based on the primary efficacy analyses of the difference in proportion of complete wound closure (defined as 100% closure) at Weeks 22 and 24 or at Weeks 24 and 26 between the B-VEC and the placebo-treated DEB wounds.

6.1.11.2 Analyses of Secondary Endpoints

Key Secondary Endpoint: The difference in proportion of DEB wound closure in B-VEC-treated and placebo-treated intra-subject primary wound sites at Weeks 8 and 10 or Weeks 10 and 12.

Table 15 summarizes the key efficacy endpoint analysis. Among 31 randomized wound pairs, 21 of the 31 (67.7%) B-VEC treated wounds achieved complete closure. Seven of the 31 (22.6%) placebo-treated wounds achieved complete closure. The treatment difference was 45.2% [95% CI: 21.8, 68.5; p= 0.003].

Table 15. McNemar Test Key Efficacy Endpoint Analysis (Sensitivity): Primary Wound Pairs at Weeks 8 & 10 or Weeks 10 & 12 – ITT Population (N=31)

Responder/Non responder Group	B-VEC Responder	B-VEC Non-Responder	Overall	Treatment Difference (95% CI)	P-value[1]
Placebo responder	4 (12.9)	3 (9.7)	7 (22.6)	45.2 (21.8, 68.5)	0.003
Placebo non-responder	17 (54.8)	7 (22.6)	24 (77.4)	-	-
Overall	21 (67.7)	10 (32.3)	-	-	-

Source: The reviewer adapted from the Applicant's response to clinical information request, submitted to BLA 125774/11 (module 1.11.3) on September 30, 2022.
1. p-value is based on exact McNemar test. The missing primary efficacy endpoints are imputed by worst-case scenario: for the missing endpoints in B-VEC group, imputed as non-responder; for the missing endpoints in placebo group, imputed as responders.
Abbreviations: B-VEC, beremagene geperpavec-svdt; CI, confidence interval; ITT, intent-to-treat.

Reviewer Comment:
The efficacy of B-VEC was supported by analyses of the key secondary efficacy endpoint, i.e., the difference in proportion of complete wound closure (defined as 100% closure) at Weeks 8 and 10 or at Weeks 10 and 12 between the B-VEC and the placebo-treated DEB wounds.

6.1.11.3 Subpopulation Analyses

The following subgroup analyses were performed for the primary efficacy endpoint. The subgroup analyses were not prespecified. The randomization of the primary wound pair was not stratified by any baseline covariates. Therefore, all the subgroup analyses were considered post hoc analyses. The Applicant provided the following subgroup descriptive statistical analysis.

By Wound Surface Area

There were only three primary wounds in two subjects with a baseline wound surface area of 40 cm² or more. Thus, the "20 to <40 cm²" and "40 to 60 cm²" categories were combined into one subgroup.

Although the primary wound pairs were matched as closely as possible, there were 3 subjects (B-VEC-03-(b) (6), B-VEC-03-(b) (6), and B-VEC-03-(b) (6), each of whom had one wound <20 cm² and the other wound ≥20 cm². Table 16 displays the subgroup analysis results by wound surface area. In summary,

- For <20 cm² subgroup (n=21), 61.9% of B-VEC-treated wounds compared with 33.3% of placebo-treated wounds (difference, 28.6 percentage points: 95% CI, -1.4% to 58.5%),
- For ≥20 cm² subgroup (n=10), 60.0% of B-VEC-treated wounds compared with 20.0% of placebo-treated wounds (difference, 40.0 percentage points: 95% CI, -9.6% to 89.6%).

Table 16. Primary Efficacy Endpoint Subgroup Analysis by Wound Surface Area: Primary Wound Pairs at Weeks 22 & 24 or Weeks 24 & 26, ITT Population (N=31)

Wound Surface Area	B-VEC Responder	B-VEC Non-Responder	Overall	% Difference (95% CI)
<20 cm²	-	-	-	28.6 (-1.4, 58.5)
Placebo responder	4 (19.0)	3 (14.3)	7 (33.3)	-
Placebo non-responder	9 (42.9)	5 (23.8)	14 (66.7)	-
Overall	13 (61.9)	8 (38.1)	-	-
≥20 cm²	-	-	-	40.0 (-9.6, 89.6)
Placebo responder	0 (0.0)	2 (20.0)	2 (20.0)	-
Placebo non-responder	6 (60.0)	2 (20.0)	8 (80.0)	-
Overall	6 (60.0)	4 (40.0)	-	-

Source: The reviewer adapted from the Applicant's response to clinical information request, submitted to BLA 125774/15 (module 1.11.3) on October 14, 2022.
Abbreviations: B-VEC, beremagene geperpavec-svdt; CI, confident interval; ITT, intent-to-treat.

By Age Group

Analysis of the primary efficacy endpoint at 6 months by age group in the ITT population showed the following responder rates (Table 17):

- For subjects ≤12 years (n=10), 80.0% of B-VEC-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), 55.6% of B-VEC-treated wounds compared to 33.3% of placebo-treated wounds (difference, 22.2 percentage points: 95% CI, -29.1% to 73.6%).
- For subjects >18 years (n=12), 50.0% of B-VEC-treated wounds compared to 33.3% of placebo-treated wounds (difference, 16.7 percentage points: 95% CI, -28.6% to 61.9%).

Table 17. Primary Efficacy Endpoint Subgroup Analysis by Age Groups: Primary Wound Pairs at Weeks 22 &24 or Weeks 24 & 26, ITT Population (N=31)

Wound Surface Area	B-VEC Responder	B-VEC Non-Responder	Overall	% Difference (95% CI)
≤12 years	-	-	-	60.0 (29.6, 90.4)
Placebo responder	2 (20.0)	0 (0.0)	2 (20.0)	-
Placebo non-responder	6 (60.0)	2 (20.0)	8 (80.0)	-
Overall	8 (80.0)	2 (20.0)	-	-
>12 & ≤18 years	-	-	-	22.2 (-29.1, 73.6)
Placebo responder	1 (11.1)	2 (22.2)	3 (33.3)	-
Placebo non-responder	4 (44.4)	2 (22.2)	6 (66.7)	-
Overall	5 (55.6)	4 (44.4)	-	-
>18 years	-	-	-	16.7 (-28.6, 61.9)
Placebo responder	1 (8.3)	3 (25.0)	4 (33.3)	-
Placebo non-responder	5 (41.7)	3 (25.0)	8 (66.7)	-
Overall	6 (50.0)	6 (50.0)	-	-

Source: The reviewer adapted from the Applicant's response to clinical information request, submitted to BLA 125774/15 (module 1.11.3) on October 14, 2022.
Abbreviations: B-VEC, beremagene geperpavec-svdt; CI, confident interval; ITT, intent-to-treat.

Reviewer Comment:
Subgroup analyses of the primary efficacy endpoint by wound surface area and age group were considered as post hoc analyses because they were not prespecified and the subgroup variables were not stratified at randomization. The numerically higher rate of wound closure in

the B-VEC group in all subgroups supports the efficacy established based on the analyses of the primary endpoint and the key secondary endpoint.

6.1.11.4 Dropouts and/or Discontinuations

Please refer to Section 6.1.10.3

6.1.12 Safety Analyses

6.1.12.1 Methods

The safety population includes the ITT population that consists of all 31 subjects who were randomized and received treatment.

Among the 31 subjects, five subjects were enrolled in Study KB103-001 using different wounds and rolled over to Phase 3 with an adequate washout period (Table 13).

6.1.12.2 Overview of Adverse Events

Among the 31 subjects, 18 subjects (58.1%) reported 45 AEs. There were no deaths in the study. Three subjects experienced 5 SAEs. Most of the AEs were mild or moderate in severity. No AEs led to treatment discontinuation.

AEs were coded using MedDRA Version 24.1.

Table 18 listed all the reported AEs by System Organ Class and Preferred Term.

Table 18. Adverse Events Reported in at Least One Subject by System Organ Class and Preferred Team (N=31) – B-VEC-03

System Organ Class Preferred Term	B-VEC Treated Wound n/ [E] (%)	Placebo Treated Wound n/ [E] (%)	B-VEC Treated Secondary Wound n/ [E] (%)	Non-Treated Skin Site n/ [E] (%)	Not Collected n/ [E] (%)	Total (N=31) n/[E] (%)
Any AE	-	-	-	-	-	18/ [45] (58.1)
Skin and subcutaneous tissue disorders	-	-	-	-	-	10/ [19] (32.3)
Pruritis	-	-	-	-	3/ [4] (9.7)	3/ [4] (9.7)
Erythema	-	-	-	-	2/ [2] (6.5)	2/ [2] (6.5)
Rash	-	-	-	-	2/ [2] (6.5)	2/ [2] (6.5)
Blister	-	-	-	-	1/ [1] (3.2)	1/ [1] (3.2)
Dermatitis acneiform	-	-	-	-	1/ [1] (3.2)	1/ [1] (3.2)
Dermatitis contact	-	-	-	-	1/ [1] (3.2)	1/ [1] (3.2)
Hand dermatitis	-	-	-	1/ [1] (3.2)	-	1/ [1] (3.2)
Skin lesion[1]	-	-	-	1/ [1] (3.2)	-	1/ [1] (3.2)
Skin plaque[1]	-	-	-	1/ [1] (3.2)	-	1/ [1] (3.2)
Urticaria	-	-	-	-	1/ [1] (3.2)	1/ [1] (3.2)
Xanthoma	-	-	-	1/ [1] (3.2)		1/ [1] (3.2)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	-	-	-	-	-	3/ [4] (9.7)
Squamous cell carcinoma	-	-	-	3/ [4]	-	3/ [4] (9.7)

System Organ Class Preferred Term	B-VEC Treated Wound n/ [E] (%)	Placebo Treated Wound n/ [E] (%)	B-VEC Treated Secondary Wound n/ [E] (%)	Non-Treated Skin Site n/ [E] (%)	Not Collected n/ [E] (%)	Total (N=31) n/[E] (%)
Infections and infestations	-	-	-	-	-	1/ [1] (8.3)
Cellulitis	-	1/ [1] (3.2)	-	-	-	1/ [1] (3.2)
Surgical and medical procedure	-	-	-	-	-	1/ [1] (3.2)
Wound drainage	-	-	1/ [1] (3.2)	-	-	1/ [1] (3.2)
General disorders and administration site conditions	-	-	-	-	-	4/ [5] (12.9)
Chills	-	-	-	-	-	3/ [3] (9.7)
Fatigue	-	-	-	-	-	1/ [1] (3.2)
Pyrexia						1/ [1] (3.2)
Respiratory, thoracic, and mediastinal disorders	-	-	-	-	-	3/ [4] (9.7)
Cough	-	-	-	-	-	2/ [2] (6.5)
Rhinorrhea	-	-	-	-	-	2/ [2] (6.5)
Gastrointestinal disorders	-	-	-	-	-	2/ [3] (6.5)
Diarrhea	-	-	-	-	-	1/ [1] (3.2)
Nausea	-	-	-	-	-	1/ [1] (3.2)
Vomiting						1/ [1] (3.2)
Musculoskeletal and connective tissue disorders	-	-	-	-	-	2/ [2] (6.5)
Arthralgia	-	-	-	-	-	1/ [1] (3.2)
Pain in extremity						1/ [1] (3.2)
Blood and lymphatic system disorders	-	-	-	-	-	1/ [1] (3.2)
Anemia	-	-	-	-	-	1/ [1] (3.2)
Infections and infestations	-	-	-	-	-	1/ [1] (3.2)
COVID-19	-	-	-	-	-	1/ [1] (3.2)
Injury, poisoning and procedural complications	-	-	-	-	-	1/ [1] (3.2)
Fracture displacement	-	-	-	-	-	1/ [1] (3.2)
Investigations	-	-	-	-	-	1/ [1] (3.2)
Blood culture positive	-	-	-	-	-	1/ [1] (3.2)
Nervous system disorders	-	-	-	-	-	1/ [1] (3.2)
Dizziness	-	-	-	-	-	1/ [1] (3.2)

Source: The reviewer adapted from Applicant's response to clinical IR document submitted to BLA 125774/3 (module 1.11.3) on August 1, 2022.
[1]Skin lesion and skin plaque occurred in the same subject (b) (6) who was subsequently diagnosed with squamous cell carcinoma at the same site (dorsum of left hand). See narrative for Subject (b) (6) provided in 1.11.3 Clinical Information Amendment response submitted on 28-JUL-2022.
Abbreviations: AE, adverse event; B-VEC, beremagene geperpavec-svdt

The AEs observed with a cumulative incidence of >5% in the study include pruritus (Itching), chills, SCC, erythema (redness), rash, cough, and rhinorrhea (runny nose). SCC was removed as a potential adverse reaction because among the three SCC cases: in two cases, the SCC lesions occurred in areas that was not directly exposed to B-VEC, and in one case, the lesion was present prior to enrollment, but was biopsied and diagnosed shortly after starting B-VEC treatment to a different region. The Applicant reported the location and timing of SCC events were not consistent with causality and thus were not considered to be an adverse reaction.

Reviewer Comment:
The reviewer reviewed the three SCC cases and agrees with the Applicant's conclusion that the three SCC cases were not related to the B-VEC treatment.

SCC is frequently diagnosed in subjects with DEB who are known to be at increased risk for skin cancer due to chronic wound healing (Condorelli et al. 2019). By mid-adulthood, nearly all subjects will have had at least one SCC (Fine et al. 2008). Further, B-VEC does not replicate in the subject's cells or integrate into the subject cells' native genetic material indicating the product is not oncogenic.

The most frequent adverse reactions (incidence >5%) observed in the study to be included in the USPI are summarized in Table 19.

Table 19. Adverse Reactions (Incidence >5%) Following Treatment With B-VEC (N=31) - B-VEC-03

Adverse Reactions	Subjects n (%), (N=31)
Itching	3 (10)
Chills	3 (10)
Redness	2 (6.)
Rash	2 (6.)
Cough	2 (6.)
Runny nose	2 (6.)

Source: The reviewer adapted from the table 9 (page 35) of Clinical Overview (module 2.5) submitted to BLA 125774/0.

Reviewer Comment:
The intra-subject randomization and comparison of DEB wounds confounds the systemic safety evaluation. The matched wounds would have served as concurrent control in evaluating both efficacy and local safety after the topical application of B-VEC. However, the exact location of the AEs associated with skin and subcutaneous tissue (e.g., pruritis, erythema, and rash) were not collected in the phase 3 study (Table 18). Based on information request (IR) communication, the Applicant conservatively categorized the AEs in Table 19 as related to the B-VEC-treated wounds.

The reviewer has no objection to the applicant's proposal to include Table 19 in the USPI. The AEs are described in plain language.

The reviewer considers the systemic AEs are unlikely related to the B-BEC treatment because the pharmacokinetic data suggest a lack of systemic exposure after topical application of B-VEC on the DEB wounds.

6.1.12.3 Deaths

No subjects in Study B-VEC-03 died.

6.1.12.4 Nonfatal Serious Adverse Events

Three subjects experienced five SAEs. None of the SAEs was considered B-VEC related as assessed by the investigator.

Subject (b) (6) Cellulitis

The subject was a 19-year-old male who received his first study treatment on (b) (6) . His medical history included allergy to lisinopril (2019), iron deficiency anemia (2010), mildly dilated left ventricle (2019), malnutrition (2003), myopia (2014), inflammation (2001),

esophageal stricture (2012), hand syndactyly (2008), cardiomyopathy (2019), itch (2003), astigmatism (2014), and RDEB (2017, based on genetic confirmation).

The subject was hospitalized for cellulitis of the right leg from (b) (6) (Day 193) to (b) (6) (Day 203). Per the SAE admission summary, the subject reported that he accidently flipped a dirty dog water bowl on this right leg and thigh the day before symptoms started. The subject was treated with multiple antibiotics and the cellulitis was resolved after 3 weeks.

The last dose of B-VEC prior to the SAE was on (b) (6) (Day 178 [Week 26]). The right upper thigh (Primary Wound P1) was treated with placebo during the study and the left upper thigh received B-VEC (Primary Wound P2). On Day 178 (Week 26), both primary wounds were assessed as open, and no AEs were reported. Secondary open-label wounds were located at the right and left upper arms.

As the cellulitis occurred on the right leg, which did not receive active treatment with B-VEC, the investigator and Applicant conclude that the SAE was not related to treatment.

Reviewer comment:
The reviewer agrees with the Applicant's assessment that the SAE was not related to treatment. The location of cellulitis is not on or near the site of B-VEC application. The cause of the cellulitis was likely related to injury occurred on the right leg the day before the onset of symptoms.

Subject (b) (6): Diarrhea and Anemia

The subject is a 10-year-old Asian male who received his first study treatment on (b) (6) . His medical history included iron deficiency anemia (2010), microstomia (2016), xerosis cutis (2015), constipation (2010), diarrhea (2011), itch (2010), low baseline energy (2016), dilated left ventricle (2019), sleep disturbances (2019), vitamin D deficiency (2018), corneal abrasions (2018), and RDEB (2010, based on genetic confirmation).

The subject was hospitalized 3 times. Once for diarrhea (b) (6) [Days 50-53]) and the subject received cefepime, saline, cefdinir, clindamycin, and packed red blood cells. Twice for severe anemia (b) (6) [Days 114-116] and (b) (6) [Days 129-131]). All three SAEs resolved and the subject continued treatment of B-VEC during the trial until completion.

Given, the subject has a medical history of both diarrhea and anemia, and anemia is a characteristic feature of patients with DEB, the investigator and the Applicant considered the SAEs as not related to B-VEC treatment.

Reviewer comment:
The reviewer agrees with the Applicant's assessment that the SAEs was not related to treatment. The subject had a history of diarrhea and anemia. Anemia is a common clinical manifestation of DEB. The lack of systemic exposure after topical application of B-VEC further averted the relatedness of the SAEs to the B-VEC treatment.

Subject (b) (6): Positive Blood Culture

This subject is a 23-year-old White male who received his first study treatment on (b) (6) His medical history included end stage renal disease (2008), anemia (2003), asthma (2003), ectropion (2020), keratitis (2005), gastric tube placement (2003), keloids (2007), gastroesophageal reflux disease (2005), methicillin-resistant *Staphylococcus aureus* skin

infection (2005), constipation (1998), cardiomyopathy (2014), *S. aureus* positive blood culture, and RDEB (2016, based on genetic confirmation). The subject has a hemodialysis (HD) catheter on the right chest and has been on 3 times weekly hemodialysis for 9 years that continued during his participation in the Phase 3 trial.

At a medical appointment on (b) (6) (Day 84), it was noted that he had a positive blood culture. The subject reported that he was feeling well overall and was told to come to the hospital because of the positive culture. The subject remained asymptomatic except the HD line had been overdue for replacement and redness was noticed around the catheter. The HD line was replaced in October 2020.

The placebo-treated wound was located on the right upper extremity (Primary Wound P2) and the primary B-VEC-treated wound was located on the left upper extremity (Primary Wound P1); secondary open-label wounds were located on his mid upper back, forehead, right forearm, and left knee. On Day 78, the last assessment prior to the SAE, both primary wounds were assessed as closed.

The investigator and Applicant determined the catheter was considered the most likely source of the positive blood culture given the subject's history of prior line infections, delayed replacement of indwelling HD catheter, redness at the catheter site, and positive wound culture from the HD catheter.

Reviewer Comment:
The reviewer agrees with the Applicant's assessment that the SAE was not related to treatment. The indwelling HD catheter is likely the source of asymptomatic bacteremia.

6.1.12.6 Clinical Test Results

No clinically meaningful changes associated with treatment were observed in clinical laboratory values (hematology and serum chemistry), vital signs, or physical examination findings.

6.1.13 Study Summary and Conclusions

Study B-VEC-03 was a multicenter, intra-subject randomized, placebo controlled, double-blind efficacy and safety Phase 3 study of B-VEC for the topical treatment of DEB wounds. The study as designed was adequate and well-controlled.

Efficacy was demonstrated based on the primary endpoint of the difference in the proportion of complete wound closure (defined as 100% wound closure as indicated by skin re-epithelialization without drainage) at 24 Weeks confirmed at two consecutive study visits 2 weeks apart, between the B-VEC and the placebo-treated DEB wounds in the primary wound pairs. Twenty (20) of the 31 (64.5%) B-VEC treated wounds achieved complete closure. Eight of the 31 (25.8%) placebo-treated wounds achieve complete closure. The treatment difference was 38.7% (95% CI: 13.9, 63.5; p= 0.012). Efficacy was supported by the key secondary endpoint of the difference in proportion of complete wound closure at Weeks 8 and 10 or at Weeks 10 and 12 between the B-VEC and the placebo treated DEB wounds in the primary wound pairs. Twenty-one (21) of the 31 (67.7%) B-VEC treated wounds achieved complete closure. Seven of the 31 (22.6%) placebo treated wounds achieved complete closure. The treatment difference was 45.1% (95% CI: 21.8, 68.5; p= 0.003).

The safety population includes all the enrolled 31 subjects. The systemic safety evaluation was confounded due to the intra-subject randomization of the DEB wounds. There were no deaths in

the Phase 3 study. Three subjects experienced five SAEs. None of the SAEs was considered related to B-VEC treatment. The most frequent adverse reactions (incidence >5%) observed in the study include pruritis, chills, erythema, rash, cough, and rhinorrhea. There were no discontinuations due to adverse reactions. The overall safety evaluation did not raise a concern even if all the observed AEs were conservatively categorized as related to the B-VEC treatment.

6.2 Trial #2: Study KB103-001

Study Title: A Phase 1/2 Study of B-VEC, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB).

6.2.1 Objectives (Primary, Secondary, etc.)

Primary: Safety

Secondary:

- PD activity (molecular correction) associated with functional COL7 expression assessed by IF and IEM.
- Preliminary efficacy as assessed on wound closure, Investigator's Global Assessment, and pain scale.

6.2.2 Design Overview

Study KB103-001 was a FIH, Phase 1/2, single-center, open-label, randomized, intra-subject, placebo (vehicle) controlled study to assess safety, molecular correction (pharmacodynamics, PD), and preliminary efficacy of B-VEC for the treatment of DEB.

The study was divided into 4 phases that corresponded to protocol revisions: Phase 1, Phase 2a, Phase 2b, and Phase 2c. The protocol revisions include primary objectives, dosing, age of subjects, and wound areas based on the preliminary safety, efficacy, and PD data from the previous versions. Phase 1 and 2b incorporated intradermal injection of B-VEC to intact skin for evaluation of PD endpoints.

Prior to application of B-VEC, the investigator selected 2 size-matched wounds (one wound was randomized to B-VEC and the other to placebo) from each subject in Phase 1, and up to three size-matched target wounds (two wounds were randomized to B-VEC and one was randomized to placebo) from each subject in Phases 2a, 2b, and 2c for intra-subject randomization. The Phase 1/2 study consisted of various dosing regimens and treatment cycles (including dosing interval and duration of and treatment) among subjects.

6.2.3 Population

Inclusion Criteria:

1. Clinical diagnosis of RDEB
2. Age:
    a. Phase 1: ≥18 years old
    b. Phase 2a: ≥5 years old
    c. Phase 2b: ≥2 years old
    d. Phase 2c: ≥2 years old
3. Confirmation of RDEB diagnosis by genetic testing, IF, and IEM

4. LH24 antibody negative (non-collagenous 2 domain negative [NC2-]) and NC1 domain positive [NC1+])
   Note: This criterion was applied to the first 2 adults enrolled in the Phase 1 study. Subsequent subjects can be NC1+ or NC1-)
5. Confirmed RDEB *COL7A1* mutations
6. Wound that meets the wound size/surface area entry criteria:
   a. Phase 1: Two wounds up to 10 cm^2; 1 randomized to B-VEC and 1 randomized to placebo
   b. Phase 2a and 2b: At least 3 wounds up to 20 cm^2; 2 wounds randomized to B-VEC and 1 randomized to placebo
   c. Phase 2c: At least 2 wounds up to 50 cm^2; at least 1 randomized to B-VEC and 1 randomized to placebo

Exclusion Criteria

1. The presence of medical illness expected to complicate participation and/or compromise the safety of this technique, such as active infection with human immunodeficiency virus, hepatitis B (as determined by hepatitis B surface antigen screening), or hepatitis C (as determined by detection of hepatitis C antibodies or positive result of hepatitis C polymerase chain reaction analysis)
2. Serum antibodies to COL7 demonstrated on enzyme-linked immunosorbent assay (ELISA), (b) (4) IF microscopy, (b) (4) , or cell-mediated immunity to (b) (4) (subjects with negative results within 12 months of screening are eligible)
3. Active infection in the area that will undergo application
4. Evidence of systemic infection
5. Known allergy to any of the constituents of the product
6. Current evidence or a history of SCC in the area that will undergo treatment
7. Active drug or alcohol addiction
8. Hypersensitivity to local anesthesia (lidocaine/prilocaine cream)
9. Receipt of chemical or biological study product for the specific treatment of RDEB in the past three months
10. Specific wounds that have previously been administered investigational gene or cell therapy
11. Subjects who have taken systemic antibiotics within seven days
12. Positive pregnancy test or breast-feeding

6.2.4 Study Treatments or Agents Mandated by the Protocol

The Phase 1/2 study consisted of four phases with various doses and dosing regimens (including dosing interval and duration of treatment) among subjects. Table 24 describes doses and dosing regimens for topical applications of each subject, and Table 25 describes doses and dosing regimens for intradermal injections.

6.2.5 Directions for Use

The drug substance was (b) (4) to administration. The excipient gel was stored at room temperature. Mixing occurred on a hard surface at the study site prior to administration. Topically administrated B-VEC consisted of thawed cryopreserved drug product mixed with excipient gel. Topically administrated placebo consisted of isotonic saline mixed with excipient gel.

6.2.6 Sites and Centers

The study was conducted at one site at Stanford University Dermatology Clinic.

6.2.7 Surveillance/Monitoring

The assessment schedule for the Phase 1/2 Study is detailed in Table 20.

Table 20. Schedule of Events

Procedures	Screen/ BL	Cycle #1 Dose days[1]	Cycle #1 Last dose[1]	OP #1[2]	Cycle #2 Dose days[1]	Cycle #2 Last dose[1]	OP #2 C2 +1mo[3,4]	OP #2 C2 +2mo[3,4]	OP #2 C2 +3mo[3,4]	LTFU
Urine pregnancy test	X	-	-	-	-	-	-	-	-	-
HIV, Hep B, Hep C testing	X	-	-	-	-	-	-	-	-	-
Hematology & chemistry[5]	X	-	X	-	-	X	X	X	X	-
COL7 antibody assay	X	-	X	-	-	X	X	X	X	-
HSV antibody assay	X	-	X	-	-	X	X	X	X	-
Wound area assignment	X	-	-	-	-	-	-	-	-	-
Pre-dose tattoos	X	-	-	-	-	-	-	-	-	-
Concomitant medications	X	X	X	-	X	X	X	X	X	X
Adverse events	X	X	X	-	X	X	X	X	X	X
Viral shedding (skin swab)	X	X	X	-	X	X	X	X	X	-
Viral shedding (blood and urine)	X	-	X	-	-	X	X	X	X	-
Physical exam	X	-	-	-	-	-	-	-	X	-
PRO assessment	X	X	X	-	X	X	X	X	X	-
Global wound assessment	X	X	X	-	X	X	X	X	X	-
Vital signs	X	X	X	-	X	X	X	X	X	-
At-home wound imaging[6]	-	X	X	X	X	X	X	X	X	-
On-site wound imaging	X	X	X	-	X	X	X	X	X	-
Wound stenciling	X	X	X	-	X	X	X	X	X	-
IP administration	X	X	X	-	X	X	X	X	X	-
Wound biopsy[7]	X	-	X	-	-	X	X	X	X	-

Source: The reviewer adapted from Study Report for KB103-001, submitted to BLA 215774/0 on June 20, 2022

1. Dosing every 2-3 days for ≤3 Months
2. Home images variable
3. At-home monitoring and monthly on site visits 3 months after C2
4. Visit windows for the OP #2 visits are +/- 1 week
5. After screening/baseline, performed only as clinically indicated to minimize blood draws
6. At-home wound imaging occurs throughout the study during bandage changes
7. Biopsies are performed at the discretion of the Investigator and Applicant.

Abbreviations: COL7, human type VII collagen; Hep, hepatitis; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IP, investigational product; OP, observation period; PRO, patient-reported outcome.

6.2.8 Endpoints and Criteria for Study Success

The primary endpoint is safety.

The primary efficacy endpoint (Phase 1 and 2b) is molecular correction (PD activity) associated with functional COL7 expression assessed by IF and IEM.

The preliminary clinical efficacy endpoints include:

- The proportion of DEB complete wound closure defined as ≥90% reduction in wound surface from baseline) by the timepoints (Weeks 8, 10, and 12).

- The time to wound closure, defined as the time from the first treatment to complete wound closure defined as ≥90% reduction in wound surface from baseline.

Reviewer Comment:
The PD data provide mechanistic support and serve as confirmatory evidence of effectiveness of B-VEC for the treatment of DEB wounds. This assessment is described and discussed in Section 4.2.2 of this review. Further details may be found in Dr. Million Tegenge's Clinical Pharmacology review.

The clinical efficacy analyses are considered exploratory because of the limitations on the study design and efficacy analyses in evaluating efficacy. The clinical efficacy analyses are described and discussed in Section 6.2.11 (efficacy analysis) of this review.

6.2.9 Statistical Considerations & Statistical Analysis Plan

The statistical analyses were descriptive.

6.2.10 Study Population and Disposition

The study enrolled nine unique subjects. Three of the nine subjects enrolled in both Phase 2a and Phase 2b with adequate washout period between the two phases. The three subjects contributed different wounds for treatment and evaluation in Phase 2a and Phase 2b, except for one subject who had a chronic dorsal foot wound treated in Phase 2a and achieved partial closure, and the same wound was selected for continued treatment in Phase 2b. For purposes of analysis, the 3 subjects were counted separately in the different phases, so the total number of subjects was 12.

All the subjects received at least 4 weeks of treatment.

6.2.10.1 Populations Enrolled/Analyzed

The safety population include all 12 subjects enrolled in the Study KB103-001.

6.2.10.1.1 Demographics

Among the 12 subjects enrolled (9 males, 3 females), ages ranged from 10 to 35 years (mean: 20.3) and all subjects were white. There were five pediatric subjects.

Table 21. Demographic and Baseline Characteristics (Safety Population): KB103-001

Demographic Characteristic	**Safety Population N=12**
Age (years)	-
Mean (SD)	20.3 (8.05)
Median (minimum, maximum)	19.5 (10, 35)
Age by category, n (%)	-
≤12 years	1 (8.3)
>12 and ≤18 years	5 (41.7)
>18 years	6 (50.0)
Sex, n (%)0	-
Male	9 (75.0)
Female	3 (25.0)

Demographic Characteristic	Safety Population N=12
Race, n (%)	-
Non-White	0
Asian	0
American Indian or Alaska Native	0
White	12 (100)
Ethnicity, n (%)	-
Hispanic or Latino	3 (25.0)
Not Hispanic or Latino	9 (75.0)

Source: The Applicant's response to clinical information request, submitted to BLA 125774/04, section 2.5 Clinical Overview, on August 1, 2022
Abbreviations: SD, standard deviation.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All subjects had genetically confirmed RDEB. The mean wound surface area is 9.08 cm^2 with a median of 5 cm^2.

6.2.10.1.3 Subject Disposition

All 12 subjects received at least 4 weeks of treatment and will be included in the safety analyses.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The primary endpoint is safety. Please refer to section 6.2.12 for safety analyses.

The primary efficacy endpoint (Phase 1 and 2b) is molecular correction (PD activity) associated with functional COL7 expression assessed by IF and IEM. Please refer to section 4.4.2 for PD analyses.

6.2.11.2 Analyses of Secondary Endpoints

- The difference in proportion of DEB wound closure defined as ≥90% reduction in wound surface area from baseline in B-VEC-treated and placebo-treated wound sites at Weeks 8 and 10 and 12.

Reviewer comment:
The wound closure definition is inconsistent with the definition of complete wound closure that is considered clinically meaningful and used for regulatory decision making. According to FDA guidance for industry: "Chronic Cutaneous Ulcer and Burn Wounds — Developing Products for Treatment," complete wound closure should be defined as skin re-epithelialization without drainage or dressing requirements confirmed at two consecutive study visits 2 weeks apart.

Table 22 Summarizes this efficacy endpoint analysis based on observed data.

Table 22. Wound Closure, ITT Population (N=12, Observed Data, Study KB-103-001)

Time Point	B-VEC Number of Wound Closure/Total Wounds (% of Wound Closure)	Placebo Number of Wound Closure/Total Wounds (% of Wound Closure)
Week 8	14/17 (82.4)	0/8 (0)
Week 10	12/16 (75.0)	2/6 (33.3)
Week 12	12/14 (85.7)	1/7 (14.3)

Source: The reviewer adapted from the table 3 (page 19) of Clinical Overview (module 2.5) submitted to BLA 125774/0.
Note: Wound closure was defined as ≥90% reduction in wound surface area from baseline.
Abbreviations: B-VEC, beremagene geperpavec-svdt; CI, confidence interval; ITT, intent-to-treat

- The time to wound closure, defined as the time from the first treatment to wound closure defined as ≥90% reduction in wound surface from baseline.

  Table 23 summarizes this efficacy endpoint analysis based on observed data.

Table 23. Time to and Duration of Wound Closure, ITT Population (Observed Data, Study KB-103-001)

Assessment/ Time-to Event Analysis	B-VEC	Placebo
Time to complete closure, days, Median (95% CI)[a]	13.5 (8, 21)	22.5 (8, 64)
Duration of closure, days Median (95% CI)[a]	103 (94, 118)	16.5 (0, 66)

Source: The reviewer adapted from the table 4 (page 20) of Clinical Overview (module 2.5) submitted to BLA 125774/0.
Note: Wound closure was defined as ≥90% reduction in wound surface area from baseline. Duration of closure was defined as the time from wound closure to the first reopening of the same wound.
a: The median estimate and 95% CI were derived using the Kaplan-Meier method.
Abbreviations: B-VEC, beremagene geperpavec-svdt; CI, confidence interval

Reviewer comment:
The study design and efficacy analyses are limited in evaluating efficacy,

1. The study was not adequately powered due to very small sample size in each phase of the study and each subject received varying doses and dosing regimens.
2. The wound closure was not appropriately defined.
3. The open-label design compromises the efficacy assessment.
4. The analyses were based on the observed data. No missing data handling was specified in the analyses.

The above limitations would subject the analyses to significant bias and limit the interpretation of the efficacy data. Although the efficacy findings suggested clinical benefit of B-VEC on DEB wounds, the efficacy assessment in the Phase 1/2 study is considered exploratory. In addition, the weekly dosing interval assessed in the Phase 3 study was not assessed in the Phase 1/2 study. Therefore, preliminary clinical efficacy findings from Study KB103-001 will not be included in Section 14 of the USPI.

The extent of exposure of all subjects in study KB103-001 is shown in Table 24 and Table 25. In addition to topical application (Table 24), Phase 1 and 2b incorporated intradermal injection of B-VEC to intact skin (Table 25) for evaluation of molecular correction/mechanistic endpoints.

Table 24. Summary of Topical Application for Study KB103-001

Subject	Phase	B-VEC Topical Dose (PFU/Wound/ application)	Number of B-VEC-Treated Wounds	Dosing in Study Days[1]
KB103-001 (b) (6)	1	~1×10^8	1	1, 3, 29, and 30
KB103-001	1	~1×10^8	1	1, 3, 15, 28, 30, and 43
KB103-001	2a	3×10^8	2	1, 2, 3, 4, 5, 34, 44, and 73
KB103-001	2a	6×10^8	2	1, 2, 3, 4, and 5
KB103-001	2a	3×10^8	2	1, 2, 3, 4, 5, and 37
KB103-001	2a	3×10^8	2	1, 2, 3, 4, 5, 37, and 46
KB103-001	2b	2×10^8-8×10^8	2	1, 4, 6, 8, 11, 13, 15, 18, 29, and 71
KB103-001	2b	1×10^8-1.2×10^9	2	1, 3, 5, 9, 12, 15, 17, and 29
KB103-001	2b	3×10^8-8×10^8	2	1, 5, 8, 10, 12, 15, 33, and 61
KB103-001	2b	1×10^8-1×10^9	2	1, 2, 5, 8, 10, 12, 15, 33, and 64
KB103-001	2b	1×10^8-5×10^8	2	1, 2, 5, 8, 10, 12, 15, 33, 37, 38, and 60
KB103-001	2c	8×10^8-1.57×10^9	1	Cycle 1: 1, 2, 4, 6, 7, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, and 25 Cycle 2: 37, 38, 39, 40, 41, 43, 44, 45, 46, 47, 49, 50, 51, 52, 53, 54, 56, 57, 58, 59, and 60

Source: The reviewer adapted from Applicant's response to clinical IR document submitted to BLA 125774/3 on August 1, 2022 (module 1.11.3)
1. Study days are relative to the first dosing date listed as Day 1.
Abbreviations: B-VEC, beremagene geperpavec-svdt; IR, information request; PFU, plaque forming units

Table 25. Summary of Intradermal Injection for Study KB103-001

Subject	Phase	B-VEC Intradermal Volume (µL)	PFU/mL	PFU/Injection	Dosing in Study Days [a]
KB103-001- (b) (6)	1	1400-1500	8×10^7	~1×10^8	1, 3, 28, and 30
KB103-001-	1	1000-1500	8×10^7	~1×10^8	1 and 3
KB103-001-	2b	50	4×10^9	~2×10^8	4 and 29
KB103-001-	2b	30- 67	4×10^9	~2×10^8	1 and 9
KB103-001-	2b	40	4×10^9	~2×10^8	2 and 33
KB103-001-	2b	70	4×10^9	~2×10^8	2
KB103-001-	2b	50	4×10^9	~2×10^8	2

Source: The reviewer adapted from Applicant's response to clinical IR document submitted BLA 125774/3 on August 1, 2022 (module 1.11.3)
a. Study Days are relative to the first dosing date listed as Day 1.
Abbreviations: B-VEC, beremagene geperpavec-svdt; IR, information request; PFU, plaque forming units.

6.2.12.2 Overview of Adverse Events

AEs were coded using MedDRA Version 21.1.

Thirty-five treatment-emergent adverse events (TEAEs) were reported in 9 of the 12 subjects (Table 26); 33 AEs were mild in severity and two AEs were moderate; none were severe. The

two moderate AEs of itching and redness occurred in one subject on the face where no B-VEC was applied.

Among the 35 TEAEs, the Applicant considers 19 as probable or possible drug-related AEs in five subjects. These AEs were injection site pain, purulent discharge, application site pruritus, injection site swelling, application site erythema, application site rash, fatigue, feeling cold, injection site erythema, product taste abnormal, pyrexia, throat irritation, and wound complication (itch on arm wounds). Twelve of the 19 AEs were associated with intradermal injections. The local AEs (Table 27) associated with topical application were reported in four subjects. The AEs are mild and resolved within 24 hours.

Table 26. Adverse Events Reported in AT LEAST One Subject by System Organ Class and Preferred Term (Safety Population) – KB301-001

System Organ Class Preferred Term	B-VEC Treated Wound n/ [E] (%)	Placebo Treated Wound n/ [E] (%)	Non-Treated Skin Site n/ [E] (%)	Not Collected n/ [E] (%)	Total (N=12) n/[E] (%)
Any AE (including those associated with intradermal injection)	-	-	-	-	9/ [35] (75.0)
Skin and subcutaneous tissue disorders	-	-	-	-	3/ [5] (25.0)
Erythema	-	-	-	1/ [1] (8.3)	1/ [1] (8.3)
Pruritis	-	-	-	1/ [1] (8.3)	1/ [1] (8.3)
Rash	-	-	-	1/ [2] (8.3)	1/ [2] (8.3)
Rash generalized	-	-	-	1/ [1] (8.3)	1/ [1] (8.3)
Infections and infestations	-	-	-	-	2/ [3] (16.7)
Purulent discharge	1/ [1] (8.3)	1/ [1] (8.3)	-	-	1/ [2] (8.3)
Wound infection pseudomonas	-	-	-	1/ [1] (8.3)	1/ [1] (8.3)
General disorders and administration site conditions	-	-	-	-	2/ [2] (16.7)
Application site bruise	-	-	-	1/ [1] (8.3)	1/ [1] (8.3)
Application site rash	-	-	-	1/ [1] (8.3)	1/ [1] (8.3)
Investigations	-	-	-	2/ [2] (16.7)	2/ [2] (16.7)
Bacterial test positive	-	-	-	2/ [2] (16.7)	2/ [2] (16.7)
Injury, poisoning, and procedural complications	-	-	-	-	1/ [1] (8.3)
Wound complication[1]	1/ [1] (8.3)	1/ [1] (8.3)	-	-	1/ [1] (8.3)
Surgical and medicinal procedures	-	-	-	-	1/ [1] (8.3)
Wound treatment	1/ [1] (8.3)	-	-	-	1/ [1] (8.3)
Gastrointestinal disorders	-	-	-	-	2/ [2] (16.7)
Diarrhea	-	-	-	-	1/ [1] (8.3)
Nausea	-	-	-	-	1/ [1] (8.3)
Infections and infestations	-	-	-	-	2/ [2] (16.7)
Bacterial vaginosis	-	-	-	-	1/ [1] (8.3)
Pharyngitis streptococcal	-	-	-	-	1/ [1] (8.3)
Respiratory, thoracic, and mediastinal disorders	-	-	-	-	2/ [2] (16.7)
Nasal congestion	-	-	-	-	1/ [1] (8.3)
Throat irritation	-	-	-	-	1/ [1] (8.3)

System Organ Class Preferred Term	B-VEC Treated Wound n/ [E] (%)	Placebo Treated Wound n/ [E] (%)	Non-Treated Skin Site n/ [E] (%)	Not Collected n/ [E] (%)	Total (N=12) n/[E] (%)
Immune system disorders	-	-	-	-	1/ [1] (8.3)
Drug hypersensitivity	-	-	-	-	1/ [1] (8.3)
Product issues	-	-	-	-	1/ [1] (8.3)
Product taste abnormal	-	-	-	-	1/ [1] (8.3)
Surgical and medicinal procedures	-	-	-	-	1/ [1] (8.3)
Gastrostomy	-	-	-	-	1/ [1] (8.3)

Source: Reviewer adapted from Applicant's response to clinical IR document submitted to BLA 125774/10 (module 1.11.3) on August 1, 2022.
Abbreviations: AE, adverse event; B-VEC, beremagene geperpavec-svdt

Table 27. AEs Related to Topical Application for the Phase 1/2 (Study KB103-001)

Subject	Preferred Term	Severity
KB103-001 (b) (6)	Purulent discharge[1]	Mild
KB103-001	Wound treatment[1]	Mild
KB103-001	Erythema[2]	Moderate
KB103-001	Pruritus[2]	Moderate
KB103-001	Application site rash	Mild
KB103-001	Rash[3]	Mild
KB103-001	Rash[3]	Mild
KB103-001	Wound complication[1]	Mild
KB103-001	Application site bruise	Mild
KB103-001	Rash generalized	Mild

Source: Reviewer adapted from Applicant's response to clinical IR document submitted on August 1, 2022 (module 1.11.3) and KB103-001 CSR Listing 16.2.7
1. Occurred at multiple wound sites
2. These associated AEs were located on the face where no IP was applied
3. The associated AEs were on body at unspecified locations
Abbreviations: AE, adverse event; CSR, clinical study report; IP, investigational product; IR, information request.

Reviewer Comment:

Several issues were identified when analyzing the safety data in Study KB103-001:

- Subjects received varying doses and dosing regimens, which are different from the dose and dosing regimen in the Phase 3 study or in the proposed USPI.
- Phase 1 and 2b incorporated intradermal injection of B-VEC to intact skin for evaluation of PD endpoints. The intradermal injection was not the intended route of administration post-approval.
- The Applicant reported most of drug-related AEs observed were associated with intradermal route of administration.
- The exact location of some of the AEs associated with skin and subcutaneous tissue (e.g., pruritis, erythema, and rash) were not collected in the Phase 1/2 study (Table 26).
- The relatedness of some of the AEs to the topical application of B-VEC is unlikely because the AEs occurred either at the locations where no IP was applied, at unspecified locations, or at multiple wound sites including the placebo-applied wound sites (Table 27).
- The systemic safety evaluation was confounded due to the intra-subject randomization. In addition, it is challenging to assess the relatedness of AEs to the B-VEC treatment in the context of the complicated clinical manifestations of the disease and multiple concomitant treatments used in this population.

The reviewer considers the systemic AEs are unlikely related to the B-BEC treatment because the pharmacokinetic data suggested a lack of systemic exposure after topical application of B-VEC on the DEB wounds.

Therefore, the Applicant proposed to describe the safety profile of B-VEC primarily based on the safety experience of the 31 subjects who participated in the Phase 3 study. The reviewer agrees with the Applicant's proposal given the challenges of integrating the safety findings between the two clinical studies for the issues listed above.

Nevertheless, the safety findings in the Phase 1/2 study did not raise any concern.

6.2.12.3 Deaths

There were no deaths in Study KB103-001

6.2.12.4 Nonfatal Serious Adverse Events

There were no SAEs reported in Study KB103-001.

6.2.12.5 Adverse Events of Special Interest

Not applicable.

6.2.12.6 Clinical Test Results

No clinically meaningful changes associated with treatment were observed in clinical laboratory values (hematology and serum chemistry), vital signs, or physical examination findings.

6.2.12.7 Dropouts and/or Discontinuations

There were no AEs leading to discontinuation of treatment reported in Study KB103-001

6.2.13 Study Summary and Conclusions

Study KB103-001 was a FIH, Phase 1/2, single-center, open-label, intra-subject randomized, placebo-controlled study to assess safety, PD, and preliminary efficacy of B-VEC for the treatment of DEB. The study consisted of four phases: Phase 1, Phase 2a, Phase 2b, and Phase 2c. Twelve subjects were enrolled. The 12 subjects consist of nine unique subjects as three of the 12 subjects were enrolled in both Phase 2a and Phase 2b with adequate washout period. All subjects received topical application of B-VEC on selected wounds. In addition, Phase 1 and 2b incorporated intradermal injection of B-VEC to intact skin for evaluation of molecular correction/mechanistic endpoints.

Nine of the 12 subjects reported 35 TEAEs. All the TEAEs were mild to moderate in severity. Majority of the AEs were associated with intradermal injections of B-VEC which is not the intended route of administration of the product. The causal relationship of local AEs to the topical application of B-VEC is not clear because whether an AE was associated with topical application of B-VEC was not collected. The systemic safety evaluation was confounded due to the intra-subject comparison design of the study; however, the lack of systemic exposure following topical application of B-VEC on DEB wounds indicates that the observed systemic AEs were unlikely related to the B-VEC treatment. The overall safety evaluation in the Phase 1/2 study did not raise any concern.

The PD activity (expression, secretion, and localization of COL7 transgene) was demonstrated in nine skin biopsies (n=6 unique subjects) in Phase 1/2 study.

The preliminary clinical efficacy assessment in the Phase 1/2 study suggests clinical benefit of B-VEC on DEB wounds. However, it is considered exploratory due to several limitations, including various doses and dosing regimens administered to each subject, small sample size in each phase of the study, the open-label design, the different definition of wound closure and lack of strategy to handle missing data.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

7.1.1 Methods of Integration

An integrated overview of efficacy based on an analysis using pooled data from all subjects treated with B-VEC in the Phase 1/2 (Study KB103-001) and Phase 3 (Study B-VEC-03) studies was not performed. The clinical efficacy assessment in the Phase 1/2 study was considered exploratory because:

- Subjects received varying doses and dosing regimens which are different from the weekly dose based on the wound size and age in the Phase 3 study and post-approval.
- The study design and efficacy analyses had limitations in evaluating efficacy.
  - There was a small sample size in each phase of the study and each subject received varying doses and dosing regimens.
  - The open-label design, the inappropriately defined wound closure and the efficacy analyses based on the observed data without counting the missing data would subject the analyses to significant bias and further limit the interpretation.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

An integrated overview of safety based on an analysis using pooled data from all subjects treated with B-VEC in the Phase 1/2 (Study KB103-001) and Phase 3 (Study B-VEC-03) studies was not performed, because in the Phase 1/2 study:

- Subjects received varying doses and dosing regimens which are different from the dosing instructions in the Phase 3 study and post-approval (i.e., weekly topical application based on the wound size and the subject's age).
- Phase 1 and Phase 2b of the study incorporated intradermal injection of B-VEC to intact skin for PD evaluation. The intradermal injection was not intended for commercial use.
- Most drug-related AEs were reported as associated with intradermal route of administration, which was only used for PD evaluation and was not used in the Phase 3 study or intended for commercial use.
- The exact location of some the AEs associated with skin and subcutaneous tissue were not collected in the phase 1/2 study (Table 26).
- The systemic safety evaluation was confounded due to the intra-subject randomization. It is challenging to assess the relatedness of AEs to the B-VEC treatment in the context of the complicated clinical manifestations of the disease and multiple concomitant treatments used in this population.

- The systemic AEs are unlikely related to the B-BEC treatment because the pharmacokinetic data suggested a lack of systemic exposure after topical application of B-VEC on the DEB wounds.
- The overall safety evaluation in the Phase 1/2 study did not raise any concern.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There are no data with B-VEC application in pregnant women to inform a drug-associated risk. Animal developmental and reproductive toxicity studies have not been conducted with B-VEC.

9.1.2 Use During Lactation

There is no information available on the presence of B-VEC in human milk, the effects on the breastfed infant, or the effects on milk production. Animal lactation studies have not been conducted with B-VEC.

9.1.3 Pediatric Use and PREA Considerations

The safety and effectiveness of B-VEC was studied in pediatric patients. The safety and efficacy findings of B-VEC in pediatric patients were similar to safety and efficacy findings in adult patients. B-VEC is not subject to PREA, since the product received Orphan Drug designation.

9.1.4 Immunocompromised Patients

The safety and effectiveness of B-VEC in immunocompromised patients was not studied.

9.1.5 Geriatric Use

Clinical studies did not include geriatric patients aged 65 years and over.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

10. CONCLUSIONS

B-VEC demonstrated substantial evidence of effectiveness for the treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa with mutation(s) in *the collagen type VII alpha 1 chain* (*COL7A1*) gene based on primary evidence of effectiveness from an adequate and well controlled Phase 3 study, plus confirmatory evidence from the PD activity (expression and localization of COL7 transgene) demonstrated in the Phase 1/2 study.

The risks of B-VEC are characterized based on a safety database of 31 subjects in the Phase 3 study. Although the safety database is small, it is acceptable for this serious and rare disease with significant unmet medical need taking into consideration the benefit and risk of the treatment.

The reviewed safety data do not warrant a REMS, or a safety PMR clinical study.

B-VEC demonstrated a favorable benefit/risk profile for the treatment of wounds in patients 6 months of age and older with DEB, with mutation(s) in the *COL7A1* gene.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 28. Benefit-Risk Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• DEB is a skin fragility disorder characterized by blistering of the skin and mucosal membranes that heal with scarring. The onset of symptoms usually occurs at birth or in early childhood. Death may occur prematurely due to complications. • DEB is caused by mutations in the *COL7A1* gene, which results in reduced or absent levels of biologically active COL7. COL7 is a structural component of anchoring fibrils which stabilize the dermo-epidermal adherence. • DEB can be inherited in an autosomal dominant (DDEB) or recessive (RDEB) fashion. Patients with DDEB has lower than normal functional anchoring fibrils, and patients with RDEB has no functional anchoring f brils. • The estimated prevalence of RDEB in the US was estimated to be 1.35 persons per million inhabitants and DDEB was estimated to be 1.49 persons per million inhabitants.	• DEB is a rare and serious genetic condition.
Unmet Medical Need	• There is no FDA-approved treatment for DEB. • Management of DEB is supportive.	There is a significant unmet medical need for the treatment of DEB.

Clinical Benefit	• The primary evidence of effectiveness is based on the improvement of wound closure observed in the randomized, double-blind, intra-subject placebo-controlled study for 26 weeks (n=31) phase 3 clinical study.
	  ○ Efficacy was demonstrated based on the primary endpoint of the difference in the proportion of complete (100%) wound closure at 24 Weeks confirmed at two consecutive study visits 2 weeks apart, assessed at Weeks 22 and 24 or at Weeks 24 and 26, between the VYJUVEK-treated and the placebo-treated wounds. 20 of the 31 (64.5%) B-VEC treated wounds achieved complete closure. Eight of the 31 (25.8%) placebo-treated wounds achieve complete closure. The treatment difference was 38.7% (95% CI: 13.9, 63.5; p= 0.012).
	  ○ Efficacy was supported by the key secondary endpoint of the difference in proportion of complete wound closure (defined as 100% closure) at Weeks 8 and 10 or at Weeks 10 and 12 between the B-VEC and the placebo-treated DEB wounds. 21 of the 31 (67.7%) B-VEC treated wounds achieved complete closure. Seven of the 31 (22.6%) placebo-treated wounds achieve complete closure. The treatment difference was 45.2% (95% CI: 21.8, 68.5; p= 0.003.
	• The PD activity (expression, secretion, and localization of COL7 transgene) of B-VEC was demonstrated in six (6) subjects (9 biopsy sites) in the Phase 1/2 study.
		• The Phase 3 study (study B-VEC-03) was adequate and well-controlled.
		• Weekly B-VEC topical application was effective to promote DEB wounds closure in the Phase 3 study.
		• The PD activity of B-VEC was demonstrated in the Phase 1/2 study.
		• The substantial evidence of effectiveness was demonstrated based primary evidence from the Phase 3 study plus confirmatory evidence of effectiveness of the PD activity (expression and localization of COL7 transgene) of B-VEC in the Phase 1/2 study.

Risk	• The safety profile was primarily based on data from the 31 subjects aged from one year to 44 years in the Phase 3 study. • The most frequent adverse reactions (incidence >5%) include pruritis, chills, erythema, rash, cough, and rhinorrhea. • The safety profile of two subjects with autosomal recessive DEB of six and seven months old, respectively in the open-label study (Study B-VEC-EX-02) was similar to that of the Phase 3 study.	• The risks of B-VEC are characterized based on 31 subjects in the Phase 3 study. • The size of the safety database for B-VEC is small but adequate for this rare and serious condition considering the benefit and risk of the treatment • The overall safety profile did not raise any concern.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	The risk management plan includes: • An open-label extension (OLE) study (B-VEC-EX-02) and a 5-year long-term follow-up (LTFU) study (KRYS-LTFU-01) • A routine pharmacovigilance plan for post-approval safety monitoring	• The risks can be mitigated through routine medical management, adequate prescr bing information, ongoing OLE and LTFU studies and the routine post-marketing pharmacovigilance plan.

Abbreviations: AE, adverse event; BMZ, basement membrane zone; CCS, composite cultured skin; COL7, human type VII collagen; *COL7A1*, collagen type VII alpha 1 chain; DEB, dystrophic epidermolysis bullosa; DDEB, dominant dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; HDE, Humanitarian Device Exemption; NC1/NC2, noncollagenous domain 1/2; PD, pharmacodynamics; PMC, postmarketing commitment; PMR, postmarketing requirement; RDEB, recessive dystrophic epidermolysis bullosa; REMS, Risk Evaluation and Mitigation Strategy.

11.2 Risk-Benefit Summary and Assessment

The overall benefit/risk is favorable for the weekly topical application of VYJUVEK to the DEB wounds for patients six months of age and older with DEB with mutation(s) in the *COL7A1* gene.

VYJUVEK demonstrated substantial evidence of effectiveness for promoting wound closure in patients with DEB based on the primary evidence of effectiveness from the adequate and well-controlled Phase 3 study plus confirmatory evidence of the PD activity (expression and localization of COL7 transgene) demonstrated in the Phase 1/2 study.

The risks of VYJUVEK are characterized based on the safety database of 31 subjects in the Phase 3 study. The small safety database is acceptable considering the seriousness and rarity of DEB, and the benefit and risk of the treatment.

The safety profile of two subjects of six and seven months old, respectively in an open-label study (Study B-VEC-EX-02) supports the safety of VYJUVEK in patients aged between 6 months and less than 12 months.

The overall safety findings did not raise any concern.

The risks can be further characterized with an ongoing 5-year LTFU safety study and can be prevented or mitigated by management within routine medical practice and suitable prescribing information.

11.3 Discussion of Regulatory Options

Not applicable.

11.4 Recommendations on Regulatory Actions

Based on analyses of the clinical safety and efficacy data contained in the BLA submission, the Clinical Reviewer considers the benefit/risk profile sufficiently favorable in support of standard approval of B-VEC for the treatment of wounds in patients one year of age and older with DEB with mutation(s) in the *COL7A1* gene.

11.5 Labeling Review and Recommendations

Proprietary Name

The proposed proprietary name for B-VEC is VYJUVEK. This name has been reviewed by the Center for Biologics Evaluation and Research's Advertising and Promotional Labeling Branch and was deemed acceptable.

The suffix for inclusion in the proper name

FDA provides the suffix, -svdt, for inclusion in the proper name, beremagene geperpavec-svdt.

Prescribing Information

The prescribing information (PI) required major revisions. FDA suggested substantial changes to each section of the PI, based on available clinical trial data as well as FDA guidance on product labeling. The Clinical Reviewer considers the revised PI to be acceptable.

The overall content of the PI suitably conveys known information regarding safety and efficacy results demonstrated in the clinical studies of B-VEC.

11.6 Recommendations on Postmarketing Actions

Based on review of the safety data, neither a REMS nor a safety PMR study is needed. The postmarketing risk mitigation plans proposed by the applicant, including product labeling, spontaneous adverse event reporting as well as two ongoing studies: an OLE of the Phase 3 study (Study B-VEC-EX-02) and an observational LTFU study (Study KRYS-LTFU-01), are acceptable.

APPENDIX 1

The OLE study: Study B-VEC-EX-02

The key study objectives are:

- to provide continued use of B-VEC to patients who participated in and completed Phase 3 Protocol B-VEC-01, upon study completion,
- to provide the use of B-VEC to DEB-diagnosed patients who have not participated in the Phase 3 trial, and
- to collect safety data of subjects while on B-VEC.

The dose and dosing regimen in the OLE are the same as those of in the phase 3 study.

As of 15 December 2022, a total of 42 subjects were enrolled in the OLE study. Among those enrolled, 23 subjects had previously participated in the Phase 3 study. The data from the OLE updates will not be integrated with the Phase 3 study or included in the USPI.

The Applicant submitted interim safety updates in the 120-day safety update based on a cutoff date of 30 June 2022. Based on these interim results, the incidence of AEs in the OLE study appears similar to that in the Phase 3 study. No discernible AEs were observed between subjects who rolled over from the Phase 3 study and treatment-naïve subjects who were enrolled into the OLE study.

During the USPI negotiation, the Applicant submitted information of two subjects (Subject (b) (6) 7.4 months and Subject (b) (6): 6.2 months) who received topical application of B-VEC weekly in the OLE study to support the inclusion of patients with DEB between six months and less than 12 months of age in the proposed indication. Both subjects have autosomal RDEB. As of March 3, 2023, Subject (b) (6) received 30 treatments and Subject (b) (6) received 25 treatments. The AEs reported in these two subjects were mild and were not considered related to B-VEC treatment. No AEs have led to discontinuation of treatment.

- Subject (b) (6) had reported four AEs including cough, rhinorrhea, pyrexia, and generalized itch.
- Subject (b) (6) had reported two AEs including purple lips and Influenza.

Reviewer Comment:
The safety profile remains unchanged.

In response to IR submitted on March 27, 2023, the applicant explained that the study was not intended to track and assess wounds for complete closure, but rather the focus was on safety and the overall benefit on quality of life and treatment satisfaction, thus no detailed efficacy data is available.

The reviewer agrees with the Applicant's assessment the AEs reported in the two subjects aged seven and six months respectively are unlikely related to the B-BEC treatment because the pharmacokinetic data suggest a lack of systemic exposure after topical application of B-VEC on the DEB wounds.

The reviewer considers the safety findings in the two young subjects (Subject (b) (6) and Subject (b) (6)) support the inclusion of patients with DEB as young as six months of age in the proposed indication. The efficacy of B-VEC on DEB wounds in patient between 6 months and

less than 12 months may be extrapolated from that of the patients aged one to 44 years studied in the Phase 3 study based on the MOA of the B-VEC and PD activity demonstrated in the Phase 1/2 study.

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