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<b>Applicant</b>	Krystal Biotech
<b>Established Name</b>	Beremagene Geperpavec (B-VEC)
<b>(Proposed) Trade Name</b>	Vyjuvek
<b>Pharmacologic Class</b>	A replication defective, non-integrating, modified herpes simplex virus-1 (HSV-1) vector expressing type VII collagen (COL7)
<b>Formulation(s), including Adjuvants, etc</b>	Topically administrated B-VEC consisted of thawed cryopreserved drug product mixed with an excipient gel, Methocel™.
<b>Dosage Form(s) and Route(s) of Administration</b>	Suspension; Topical
<b>Dosing Regimen</b>	Based on age (range 1.6 to 3.2×10 <sup>9</sup> PFU/week) and wound area (range 4×10 <sup>8</sup> to 1.2×10 <sup>9</sup> PFU/wound). Subjects were dosed topically for up to 26 weeks or until wound closure.
<b>Indication(s) and Intended Population(s)</b>	Dystrophic epidermolysis bullosa (DEB); Children, adolescents, and adults with DEB.



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## GLOSSARY

Abbreviation	Definition
AE	Adverse Event
BLA	Biologics Licensure Application
B-VEC	Beremagene Geperpavec
CI	Confidence Interval
COL7	Collagen VII
DDEB	Dominant Dystrophic Epidermolysis Bullosa
DEB	Dystrophic Epidermolysis Bullosa
DSMB	Data Safety Monitoring Board
FDA	Food And Drug Administration
HSV	Herpes Simplex Virus
ITT	Intent-To-Treat
MAR	Missing At Random
mITT	Modified Intent-To-Treat
PP	Per-Protocol
RDEB	Recessive Dystrophic Epidermolysis Bullosa
SAE	Serious Adverse Event
STD	Standard Deviation
US	United States

## 1. EXECUTIVE SUMMARY

Beremagene geperpavec (B-VEC) is an engineered non-replicating herpes simplex virus (HSV) type 1-based vector coding human COL7A1 that can be applied topically to promote functional COL7 expression in the skin. This Biologics Licensure Application (BLA) seeks licensure of B-VEC for the treatment of Dystrophic epidermolysis bullosa (DEB) in children, adolescents, and adults. DEB is a group of heritable skin diseases characterized by skin fragility, blister formation, milia, and scarring. DEB is the result of mutations to the COL7A1 gene encoding type VII collagen (COL7).

The primary source of evidence to support this application is a Phase 3, intrasubject randomized, placebo-controlled, double-blind and multicenter study (Study B-VEC-03). The study enrolled 31 subjects. Two comparable wounds (the primary wound pair) of each patient were selected and randomized to receive either topical application of B-VEC or placebo. The pre-specified primary efficacy endpoint was proportion of responder wounds defined as wounds that were healed for at least 2 consecutive weeks (either Week 22 and Week 24, or Week 24 and Week 26). Results summarized in this memo are based on the database locked on November 19, 2021.

The exact McNemar test for the primary efficacy endpoint showed a significant treatment effect of B-VEC ( $p$ -value = 0.01) as compared to placebo. The number (proportion) of responder wounds in B-VEC treatment arm and placebo arm is respectively 20 (64.5%)

and 8 (25.8%). The difference of proportions (95% CI) between two arms is 38.7% (13.9%, 63.5%).

There were no deaths during the study. Three subjects experienced a total of 5 serious adverse events (SAEs). None of the SAEs was considered drug-related as assessed by the investigator.

Study B-VEC-03 met its primary efficacy objective: the pre-specified null hypothesis of the absence of a treatment effect on wound healing was rejected. The statistical analysis results provide sufficient evidence to support the applicant's proposed indication of B-VEC in this BLA.

## 2. CLINICAL AND REGULATORY BACKGROUND

### 2.1 Disease or Health-Related Condition(s) Studied

DEB is a group of heritable skin diseases characterized by skin fragility, blister formation, milia, and scarring (Intong, 2012).<sup>1</sup> Severe generalized recessive dystrophic epidermolysis bullosa (RDEB), formerly termed Hallipeau-Siemens, is characterized by extensive blistering and scarring of the skin and mucosal membranes. Blisters and erosions affect skin as well as certain mucosa exposed to disruptive external environment, including oropharynx, esophagus, rectum, genitourinary system and eyes. Healing of erosions results in debilitating scarring. Damage to the mouth and esophagus can make it difficult to chew and swallow food, leading to chronic malnutrition and slow growth. Complications from extensive scarring can include fusion of the fingers and toes, joint deformities, and vision impairment.

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

Table 1 summarizes the major pre- and post-submission regulatory activities associated with this BLA.

Table 1. Summary of major Pre- and Post-submission regulatory activities

Date	Milestone
10/13/2016	Pre-IND Meeting
12/29/2016	Rare Pediatric Disease Designation Granted (RPD-2016-95)
11/02/2017	Orphan Drug Designation Granted (DRU-2016-5588)
03/26/2018	IND Submission
05/23/2018	Fast Track Designation Granted
06/21/2019	RMAT Designation Granted
10/22/2019	RMAT - Initial Meeting
02/04/2020	EOP2 Meeting
02/06/2020	Division of Manufacturing and Product Quality Meeting
04/14/2021	FDA Communication (Accepted Statistical Analysis Plan for Phase 3 study)
04/21/2021	Human Factor Validation Protocol Review Meeting
07/16/2021	Agreement Human Factors Protocol Assessment
07/30/2021	Pre-BLA (CMC) Meeting
09/27/2021	Proprietary Name (Vyjuvek™) Acceptance (tentative)
01/21/2022	B-VEC Commercial Presentation and Distribution Meeting
03/25/2022	Pre-BLA Meeting
04/08/2022	FDA Communication (Accepted Human Factor Validation Study Report)
06/20/2022	BLA 125774 submission
08/18/2022	BLA filed. Filing Letter issued to Applicant
01/03/2023	Major Amendment and Extension of Review Clock by 3 Months from 02/17/2023 to 05/17/2023
05/17/2023	PDUFA Action Due Date

(Source: Module 2.5 Clinical Overview Table 2, p. 12; FDA statistical reviewer's summary)

### 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

#### 3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

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

#### 5.1 Review Strategy

The primary source of evidence to support the efficacy and the safety of the proposed product comes from study B-VEC-03 (GEM-3) and the review of it is the focus of this review memo.

## **5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review**

The basis of this statistical memo includes review of clinical study reports and data sets submitted under module 5 of BLA 125774/0.0; and IR response under BLA 125774/0.11, 0.15 and 0.25.

## **5.3 Table of Studies/Clinical Trials**

Table 2 summarizes the four studies included in the BLA submission. Results from study B-VEC-03 (GEM-3) form the primary evidence of safety and efficacy of B-VEC for the BLA application.

The safety and preliminary efficacy evaluation from Study KB103-001 is considered exploratory because the study objectives varied in the four phases of the study, resulting in various doses, dosing regimens and route of administration used in each phase of the study. The safety and efficacy results of this study are not described in the PI. Therefore, they are not included in this memo.

The applicant submitted 120-day safety and efficacy updates from the ongoing OLE Study B-VEC-EX-02. The data from the 120-day updates was reviewed separately and not integrated with the Study B-VEC-03 because of different investigational conditions of the two studies. The results from Study B-VEC-EX-02 is not included in the PI, and therefore not included in this memo.

Table 2. Studies in the BLA application

Study code	Study design + Study population	Study status	Sample size*
KB103-001	Phase 1/2, single center, open-label, intrasubject randomized, placebo-controlled trial for subjects $\geq 2$ years of age with diagnosis of recessive dystrophic epidermolysis bullosa (RDEB)	Complete	12
B-VEC-03 (GEM-3) (pivotal)	Phase 3, multicenter, double-blind, intrasubject randomized, placebo-controlled trial for subjects $\geq 6$ months of age with diagnosis of dominant dystrophic epidermolysis bullosa (DDEB) or RDEB	Complete	31
B-VEC-EX-02	Cohort 1: open-label treatment extension for subjects who completed B-VEC-03 and newly enrolling subjects with DEB Cohort 2: continued assessment of subjects who completed B-VEC-03 (no further B-VEC treatment)	Ongoing	Planned: Cohort 1: ~40 Cohort 2: ~10 Enrolled as of June 30, 2022: Cohort 1: 35 Cohort 2: 0
KRYS-LTFU-01	Long-term safety follow-up, multicenter, prospective, observational, cohort study for all participants who received at least one gene therapy treatment in a previous Krystal Biotech, Inc.-sponsored study	Ongoing	Determined by parent protocol

\* Database lock date = November 19, 2021 for Study VEC-03 (GEM-3).  
(Source: Module 5.2 Tabular Listing of All Clinical Studies; FDA statistical reviewer's summary)

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Study B-VEC-03 (GEM-3)

#### 6.1.1 Objectives

Primary:

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



### 6.1.2 Design Overview

This was a Phase 3, multicenter, intrasubject randomized, placebo-controlled, double-blind study of B-VEC for the topical treatment of DEB wounds. The planned sample size was 30 to 32 subjects, and the actual sample size was 31 subjects. Two comparable wounds (the primary wound pair) of each subject were selected and randomized to receive weekly either topical application of B-VEC or placebo, for up to 26 weeks or until wound closure.

### 6.1.3 Population

The study population is subjects 6 months or older with DEB.

### 6.1.4 Study Treatments or Agents Mandated by the Protocol

Topically administrated B-VEC consisted of thawed cryopreserved drug product mixed with an excipient gel, Methocel™. Placebo consisted of excipient gel, mixed with isotonic saline, without the active drug product. Wounds were randomized to receive weekly treatment of 1 unit-dose of B-VEC or placebo. The unit dose was based on wound area:

- <20 cm<sup>2</sup>: 4×10<sup>8</sup> PFU (plaque-forming units)/wound
- 20 to 40 cm<sup>2</sup>: 8×10<sup>8</sup> PFU/wound
- 40 to 60 cm<sup>2</sup>: 1.2×10<sup>9</sup> PFU/wound

In addition, the maximum weekly dose of B-VEC was based on the subject's age:

- ≥6 months to <3 years: 1.6×10<sup>9</sup> PFU/week
- (b) (4)
- ≥6 years: 3.2×10<sup>9</sup> PFU/week

### 6.1.6 Sites and Centers

Three centers in US

### 6.1.7 Surveillance/Monitoring

A data safety monitoring board (DSMB) was responsible for ensuring the safety of the subjects and alerting the sponsor to any safety issues related to the conduct of the study. The DSMB reviewed blinded data including general study/enrollment information, laboratory results, and adverse events (AEs). After reviewing all available data, the DSMB had no concerns with the safety data available at the time of the meeting and voted to continue the study without modification.

### 6.1.8 Endpoints and Criteria for Study Success

#### **Primary Endpoint**

Responder wounds defined as meeting any of the following conditions:

- Healed on Week 22 and Week 24, or
- Healed on Week 24 and Week 26

#### **Key Secondary Endpoint**

Responder wounds that meet any of the following conditions:

- Healed on Week 8 and Week 10, or
- Healed on Week 10 and Week 12.

#### **Other Secondary Endpoint**

Change in pain severity VAS score at Week 22, Week 24, and Week 26 for each B-VEC-treated wound versus placebo-treated wound for ages 6 and above.

#### 6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical considerations proposed in the study protocol are described in the following:

##### Design features:

Two matched primary wounds of 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. Specifically,  $H_0: \text{Prob}(B) = \text{Prob}(C)$  vs.  $H_a: \text{Prob}(B) \neq \text{Prob}(C)$ , where  $\text{Prob}(B)$  and  $\text{Prob}(C)$  are the probability of the occurrence of discordant pairs B (i.e., responder in B-VEC and non-responder in Placebo in a wound pair) and C (i.e., non-responder in B-VEC and responder in Placebo in a wound pair), as in the  $2 \times 2$  discordant table (Table 3).

Table 3.  $2 \times 2$  discordant table

		Placebo		Row total
		Responder	Non-responder	
B-VEC	Responder	A	B	N1
	Non-responder	C	D	N2
	Column total	M1	M2	T

(Source: FDA statistical reviewer's summary)

##### Analysis populations:

**Safety Analysis set** included all subjects who were administered either B-VEC or placebo.

**Intent-to-Treat (ITT) Analysis set** included subjects whose primary wounds were randomized, regardless of whether they received randomized treatment or not.

**Modified intent-to-treat (mITT) Analysis set** included subjects whose primary wounds were randomized and received B-VEC or placebo treatment with at least one post baseline primary endpoint assessment.

**The per-protocol (PP) Analysis set** includes all the safety population subjects who completed the study without any major protocol deviations.

##### Statistical methods:

The primary and secondary efficacy analysis were conducted on the ITT analysis set.

##### **Primary 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 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 at the Type I error rate of 0.05 if the primary efficacy endpoint was tested significant.

### **Other secondary endpoints**

Change in pain severity VAS score: The least square mean difference between B-VEC and placebo arms was estimated with a 95% confidence interval.

### Interim Analyses:

No interim analysis was planned or performed.

### Sample size and power calculation:

The sponsor assumed a response rate of 75% for wounds in B-VEC treatment arm and 25% for wounds in placebo arm, and estimated the expected proportion of discordant pairs. Specifically, among the 75% wounds that respond to the B-VEC treatment, 75% of their matched wounds were expected to not respond to placebo treatment. Therefore, the proportion of the discordant pairs that respond to B-VEC but do not respond to placebo is estimated at 56.25%. Similarly, among the 25% wounds that do not respond to the B-VEC treatment, 25% of their matched wounds were expected to respond to placebo treatment. So the proportion of the discordant pairs that do not respond to B-VEC but respond to placebo is 6.25%. Therefore, the estimated proportion of all discordant pairs is 62.5%. With a two-sided Type I error rate of 0.05 and 90% power, the sample size was determined at 24 subjects (i.e., 24 wound pairs) for the exact McNemar test. Assuming a 20% - 25% dropout rate due to concerns about the COVID-19 dropouts and burden of weekly visit to the clinical sites, the targeted sample size was 30 to 32 subjects. The actual sample size was 31 subjects.

### Sensitivity analyses:

The sensitivity analyses for the primary and secondary efficacy endpoints were conducted by repeating the primary analysis on the mITT and PP analysis set.

### Subgroup analyses:

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

- wound surface area:
  - $<20 \text{ cm}^2$
  - $\geq 20 \text{ cm}^2$
- age of the subjects:
  - $\leq 12$  years
  - $>12$  and  $\leq 18$  years
  - $>18$  years

### Missing data and Imputation:

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

- For the missing endpoints in B-VEC group, treat all missing endpoints as non-responder.
- For the missing endpoints in placebo group, treat all missing endpoints as responder.

***Statistical Reviewer comment:***

*In the original submission BLA 125774/0.0, the applicant used the multiple imputation (MI) method assuming a Missing at Random (MAR) missingness mechanism to impute the missing primary 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. FDA has concerns that the missing values may not be properly imputed for the following reasons:*

- *The complete wound healing 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.*

*Therefore, FDA requests that the applicant performs the worst-case scenario imputation strategy as specified above, and used the analysis based on the worst-case scenario imputation strategy for efficacy evaluation on the primary and key secondary endpoints.*

#### 6.1.10 Study Population and Disposition

##### 6.1.10.1 Populations Enrolled/Analyzed

###### 6.1.10.1.1 Demographics

Table 4. Summary of demographic and baseline characteristics in the ITT analysis set

Characteristic	All Subjects (N=31)
Age (years)	
Mean (STD)	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)

STD=standard deviation

(Source: Section 5.3.5.1 Study Report p. 45)

#### 6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 5. Summary of baseline characteristics in the ITT analysis set

Genotype, n (%)	
Dominant DEB	1 (3.2)
Recessive DEB	30 (96.8)
Primary Wound Area (cm <sup>2</sup> ) – B-VEC	
Mean (STD)	14.4 (12.7)
Median (min, max)	10.6 (2.3, 57.3)
Primary Wound Area (cm <sup>2</sup> ) – Placebo	
Mean (STD)	15.6 (12.1)
Median (min, max)	10.4 (2.3, 51.5)
Primary Wound Area – B-VEC, n (%)	
<20 cm <sup>2</sup>	23 (74.2)
20 to <40 cm <sup>2</sup>	6 (19.4)
40 to 60 cm <sup>2</sup>	2 (6.5)
Primary Wound Area – Placebo, n (%)	
<20 cm <sup>2</sup>	22 (71.0)
20 to <40 cm <sup>2</sup>	8 (25.8)
40 to 60 cm <sup>2</sup>	1 (3.2)

STD=standard deviation

(Source: Section 5.3.5.1 Study Report p. 45)

### 6.1.10.1.3 Subject Disposition

Among the 31 enrolled subjects, 28 completed the study. Three subjects discontinued the study due to withdrawal by subject. 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. Subject (b) (6) withdrew consent after Week 24 due to challenges arranging (b) (6) to the study site in the setting of the COVID-19 pandemic. Subject (b) (6) chose early termination after Week 12 due to the need to relocate for (b) (6).

### 6.1.11 Efficacy Analyses

#### 6.1.11.1 Analyses of Primary Endpoint

Table 6 displays the exact McNemar test for the responder rate at Week 22 and 24 or Week 24 and 26. The results show a significant treatment effect of B-VEC (p-value = 0.01182) as compared to placebo. The number (proportion) of responder wounds in B-VEC and placebo arm is respectively 20 (64.5%) and 8 (25.8%). The difference of proportions (95% CI) of responder wounds between the two arms is 38.7% (13.9%, 63.5%).

Table 6. 2×2 discordant table and exact McNemar test for the responder rate at Week 22 and 24 or Week 24 and 26 in the ITT analysis set

		Primary B-VEC Wound		Overall	p-value [1]
		Responder	Non-Responder		
Primary Placebo Wound	Responder	4 (12.9)	4 (12.9)	8 (25.8)	0.01182
	Non-Responder	16 (51.6)	7 (22.6)	23 (74.2)	
	Overall	20 (64.5)	11 (35.5)		

[1] There were two subjects (Subject (b) (6)) who had missing values for the primary efficacy endpoint. Their assessments were missing for both B-VEC and placebo arms in week 22, 24, and 26. The p-value of exact McNemar Test was estimated based on the worst-case scenario imputation strategy.

Note: Subject (b) (6) had wound healing assessments performed remotely at Week 22 and 26 and onsite at Week 24. The assessments showed a response for the B-VEC treated wound, and a non-response for the placebo treated wound. Based on evaluation of FDA clinical team, the assessments for Subject (b) (6) were acceptable and thus not set to missing.

The primary analysis was repeated in the mITT and PP analysis set. The findings are consistent with the primary analysis using ITT as displayed in Table 7.

Table 7. Difference between the two groups in the percentage of responders

	Responder, n(%)		% Difference (95% CI)	p-value
	B-VEC Wound	Placebo Wound		
mITT, n=29	19 (65.5)	6 (20.7)	44.8 (22.2, 67.4)	0.002
PP, n=24	17 (70.8)	6 (25.0)	45.8 (20.1, 71.6)	0.007

#### 6.1.11.2 Analyses of Secondary Endpoints

##### Key secondary endpoint

Table 7 displays the exact McNemar test for the responder rate at Week 8 and 10 or Week 10 and 12. The results show a significant treatment effect of B-VEC (p-value = 0.00258) as compared to placebo. The number (proportion) of responder wounds in B-VEC and placebo arm is respectively 21 (67.7%) and 7 (22.6%). The difference of proportions (95% CI) of responder wounds between the two arms is 45.1% (21.8%, 68.5%).

Table 8. 2×2 discordant table and exact McNemar test for the responder rate at Week 8 and 10 or Week 10 and 12 in the ITT analysis set

		Primary B-VEC Wound			
		Responder	Non-Responder	Overall	p-value [2]
Primary Placebo Wound	Responder	4 (12.9)	3 (9.7)	7 (22.6)	0.00258
	Non-Responder	17 (54.8)	7 (22.6)	24 (77.4)	
	Overall	21 (67.7)	10 (32.3)		

[2] There was one subject (Subject (b) (6)) who had missing values for the key secondary endpoint. The assessment for Subject (b) (6) was missing for both B-VEC and placebo arms in week 8, 10, and 12. The p-value of exact McNemar Test was estimated based on the worst-case scenario imputation strategy.

##### Other secondary endpoint - Change in Pain Severity VAS Score

Change in Pain Severity VAS Score for subjects aged 6 and older in the ITT population showed a least square mean difference (95% CI) between B-VEC and placebo arms of 0.61 (-1.10, -0.13) at Week 22; -0.88 (-1.79, 0.03) at Week 24, and -0.56 (-1.17, 0.05) at Week 26.

##### Note:

*Clinical reviewer thinks the assessment on Pain Score for this study is not interpretable and should not be included in the PI.*

#### 6.1.11.3 Subpopulation Analyses

##### Subgroup analysis of primary endpoint (responder rate at Week 22 and 24 or Week 24 and 26) in the ITT analysis set:

- By wound surface area
  - < 20 cm<sup>2</sup> subgroup (n=21): proportions of responder wounds in B-VEC and placebo arms are 61.9% and 33.3%. Difference (95% CI) is 28.6% (-1.4%, 58.5%).
  - ≥ 20 cm<sup>2</sup> subgroup (n=10): proportions of responder wounds in B-VEC and placebo arms are 60.0% and 20.0%. Difference (95% CI) is 40.0% (-9.6%, 89.6%).
- By age group

- $\leq 12$  years (n=10): proportions of responder wounds in B-VEC and placebo arms are 80.0% and 20.0 %. Difference (95% CI) is 60.0% (29.6%, 90.4%).
- $>12$  and  $\leq 18$  years (n=9): proportions of responder wounds in B-VEC and placebo arms are 55.6% and 33.3%. Difference (95% CI) is 22.2% (-29.1%, 73.6%).
- $>18$  years (n=12): ): proportions of responder wounds in B-VEC and placebo arms are 50.0% and 33.3%. Difference (95% CI) is 16.7% (-28.6%, 61.9%).

#### 6.1.11.4 Dropouts and/or Discontinuations

Refer to Section 6.1.10.1.3 Subject Disposition.

#### 6.1.12 Safety Analyses

##### 6.1.12.1 Methods

Descriptive statistics were used to summarize safety data. The safety analysis set included 31 subjects who were enrolled in the study.

##### 6.1.12.3 Deaths

There were no deaths during the study.

##### 6.1.12.4 Nonfatal Serious Adverse Events

Three subjects experienced a total of 5 SAEs during the study. Subject (b) (6) experienced Cellulitis (right leg). Subject (b) (6) experienced Anemia (2 events) and Diarrhea. Subject (b) (6) experienced positive blood culture. None of the SAEs was considered drug-related as assessed by the investigator.

##### 6.1.12.7 Dropouts and/or Discontinuations

No AEs led to treatment discontinuation.

## 10. CONCLUSIONS

### 10.1 Statistical Issues and Collective Evidence

B-VEC (beremagene geperpavec) is an engineered non-replicating HSV type 1-based vector coding human COL7A1 that can be applied topically to promote functional COL7 expression in the skin. This BLA seeks licensure of B-VEC for the treatment of DEB in children, adolescents, and adults.

The primary source of evidence to support this application is a Phase 3, intrasubject randomized, placebo-controlled, double-blind and multicenter study (Study B-VEC-03). A total of 31 subjects were enrolled. For each subject, one primary wound is randomized to B-VEC arm and the other matched primary wound is randomized to placebo arm.



The primary efficacy endpoint is responder wounds at either Week 22 and 24 or Week 24 and 26. The number of responder wounds in B-VEC treatment arm and placebo arm is respectively 20 (64.5%) and 8 (25.8%). The difference of proportions (95% CI) of responder wounds between two arms is 38.7% (13.9%, 63.5%). The exact McNemar test based on the worst-case scenario imputation strategy showed a significant treatment effect of B-VEC (p-value = 0.01) as compared to placebo.

Three subjects experienced a total of 5 SAEs during the study, none of which was considered drug-related as assessed by the investigator. No death occurred during the study.

## **10.2 Conclusions and Recommendations**

Study B-VEC-03 met the efficacy criteria for the primary endpoint with the rejection of the pre-specified null hypothesis of no treatment effect of B-VEC on wound healing. The statistical analysis results provide substantial evidence of effectiveness to support the approval of B-VEC for the applicant's proposed indication.

## **REFERENCES**

1. Intong, R., 2012. Inherited epidermolysis bullosa: A new diagnostic criteria and classification. Clinics in Dermatology, pp. 70-77.