The GEM-3 Study

B-VEC-03
A Phase III Efficacy and Safety Study of Beremagene Geperpavec (B-VEC, previously KB103) for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)

Status:	**Final**
Protocol Version:	**1.4**
Version Date	**21-APR-2021**
IND Number:	**018100**
Investigational Product:	**B-VEC**
Phase of Development:	**Phase III**

Sponsor Approval

Sponsor Endorsement

This protocol has been approved by Krystal Biotech, Inc.

Sponsor's Authorized Officer: Suma Krishnan, M.S., M.B.A.

Chief Operating Officer
Krystal Biotech, Inc.
2100 Wharton Street, Suite 310
Pittsburgh, PA 15203

_____ _____

Signature Date

Investigator's Acknowledgement

Principal Investigator's Agreement

I have read the Phase III Protocol:

GEM-3: A Phase III Efficacy and Safety Study of Beremagene Geperpavec (B-VEC, previously "KB103") for the treatment of Dystrophic Epidermolysis Bullosa (DEB)

I have fully discussed the objectives of this trial and the contents of this protocol with the Sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the review of the study, without written authorization from Krystal Biotech, Inc. It is permissible to provide the information contained within to a subject to obtain their consent to participate.

I agree to conduct the study as outlined herein and in accordance with International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP), with applicable Food and Drug Administration (FDA) regulations set forth in 21 CFR Parts 50, 54, and 312, and all other applicable regulatory requirements.

I understand that failure to comply with the protocol requirements may lead to termination of my role as an Investigator for this study.

I understand that Krystal Biotech, Inc may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated in writing. If I should decide to withdraw from execution of the study, I will communicate my intention immediately in writing to Krystal Biotech, Inc.

Principal Investigator Name: _____

_____ _____

Signature Date

Protocol History

Protocol History	
Version and Date of Protocol	**Comments**
Version 1.0 (05-MAY-2020)	Original Version Submitted to FDA
Version 1.1 (29-JUN-2020)	Updated Version Submitted to FDA
Version 1.2 (20-OCT-2020)	Urine collection, phlebotomy and dressing viral shedding collection minimized
Version 1.3 (10-DEC-2020)	Matched Wounds capped at one (1) pair and Secondary Unmatched Wounds capped at four (4).
Version 1.4 (21-APR-2021)	Updated statistical plan and additional details on study assessments

Key Changes in the Protocol

Major changes to the protocol are summarized below. Minor administrative changes involving formatting, grammar, syntax, punctuation, and other editorial changes are not summarized in the table below.

Change and Rationale	Affected Sections
Statistical analysis for primary and key secondary endpoint measurement will be analyzed using the McNemar Test, adjusted per FDA agreement. Furthermore, the primary endpoint is defined as wounds that meet any of the following conditions: • Healed on Week 22 and Week 24, or • Healed on Week 24 and Week 26. The secondary key endpoint is defined as wounds that meet any of the following conditions: • Healed on Week 8 and Week 10, or • Healed on Week 10 and Week 12. Only wounds that are healed for at least two (2) consecutive weeks are counted as positive responses.	Synopsis; Section 2.2; Section 6.2; Section 8.1; Section 8.2; and Section 8.7
The protocol has been amended to add clarification around the assessment of the Primary Wounds, such that only the originally selected area at the Week 1 Visit, will be assessed at the Week 8, 10, 12, 22, 24 and 26 Visits. The neighboring wounds which have received treatment during the study will not be included in this assessment.	Section 2.2; Section 4.2; Section 5.1; Section 6.2; Section 8.1; Section 8.2; and Section 8.7
Per Agency's recommendation, a McNemar Test has been used for sample size calculation. In the Phase I/II study, the response rates for Weeks 8 through 12 were from 70-100% for wounds randomized to B-VEC and 0-33% for wounds randomized to placebo, respectively. Therefore, the sample size has been revised to 24 subjects assuming a response rate of 75% among wounds randomized to B-VEC and a response rate of 25% among wounds randomized to placebo. With 90% power and a two-sided Type 1 error rate of 5%, 24 subjects (i.e., 24 wound pairs) are required.	Synopsis; Section 3.0; and Section 8.3

Protocol Synopsis

<table>
<tr><td>Title</td><td>GEM-3: A Phase III Double Blinded, Placebo-Controlled, Efficacy and Safety Study of Beremagene Geperpavec (B-VEC, previously “KB103”) for the treatment of Dystrophic Epidermolysis Bullosa (DEB)</td></tr>
<tr><td>Study Number</td><td>B-VEC-03</td></tr>
<tr><td>Number of Subjects</td><td>Approximately 24 subjects</td></tr>
<tr><td>Study Phase</td><td>Phase III study</td></tr>
<tr><td>Number of Centers</td><td>3 centers</td></tr>
<tr><td>Study Objectives</td><td>The primary objective is to determine whether administration of B-VEC in addition to standard of care improves wound healing as compared to placebo in children, adolescents, and adults with Dystrophic Epidermolysis Bullosa (DEB).</td></tr>
<tr><td>Study Design</td><td>GEM-3 is a multi-center, intra-subject randomized, placebo-controlled, double blinded, Phase III study of B-VEC for the topical treatment of DEB wounds. Each subject will serve as their own control.
Definition of Unit Dose: Unit dose varies by wound area
<table>
<tr><th>Wound Area*</th><th>Unit Dose</th></tr>
<tr><td><20 cm^2</td><td>4×10^8 PFU/wound</td></tr>
<tr><td>20 to 40 cm^2</td><td>8×10^8 PFU/wound</td></tr>
<tr><td>40 to 60 cm^2</td><td>1.2×10^9 PFU/wound</td></tr>
</table>
* Wound area determined by the Investigator using the validated Canfield photography quantitation at Week 1. Subsequent Secondary Wounds not selected at Week 1, will have the wound area determined during selection.

Definitions:
Weekly Treatment: 1 unit-dose of B-VEC or placebo
Treatment Cycle: Weekly Treatment until complete wound closure of wounds selected at baseline and any new surrounding wounds (neighboring wounds) during the treatment phase.
Maximum Weekly Dose per subject:
<table>
<tr><th>Age</th><th>Maximum Weekly Dose</th></tr>
<tr><td>≥ 6 months to < 3 years</td><td>1.6×10^9 PFU/week</td></tr>
<tr><td>≥ 3 years to < 6 years</td><td>2.4×10^9 PFU/week</td></tr>
<tr><td>≥ 6 years</td><td>3.2×10^9 PFU/week</td></tr>
</table>
Matched Wounds: Two matched wounds similar in size, located in similar anatomical regions, and have similar appearance.
Two matched wounds in a 1:1 ratio per subject will be selected to evaluate the primary and secondary endpoints. The matched wounds will be randomized, such that one wound will receive Weekly</td></tr>
</table>

	Treatment of B-VEC and one wound will receive Weekly Treatment of placebo for a Treatment Cycle.
Study Design **(continued)**	Remaining Weekly Dose: The difference between Maximum Weekly Dose per subject per week and the sum total of the B-VEC Dose(s) applied to the Primary Wound Pair per subject per week. The Remaining Weekly Dose will be used to treat Secondary Wounds. Up to four (4) Secondary Wounds may be selected. For example: If a subject 7 years of age, presents with the primary wound pair $\leq 20cm^2$ then the Remaining Weekly Dose during a weekly visit = Difference of (3.2×10^9 PFU – (4×10^8 PFU)) = 2.8×10^9 PFU/subject/week. The Remaining Weekly Dose will be applied to secondary wounds for monitoring safety and efficacy. Re-dosing regimen During the study, if a neighboring wound near the primary wound opens up, (approximately 2-3 cm from the original wound) that wound may receive treatment at the discretion of the Investigator. When a matched primary wound and its neighboring wound/s close completely, as determined by the Investigator during a weekly visit, then no treatment will occur. Weekly treatment on that wound will resume when the originally selected wound or its neighboring wound/s is determined to be open by the Investigator at a weekly visit. The re-dosing regimen will be followed throughout the study. Secondary Wounds The Remaining Weekly Dose calculated during a weekly visit will be applied to a maximum of four (4) additional wounds ("Secondary Wounds"). Secondary Wound(s) will receive a Weekly Treatment of B-VEC for the Treatment Cycle. The number of Secondary Wounds treated will depend on wound area of the Secondary Wound(s). The total dose applied to Secondary Wounds is not to exceed the Remaining Weekly Dose. During the study, if a neighboring wound near the Secondary wound opens up, (approximately 2-3 cm from the original wound) that wound may receive treatment. When the secondary wound and the neighboring wound close completely, as determined by the Investigator during a weekly visit, then that particular wound will stop receiving treatment. For Secondary Wounds, avoid selecting wounds that are in close proximity to the Primary Wound Pair.
Primary Endpoint	**Wound Healing** The primary endpoint is the proportion of DEB primary wound sites with complete wound healing of the originally selected baseline wound in B-VEC versus placebo treated intra-subject wound sites at Weeks 22 and 24 or Weeks 24 and 26, as determined by the Investigator, to evaluate durability and repeat dosing. The complete wound healing is defined as 100% wound closure of the exact original wound surface area selected at baseline, specified as skin re-epithelialization without drainage.

Secondary Endpoints	**Key Secondary Endpoint** • Proportion of the selected primary wound sites with complete wound healing of the exact wound surface area selected at baseline (as defined in the primary endpoint) in B-VEC-treated versus placebo at Weeks 8 and 10 or Weeks 10 and 12 (as determined by the Investigator) to evaluate durability. **Secondary Endpoint** • The mean change in pain severity using a VAS score per primary wound site associated with wound dressing changes at Weeks 22, 24 and 26 for each treated versus placebo wound, for ages 6 and above on the primary wound pair. For ages below 6 years, the Face Legs Activity Cry and Consolability-Revised (FLACC-R) scale will be used.
Exploratory Endpoints	• Relative time to wound closure from baseline. • Duration of closure, as defined by the time from complete wound closure to the reopening of the Primary Wounds. • The mean change in Quality of Life in addition to Skindex score as compared to baseline at Week 26.
Safety Endpoint	• The safety and tolerability of B-VEC based on the assessment of adverse events, physical examinations, vital signs, and clinical laboratory test results.
Subject Population	**Inclusion Criteria** 1. The subject or legally appointed and authorized representative must have read, understood and signed an Institutional Review Board/Ethics Committee (IRB/EC) approved Informed Consent or Assent Form and must be able to and willing to follow study procedures and instructions. 2. Age ≥ 6 months and older at the time of Informed Consent. 3. Clinical diagnosis of the Dystrophic Epidermolysis Bullosa. 4. Confirmation of DEB diagnosis (either DDEB or RDEB) by genetic testing including COL7A1. 5. Two (2) cutaneous wounds meeting the following criteria: a. Location: similar in size, located in similar anatomical regions, and have similar appearance (Refer to Section **5.8** for more details). b. Appearance: clean with adequate granulation tissue, excellent vascularization, and do not appear infected. 6. Subjects and caregivers who, in the opinion of the Investigator, are able to understand the study, co-operate with the study procedures, and are willing to return to the clinic for all the required visits. 7. Male or Female of childbearing potential must use a reliable birth control method throughout the duration of the study and for 3 months post the last treatment. Refer to Section **4.5.1** for more details. 8. Negative Pregnancy test on Visit 1 (Week 1), if applicable.

	Exclusion Criteria 1. Medical instability limiting ability to travel to the Investigative Center. 2. Diseases or conditions that could interfere 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. 3. Current evidence or a history of squamous cell carcinoma in the area that will undergo treatment. 4. Subject's actively receiving chemotherapy or immunotherapy at Visit 1 (Week 1) 5. Active drug or alcohol addiction as determined by the Investigator. 6. Hypersensitivity to local anesthesia (lidocaine/prilocaine cream). 7. Participation in an interventional clinical trial within the past three (3) months (not including B-VEC administration). 8. Receipt of a skin graft in the past three (3) months. 9. Pregnant or nursing women.

Study Treatment, Duration and Assessments	Study Treatment Week 1 - Following randomization of the matched primary wound pair, wounds will receive one Weekly Treatment in a double-blinded manner. - The Remaining Weekly Dose will be calculated and applied to a maximum of four (4) additional wounds ("Secondary Wounds"). Secondary Wound(s) will receive a Weekly Treatment of B-VEC. The number of Secondary Wound(s) treated will depend on wound area of the Secondary Wound(s). The total dose applied to Secondary Wound(s) is not to exceed the Remaining Weekly Dose. Week 2 through 26 - Subjects will return to the clinical site for assessment of all wounds by the Investigator. - The Primary Wound Pair will receive one Weekly Treatment in a double-blinded manner. However, if one of the wounds in a matched Primary Wound Pair closes completely and there are no open neighboring wounds, as determined by the Investigator during a weekly visit, then that particular wound and its neighboring wound/s will not receive Weekly Treatment that week. Once that particular wound, or its neighboring wound/s, is determined to be open by the Investigator at a weekly visit, Weekly Treatment will continue. If the originally selected primary wound closes, its neighboring wound/s may continue to receive treatment. - If a Secondary Wound is closed completely, as well as its neighboring wound/s, as determined by an Investigator, during a weekly visit, then that particular wound and its neighboring wound/s will not receive Weekly Treatment that week. If the originally selected secondary wound closes, its neighboring wound/s may continue to receive treatment. The total dose applied to secondary wounds is not to exceed the Remaining Weekly Dose. - Subjects will come to clinic for assessment even if the originally selected wounds are closed. Safety Follow-up/Early Termination - Subjects will return to the clinical site 30 days following the last dose of B-VEC. - Subjects may roll into an Open Label Extension (OLE) Protocol. If subjects do not participate in the OLE Protocol, they will be asked to roll over into a Long-Term Follow-up Protocol (All subjects enrolled in the study who received at least a Weekly Treatment). Assessments - Safety measures include adverse events, physical examinations, vital signs, and clinical laboratory tests. All safety analyses results will be performed using the safety population. A summary of safety results will be presented for each treatment group.

Statistical Analyses	Continuous variables will be summarized in tables and will include the number of subjects, mean, standard deviation (SD), percent of coefficient of variance (CV%), median, minimum, and maximum. Categorical variables will be presented in tables as frequencies and percentages. A statistical analysis plan (SAP) will provide additional details on the approach to the analysis and data displays. **Sample Size Estimation** In the Phase I/II study, the response rates for Weeks 8 through 12 were from 70-100% for wounds randomized to B-VEC and 0-33% for wounds randomized to placebo, respectively. Assuming a response rate of 75% among wounds randomized to B-VEC and a response rate of 25% among wounds randomized to placebo, with a 90% power and a two-sided Type 1 error rate of 5%, 24 subjects (i.e., 24 wound pairs) are required. **Analysis Populations** Safety Population*:* This population is defined as all subjects who were administered with either B-VEC or placebo. Safety population will be used for all the safety analyses. Intent-to-Treat Population*:* The intent-to-treat (ITT) population includes subjects whose primary wounds were randomized with or without either B-VEC or Placebo administration. ITT population will be used for all the primary and secondary efficacy sensitivity analyses and baseline summaries. Modified Intent-to-Treat Population*:* The modified intent-to-treat (mITT) population includes subjects whose primary wounds were randomized and received B-VEC treatment with at least one post baseline primary endpoint assessment. mITT population will be used for all the primary and secondary efficacy analyses. Per Protocol Population*:* The per-protocol (PP) population includes all the safety population subjects who completed the study without major protocol deviations. PP population will be used for all the primary and secondary efficacy sensitivity analyses. **Missing Values and Imputations** Multiple imputation method will be used to handle missing data for primary efficacy analysis. For all the exploratory endpoints, the missing values will not be imputed.

Statistical Analyses (continued)	**Efficacy Analyses:** The study has a complete randomized-block design in which each subject serves as a block to receive all of the treatment conditions. In this study, each subject provides one pair of matched target wounds with one wound being treated with B-VEC and the other wound with placebo in the primary wound pair. Efficacy measurements are taken multiple times (or repeatedly) over the on-treatment period from each subject. Efficacy measures collected pre-dosing at Visit 1 (Week 1) will be considered as the baseline measurement in this study. **Analysis of Primary Efficacy Endpoint:** The primary endpoint of the proportion of DEB primary wound sites with complete wound healing of the exact wound surface area selected at baseline will be analyzed using the McNemar Test. The primary endpoint is defined as wounds that meet any of the following conditions: • Healed on Week 22 and Week 24, or • Healed on Week 24 and Week 26. Only wounds that are healed for at least two (2) consecutive weeks are counted as positive responses. **Analysis of Key Secondary Efficacy Endpoint:** The key secondary endpoint of the proportion of primary wound sites with complete wound healing of the exact wound surface area selected at baseline, will be analyzed using the McNemar Test. The primary endpoint is defined as wounds that meet any of the following conditions: • Healed on Week 8 and Week 10, or • Healed on Week 10 and Week 12. Only wounds that are healed for at least two (2) consecutive weeks are counted as positive responses. **Analysis of Secondary Efficacy Endpoint:** The following secondary endpoint will be analyzed using the Analysis of Covariance (ANCOVA) with treatment as the fixed effect and the baseline value as the covariate by the time points. 1. The mean change from baseline in pain severity VAS score per wound site associated with wound dressing changes at Weeks 22, 24 and 26 for each treated versus placebo for ages 6 and above on the primary wound pair. For ages below 6 years, the FLACC-R scale scores will be used instead VAS scores. **Safety Analyses:** Safety measures include adverse events, physical examinations, vital signs, and clinical laboratory tests. All safety analyses results will be performed using the safety population. A summary of safety results will be presented for each treatment group.
Long-term follow-up	Subjects will be asked to transfer to a long-term follow-up study, which will include up to 5 years of annual phone check-ins. Subjects may roll into the Long-Term Follow-Up Protocol at the Safety Follow-up Visit (30 days following the last dose of B-VEC).
DSMB Reviews	A data monitoring board (DSMB) will conduct regular planned safety reviews of study data as outlined in the DSMB charter.

Schedule of Events

Table 1. Visit Assessments and Procedures

	Randomized-Double Blinded Placebo-Controlled Treatment Period								Safety Follow-up/ET
Study Day	**Screen-ing[1]**	**Week 1**	**Week 2 -21**	**Week 22**	**Week 23**	**Week 24**	**Week 25**	**Week 26**	**30 days after last dose**
Daily Visit Window	**-60 to 0**	**na**	**± 3 days**						**± 4 days**
Visit	**Screening**	**1**	**2-21**	**22**	**23**	**24**	**25**	**26**	**SFU**
Obtain Consent / Assent	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 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						

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 re-collected, 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 6.2.2).
5 Both the Quality of Life (EQ-5D) and Skindex 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 has closed, as applicable.
8 Viral shedding and infectivity swabs will be collected from the primary matched wounds only and will be collected whether or not the wound is open or closed.
9 Subjects are required to bring the study visit wound dressing back to the site. Primary wounds will be separately bagged. Secondary wound dressing may be bagged together. Once returned to the site, viral shedding swabs will be collected for all Primary Wounds dressings that came into contact with the subject's skin. Attempt collection of (4) four consecutive VS dressing returns, if unable, collect at least (4) four dressing VS per subject. Once four (4) VS samples have been collected from the Primary Wound Pair, all dressing may be bagged together and returned to the site for disposal and specimen collection will be discontinued.

Table 2. Visit Assessments and Procedures (continued)

	Randomized-Double Blinded Placebo-Controlled Treatment Period								Safety Follow-up/ET
Study Day	**Screen-ing[1]**	**Week 1**	**Week 2 -21**	**Week 22**	**Week 23**	**Week 24**	**Week 25**	**Week 26**	**30 days after last dose**
Daily Visit Window	**-60 to 0**	**na**	**± 3 days**						**± 4 days**
Visit	**Screening**	**1**	**2-21**	**22**	**23**	**24**	**25**	**26**	**SFU**
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	
COL7 & HSV Serum ADA[15]	X	X[2]						X	
Whole Blood Viral Shedding[15]	X	X[2]						X	
Investigational Product (IP) Administration[16]		X	X	X	X	X	X	X	
Roll-over to LTFU or OLE Protocol[17]									X

10 The Physical examination is described in section 0

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 to Screening/Visit 1.

12 On days in which both vitals and blood draw occur, attempt vitals prior to the blood draw. Vitals are collected every 5 visits (i.e. Visit 1; 5; 9; 13; 17; 21; 25; SFU/ET). Vitals 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 For Subjects with history of genitourinary involvement, including painful urination due to the underlying disease and or 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 is closed, no IP will be applied and application will be reinitiated 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 four (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 2-3cm away from the original matched and unmatched (Primary and Secondary) wound.

17 At the Safety Follow-up (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 a LTFU protocol

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Figures

Tables

Abbreviations

AEs .....adverse events
AF.....anchoring fibrils
ALT (SGPT) .....alanine aminotransferase, included in metabolic panel
AST (SGOT) .....aspartate aminotransferase, included in metabolic panel
BMZ.....basement membrane zone
B-VEC .....Beremagene Geperpavec
CBC.....complete blood count
CBL .....Change from baseline
CFR.....Code of Federal Regulations
CLIA .....Clinical Laboratory Improvement Amendments
CM.....centimetre
COL7.....collagen VII
COL7A1 .....collagen 7 gene
CRF.....case report form
DEB.....dystrophic epidermolysis bullosa
DNA.....deoxyribonucleic acid
DSMB.....data safety monitoring board
EB .....epidermolysis bullosa
eGFP.....enhanced green fluorescent protein
ELISA.....enzyme-linked immunosorbent assay
EM.....electron microscopy
ET.....early termination
FDA.....Food and Drug Administration
GCP .....Good Clinical Practice
GFP.....green fluorescent protein
GMP .....Good Manufacturing Practice
HEENT.....head, ears, eyes, nose, throat
Hep.....hepatitis
HIPAA .....Health Insurance Portability and Accountability Act
HIV .....human immunodeficiency virus
HSV.....herpes simplex virus
ICF .....informed consent form
IEM.....immunoelectron microscopy
IF .....immunofluorescence
Ig .....immunoglobulin
IND .....Investigational New Drug application
IP.....Investigational Product
IRB .....Institutional Review Board
ITT.....Intent-to-treat

LTFU .....long-term follow-up
MCH .....mean corpuscular hemoglobin
MCHC .....mean corpuscular hemoglobin concentration
MCV .....mean cell volume
mRNA.....messenger ribonucleic acid
NC1 .....noncollagenous 1 domain
NC2 .....noncollagenous 2 domain
NCI .....National Cancer Institute
OLE……Open Label Extension
PCR.....polymerase chain reaction
PFU .....plaque-forming units
PHI .....protected health information
PP .....per protocol
RBC.....red blood cell count
RDEB .....recessive dystrophic epidermolysis bullosa
RDW.....red blood cell distribution width
SAE .....serious adverse event
SD .....standard deviation
SOPs.....standard operating procedures
WBC.....white blood cell

Protocol

1 Introduction

1.1 Disease Background

Dystrophic epidermolysis bullosa (DEB) is a group of heritable skin diseases characterized by skin fragility, blister formation, milia, and scarring (Intong, 2012). Dystrophic epidermolysis bullosa (DEB) is one of the major forms of EB and is the result of mutations to the COL7A1 gene encoding collagen VII (Varki, et al., 2007), (Uitto & Christiano, 1994). Severe generalized recessive dystrophic epidermolysis bullosa, 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. Given the severity of this disorder and the lack of effective treatment options, there exists a clear need for alternative treatment options that focus on the root cause of the debilitating symptoms and can be administered in a minimally invasive way.

1.2 Phase I/II Results Summary

Krystal conducted a Phase I/II clinical trial entitled: “A Phase I/II 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).” The purpose of the study was to evaluate the safety and efficacy of B-VEC.

This trial was an intra-subject comparison of wounds administered topical B-VEC against wounds that were administered placebo. Wounds were randomized to be administered either topical B-VEC or topical placebo prior to administration. The first-in-human Phase I protocol enrolled 2 adult subjects, and the Phase II portion of the protocol enrolled 10 subjects: 5 adults and 5 pediatric subjects.

1.2.1 Efficacy Results

Efficacy was analyzed by looking at both mechanistic endpoints and clinical endpoints. Mechanistic endpoints include evidence of COL7 using IF and anchoring fibrils using IEM. Clinical endpoints focus on wound healing and measured parameters such as percent (%) by area of wound closure, duration of wound closure, and time to wound closure.

The IF analyses conducted post B-VEC administration revealed clearly detectable and correctly localized (at the Basement Membrane Zone, BMZ) COL7 expression by immunofluorescence in the biopsy samples from both the intradermal injection sites and topically applied wounds. Expression was observed as early as 48 hours post-administration and was continually observed at each monthly timepoint out to Day 90. The presence of the NC2 domain in conjunction with NC1 and linear deposition at the BMZ demonstrates production of functional COL7.

The IEM analyses conducted post B-VEC administration revealed clearly detectable and correctly localized anchoring fibrils at the BMZ in biopsy samples from both the intradermal injection sites and topically applied wounds. Anchoring fibrils were observed as early as Day 8 and as late as Day 97. Importantly, in the later timepoints (samples from Days 84 and 97), mature NC2-positive fibrils were observed which strongly demonstrates the presence of functional full-length COL7.

The IF and IEM results were supported by clinical wound closure data. Subject-specific wound images and wound closure data showing percent change from baseline of B-VEC- and placebo-administered wounds were used to evaluate wound area reduction, duration of closure, and time to closure.

Findings from our previous GEM Phase I/II study in which each subject served as their own control disclosed an effect size of at least 0.8 for the average percent change in wound area from baseline over 12 weeks, comparing B-VEC treatment to placebo control. The observed proportion of complete wound healing for Week 8, 10 and 12 ranged from 67% to 85% for B-VEC treatment and from 0% to 33% for placebo control and showed a statistically significant difference (p-value <.00001, based on the Cochran-Mantel-Haenszel test stratified by the timepoints of weeks) difference. At Week 12, B-VEC-treated wounds showed a median reduction of 94%, compared to a median increase of 27% for the placebo-treated wounds resulting in a statistically significant (p-value = 0.02, based on Wilcoxon rank-sum test) difference. Complementary analysis was performed to show that the 87% of subjects had at least a 75% reduction in average wound size for the B-VEC-treated wounds at week 12, compared with 14% of subjects for the placebo-treated wounds.

1.2.2 Safety Results

In every phase of the study, the safety of B-VEC was assessed through analysis of AEs, including clinically significant changes in laboratory results, vitals, and physical exam findings. In addition, viral shedding was analyzed through the collection of serum, urine, and skin swabs, and antibodies to HSV and COL7 were analyzed through collection of blood.

There were no deaths, serious adverse events or significant adverse events reported. Thirty (30) AEs were reported; twenty-nine (29) were mild in severity and one (1) was moderate in severity. The moderate AE was facial itching and redness and unrelated to the Investigational Product. All of the AEs resolved during the study and of the thirty (30), fifteen (15) were unlikely or unrelated, and fifteen (15) were possibly or probably related. Of the fifteen (15) possibly or probably related, four (4) were associated with topical B-VEC administration including rash, fever, itching and peculiar taste.

There were no clinically meaningful changes in laboratory parameters, including liver enzymes. Changes from baseline were small (usually less than 10%) and showed no distinct shifts over time.

Sera samples, collected pre-dose and during specific visits per the Schedule of Events, were evaluated for Anti-Drug Antibodies against HSV and COL7 using a qualified Plaque Reduction Neutralization Test (PRNT). Existing antibodies, as well as any changes in antibodies detected after B-VEC treatment, did not have any apparent impact on subject safety as any possibly related AEs were mild in severity and transient. Efficacy was also not impacted, as evidenced by the robust efficacy of the vector (e.g., indicated by improved wound healing, as compared to intra-subject placebo controls; the observed molecular correction of the collagen VII defect, demonstrated by linear collagen VII deposition and formation of anchoring fibrils along the Basement Membrane Zone (BMZ) by Immunofluorescence (IF) and Immunoelectron Microscopy (IEM).

2 Study Objectives and Endpoints

2.1 Study Objective

The primary objective is to determine whether administration of B-VEC in addition to standard of care improves wound healing as compared to placebo in children, adolescents, and adults with Dystrophic Epidermolysis Bullosa (DEB).

2.2 Study Endpoints

2.2.1 Overview

GEM-3 is a multi-center, intra-patient randomized, placebo-controlled, double-blinded, Phase III study of B-VEC for the topical treatment of DEB wounds. Each site will have a designated Principal Investigator.

Weekly Treatment: 1 unit-dose of B-VEC or placebo

Treatment Cycle: Weekly Treatment until complete wound closure

Maximum Weekly Dose per subject:

Age	Maximum Weekly Dose
≥ 6 months to < 3 years	1.6×10^9 PFU/week
≥ 3 years to < 6 years	2.4×10^9 PFU/week
≥ 6 years	3.2×10^9 PFU/week

Two (2) matched wounds ("Primary Wounds"), in a 1:1 ratio per subject will be selected to evaluate the primary and secondary end points. The matched wound pair will be randomized, such that one wound will receive Weekly Treatment of B-VEC and the other will receive placebo.

Remaining Weekly Dose: The difference between Maximum Weekly Dose per subject per week and the sum total of the B-VEC Dose(s) applied to the Primary Wound Pair per subject per week.

Re-dosing regimen: During the study, if one wound in the matched Primary Wound Pair and its neighboring wounds close completely, as determined by the Investigator during a weekly visit, that particular wound and its neighboring wound/s will stop receiving Weekly Treatment. Treatment of the Primary Wound and its neighboring wound/s will resume Weekly Treatment when that particular wound or neighboring wound/s is determined to be open by the Investigator during a weekly visit. During the treatment of a Primary Wound, it the originally selected wound closes, its neighboring wound (approximately 2-3cm away from the originally selected wound) wound may continue to receive treatment, at the discretion of the Investigator. If treating a neighboring wound, avoid treating if it is in close proximity to the other matched wound or a Secondary Wound. The re-dosing regimen will be followed throughout the study.

For example, if a subject age 4, presents with a primary wound pair $\leq$20 cm^2, then the Remaining Weekly Dose during a weekly visit = Difference of (2.4×10^9 PFU– (4×10^8 PFU)) = 2.0×10^9 PFU/subject/week. The Remaining Weekly Dose will be applied to Secondary Wounds for monitoring safety and efficacy.

The Remaining Weekly Dose calculated during a weekly visit will be applied to additional unmatched wounds ("Secondary Wounds"). A maximum of four (4) Secondary Wounds will receive a Weekly Treatment of B-VEC for the Treatment Cycle. The number of Secondary Wounds treated will depend on wound area of the Secondary Wound(s), and the total dose applied to Secondary Wounds is not to exceed the Remaining Weekly Dose. During the treatment of the Secondary Wounds, if a neighboring wound (approximately 2-3cm from the originally selected wound) opens, then that wound may receive treatment, at the discretion of the Investigator.

If a Secondary Wound is closed completely, as well as the neighboring wounds, as determined by an Investigator during a weekly visit, no treatment will occur. Treatment to neighboring wound/s may continue even though the originally selected Secondary Wound is closed. Avoid application to neighboring wounds in close proximity to a Primary Wound. The total dose applied to Secondary Wounds is not to exceed the Remaining Weekly Dose.

2.2.2 Primary Endpoint

The primary endpoint is the proportion of DEB primary wound sites with complete wound healing from baseline in B-VEC versus placebo treated intra-subject wound sites at Weeks 22 and 24 or 24 and 26, as determined by the Investigator, to evaluate durability and repeat dosing. The complete wound healing is defined as 100% wound closure from the exact wound area selected at baseline, specified as skin re-epithelialization without drainage. If new neighboring wounds forms, around the original traced baseline wound, during the primary and secondary evaluation time points, these wounds will not be included in the evaluation.

The primary endpoint is defined as wounds that meet any of the following conditions:

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

Only wounds that are healed for at least two (2) consecutive weeks are counted as positive responses.

2.2.2.1 Primary Endpoint Rationale

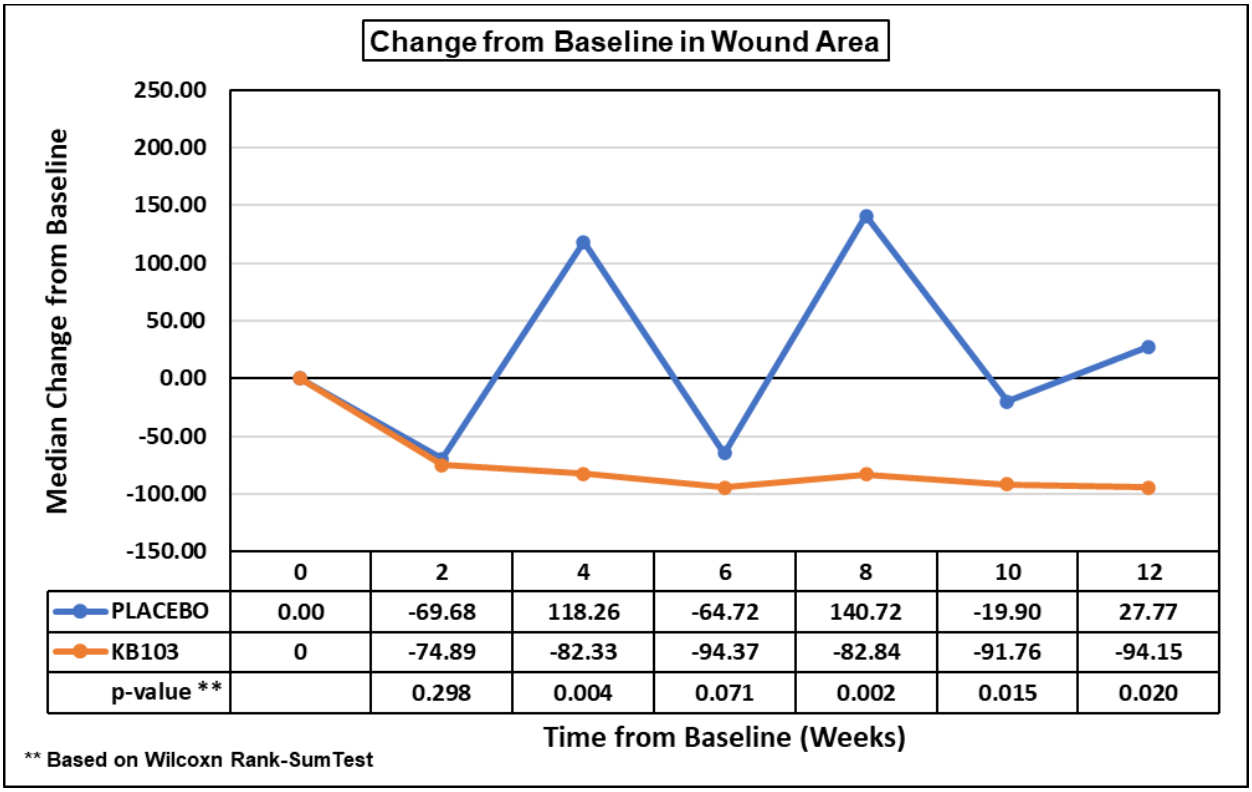
The GEM-3 pivotal study has been designed as an adequate well-controlled clinical study per Agency guidance (21 CFR 314.126) to provide substantial evidence of product effectiveness. The double-blinded, placebo-controlled study design will minimize bias on the part of subjects, and Investigators. The FDA's guidance Gene Therapy for Rare Diseases (July 2018) suggests that an intra-subject control approach, for such rare skin diseases, may be a useful design. The wounds will be matched in respect to size and anatomical location.

Complete wound healing will be defined as complete closure of the initial wound surface selected at baseline, specified as skin re-epithelialization without drainage for two (2) consecutive weeks, as evaluated by the Investigator at Weeks 22 and 24 or 24 and 26. If new neighboring wounds form around the original traced baseline wound during the primary evaluation time points, these areas will not be included in the evaluation.

B-VEC is a transient non-integrating episomal vector that can be detected up to five days in B-VEC *in vivo* studies. The Phase I/II B-VEC completed study, that has evaluated different dosing regimens shows that continuous expression of COL7 during the wound healing process allows for durability of the healed wound with no safety outcomes. Therefore, a weekly dosing regimen has been proposed based on life span of B-VEC and results from the Phase I/II clinical study that would allow for functional restoration of COL7 at basement membrane zone. It has been shown that the half-life of human COL7 is approximately 30 days. Based on a half-life assumption of about one month for COL7, a residual protein amount of 25% should be present after two months (Kuhl, et al., 2016). It is known that about 30-40% of COL7 levels are needed to protect the skin from frictional damage (Kern, et al., 2009) (Kuhl, et al., 2016) and even lower levels of COL7 may improve the phenotype of full COL7 deficiency remarkably (Fritsch, et al., 2008) (Alexeev, et al., 2011) (Schweiger-Briel, et al., 2015). The basement membrane and its constitutive components undergo constant remodeling (Kivirikko, et al., 1996) which has implications for anchoring fibril turnover approximately every 60 days to 90 days (8 weeks to 12 weeks). Therefore, the proposed evaluation of the primary endpoint at Weeks 22 and 24 or 24 and 26, for two (2) consecutive weeks, is justified.

In addition, in the previously conducted Phase 1/2 B-VEC clinical study, the placebo response (change in wound area from baseline) mimicked the frequent opening and closing of untreated DEB wounds as shown below:

Figure 1. Change in Wound Area from Baseline in B-VEC vs. Placebo Treated in Phase I/II Study



	0	2	4	6	8	10	12
PLACEBO	0.00	-69.68	118.26	-64.72	140.72	-19.90	27.77
KB103	0	-74.89	-82.33	-94.37	-82.84	-91.76	-94.15
p-value **		0.298	0.004	0.071	0.002	0.015	0.020

The usual pattern in a placebo response is often similar to active treatment with or without significant separation. Due to the nature of the DEB wounds, frequent closing and opening cycle is observed, therefore a fixed assessment may lead to a biased conclusion in comparing a normal treatment profile to an abnormal profile of a placebo response. To accommodate this variability of the placebo response, an assessment of two (2) consecutive weeks, at Weeks 22 and 24 or 24 and 26, are considered to evaluate durability of wound healing and frequency of repeat administration.

2.2.3 Key Secondary Endpoint

The key secondary endpoint is defined as the proportion of primary wound sites with complete wound healing from baseline (as defined in the primary endpoint) in B-VEC-treated versus placebo at Weeks 8 and 10 or 10 and 12 (as determined by the Investigator) to evaluate durability. The complete wound healing is defined as 100% wound closure of the originally selected wound area at baseline, specified as skin re-epithelialization without drainage. If new neighboring wounds form around the original traced baseline wound during the key secondary evaluation time points, these areas will not be included in the evaluation.

The key secondary endpoint is defined as wounds that meet any of the following conditions:

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

Only wounds that are healed for at least two (2) consecutive weeks are counted as positive responses.

2.2.3.1 Key Secondary Endpoint Rationale

As mentioned above, B-VEC is a transient non-integrating episomal vector that can be detected up to five days after administration in patients. Also as referenced above, it has been shown that the basement membrane and its constitutive components undergo constant remodeling (Kivirikko, et al., 1996) which has implications for anchoring fibril turnover approximately every 60 days to 90 days (8 weeks to 12 weeks). Therefore, the proposed evaluation of key secondary endpoint at Weeks 8 and 10 or 10 and 12 will help evaluate durability of the initial treatment.

2.2.4 Secondary Endpoint

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

2.2.4.1 Secondary Endpoint Rationale

The secondary endpoint was obtained based on input from patients with DEB, and their caregivers to provide a complete understanding of the disease or condition.

2.2.5 Safety Endpoints

The safety and tolerability of B-VEC based on the assessment of adverse events, physical examinations, vital signs, and clinical laboratory test results.

2.2.5.1 Safety Endpoint Rationale

Safety endpoints were chosen to obtain a comprehensive picture of overall safety and tolerability of B-VEC across the study period.

3 Selection of Subjects

This study is planned to enroll approximately 24 participants with DEB, aged 6 months or older at the time of Informed Consent.

The study team cooperates with national and international networks of families, researchers, and physicians who care for children and adults with EB, and it is planned to use these groups to recruit participants for this study. In addition, an email and clinical study information may be posted to national communities (EB foundations, e.g., Dystrophic Epidermolysis Bullosa Research Association of America, site-specific EB websites) regarding recruiting for this study.

3.1 Inclusion Criteria

To be eligible for inclusion, each subject must fulfill each of the following criteria:

1. The subject or legally appointed and authorized representative must have read, understood and signed an Institutional Review Board/Ethics Committee (IRB/EC) approved Informed Consent or Assent Form and must be able to and willing to follow study procedures and instructions.
2. Age ≥ 6 months and older at the time of Informed Consent.
3. Clinical diagnosis of the Dystrophic Epidermolysis Bullosa.

4. Confirmation of DEB diagnosis (either DDEB or RDEB) by genetic testing including COL7A1.
5. Two (2) cutaneous wounds meeting the following criteria:
    a. Location: similar in size, located in similar anatomical regions, and have similar appearance (Refer to section **5.8** for more details).
    b. Appearance: clean with adequate granulation tissue, excellent vascularization, and do not appear infected.
6. Subjects and caregivers who, in the opinion of the Investigator, are able to understand the study, co-operate with the study procedures and are willing to return to the clinic for all the required follow-up visits.
7. Male or Female of childbearing potential must use a reliable birth control method throughout the duration of the study and for three (3) months post last dose of B-VEC. Refer to Section **4.5.1** for more details.
8. Negative pregnancy test at Visit 1 (Week 1), if applicable.

3.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria are met:

1. Medical instability limiting ability to travel to the Investigative Center.
2. Diseases or conditions that could interfere 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.
3. Current evidence or a history of squamous cell carcinoma in the area that will undergo treatment.
4. Subject's actively receiving chemotherapy or immunotherapy at Visit 1 (Week 1).
5. Active drug or alcohol addiction as determined by the Investigator.
6. Hypersensitivity to local anesthesia (lidocaine/prilocaine cream).
7. Participation in an interventional clinical trial within the past three (3) months (not including B-VEC administration).
8. Receipt of a skin graft in the past three (3) months.
9. Pregnant or nursing women.

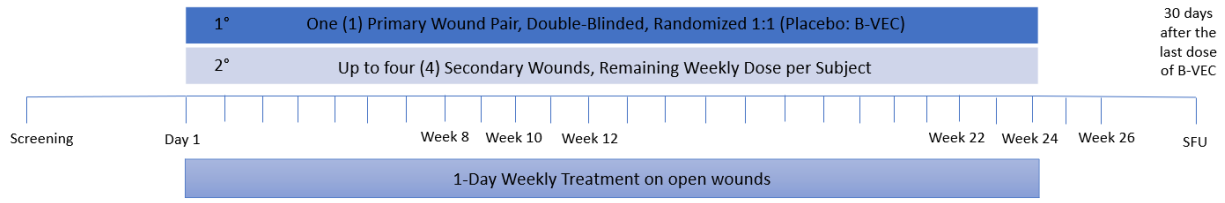
4 Study Implementation

Blood tests, or medical interventions may occur at the discretion of the Principal Investigator due to clinical changes that require evaluation or therapy. Detailed information for the study visits is provided in the sections below and in the Schedule of Events (**Table 1**).

4.1 Study Design

GEM-3 is a multi-center, intra-subject randomized, placebo-controlled, double-blind, Phase III study of B-VEC for the topical treatment of DEB wounds. A schematic of the study design is shown in **Figure 2** below.

Figure 2. B-VEC-03 Study Design



B-VEC: Beremagene Geperpavec, single dose/wound administered 4 ×10^8 PFU B-VEC/wound (<20 cm^2), 8 × 10^8 PFU B-VEC/wound (20 to 40 cm^2) or 1.2 ×10^9 PFU B-VEC/wound (40 to 60 cm^2) , once a week for up to 26 weeks, Placebo, single matching dose/ wound adminstered once a week for up to 26 weeks.

4.1.1 Study Design Rationale

The primary objective is to determine whether administration of B-VEC in addition to standard of care improves wound healing as compared to placebo in children, adolescents, and adults with Dystrophic Epidermolysis Bullosa (DEB).

The FDA's guidance Gene Therapy for Rare Diseases (July 2018) suggests that an intra-subject control approach, for such rare skin diseases, may be a useful design. Based on our previous experience (completed B-VEC Phase I/II study) and suggestions from the guidance we will continue to use the intra-subject design in the Phase III study. Each subject will serve as their own control; subjects will have two matched wounds (primary wounds). The primary wounds will be randomized such that one wound will receive B-VEC (active treatment) and the other will receive placebo (inactive treatment). The secondary wounds will receive B-VEC (active treatment), not to exceed the Remaining Weekly Dose. Subjects who enrolled under previous protocol versions, where more than one wound pair was selected, the Investigator's determined a single pair, most closely matched in size, followed by location, to be used for efficacy analysis, following the Agency's guidance.

This Phase III protocol is designed to minimize subject burden by limiting blood draws and removing the collection of biopsies. Experience from the phase I/II portion of the B-VEC trial combined with the advice provided in the FDA's guidance Epidermolysis Bullosa: Developing Drugs for Treatment of Cutaneous Manifestations (June 2019) justifies the proposed design. Molecular correction evaluation from all of the subjects from the Phase I/II study have shown full length COL7 expression by Immuno-fluorescence (IF) (staining for both NC1 and NC2 antibodies) and/or anchoring fibrils by Immuno-electron microscopy (IEM). We believe that robust molecular correction has been demonstrated with wound healing hence the proposed Phase III will mainly focus on evaluation of wound healing as the efficacy endpoint.

4.1.2 Treatment Period

Each subject visits the Investigative site at the beginning of the study for Visit 1 (Week 1) and the matched wounds are randomized (if entry criteria are met) and the assessment/treatment period begins and will continue for 25 weeks. Additionally, the subject will return to the Investigative site for a single day Safety Follow-up Visit 30 days (±4 days) from the last dose of B-VEC.

4.1.2.1 Guidance for Subjects Enrolled under Previous Protocol Versions

Subjects enrolled under previous protocol versions, in which more than one (1) Primary Wound Pair was selected, will continue to receive their randomized treatment for the duration of the study. However, the Investigator will select a single matched pair, which most closely match in both size and anatomical location. This single Primary Wound Pair will be used for evaluation and will be included in the outcome measurements.

For subjects who had more than four (4) Secondary Wounds, no new Secondary Wounds will be selected, and treatment will continue on the previously selected Secondary Wounds for the study duration. If subjects had less than four (4) Secondary Wounds selected, the Investigator may select additional Secondary Wounds, until four (4) have been selected, not exceeding the Weekly Maximum Dose.

4.2 Study Visits

Study visit procedures are performed only after a signed informed consent / assent (as applicable) is obtained. During the study, every effort should be made to adhere to the visit schedule provided in the Schedule of Events (**Table 1**).

4.2.1 Sequence of Study Procedures

The following must be taken into account regarding the sequence of study procedures:

- Questionnaires should be completed with wound dressing removal during the visit. The EQ-5D and Skindex-29 may be administered at the end of the study visit, for the subject to complete, and return at their next scheduled visit.
- At scheduled visits (refer to **Table 1**) in which a urine pregnancy test must be completed, the test must result negative, prior to applying B-VEC or placebo, for women of childbearing potential, as determined by the Investigator.
- At visits in which blood is drawn, attempt collection of vital signs prior to the blood draw.
- On days in which B-VEC and placebo administration(s) occur, all study procedures and assessments must occur pre-dose.

4.2.2 Protocol Deviations

Any deviations from the protocol are discouraged. A protocol deviation will be defined as any excursion from the protocol, or any instance of protocol noncompliance. If deviations do occur, the Principal Investigator must inform the monitor/Sponsor, and the implications of the deviation must be reviewed and discussed. Any paper documentation must be kept in the Investigator's File or Subject Binder and the Sponsor will file in the TMF. If the Investigator determines a deviation is necessary, they are to contact the Sponsor prior to the occurrence for approval, if time permits.

4.2.3 Screening

If a subject has not undergone genetic testing, which is needed for inclusion criteria, they may visit the site up to 60 days prior to Visit 1 (Week 1). The genetic test may take 6 to 8 weeks to obtain results.

- Review and signature of informed consent form/assent
- Collection of demographic data (e.g. sex, age, race, and ethnicity)
- Obtain Medical History
- Treatment/Procedural review

- Obtain Medication History
- Obtain Genetic testing specimens
- Collection of urine for viral shedding
- Collection of blood for clinical laboratory tests:
    - Complete Metabolic Panel with Direct Bilirubin
    - Complete Blood Count with Differential and Platelets
    - HSV and COL7 Serum ADA
    - Whole blood for viral shedding

4.2.4 Week 1/Visit 1 (First Day of Treatment Cycle)

- Review and signature of informed consent form/assent, if not previously obtained at Screening.
- Collection of demographic data (e.g. sex, age, race, and ethnicity), if not previously obtained at Screening
- Obtain Medical History, if not previously obtained at Screening
- Treatment/Procedural review
- Medication review
- Inclusion/Exclusion
- Selection of two (2) matched wounds to be assessed as Primary Wounds and selection of up to four (4) Secondary Wounds (not to exceed the Remaining Weekly Dose)
- Primary Wound Pain Questionnaire
    - FLACC-R (Subjects less than 6 years of age)
    - VAS (Subjects 6 years of age and older)
- Quality of Life Questionnaire (Subjects 12 years of age and older)
- Skindex Questionnaire (Subjects 12 years of age and older)
- Selection of Secondary Wounds depending on the Remaining Weekly Dose
- Wound imaging of all selected wounds
- Assess selected wounds
- Physical exam
- Vital signs
- Collection of skin swabs for viral shedding and infectivity from all the selected primary wounds
- Collection of urine for a pregnancy test, if applicable as determined by the Investigator
- Collection of urine for viral shedding, if not collected at Screening
- Collection of blood for clinical laboratory tests, if not collected at Screening:
    - Complete Metabolic Panel with Direct Bilirubin

- Complete Blood Count with Differential and Platelets
- HSV and COL7 Serum ADA
- Whole blood for viral shedding

- Randomization of wound pair
- IP administration
- AE/SAE review

4.2.5 Week 2 through 21

- Medication review
- AE/SAE review
- Treatment/Procedural review
- Wound imaging of all selected wounds
- Assess Primary Wound Closure at Visit 8, 10, and 12 only
- Assess Secondary Wound/s
- Vital signs will be collected at Visit 5, 9, 13, 17, 21, and 25 only
- Collection of skin swabs for viral shedding and infectivity from all the selected Primary Wounds
- Collection of bandage swabs for viral shedding from all the Primary Wounds, if applicable
- IP administration

4.2.6 Week 22

- Medication review
- AE/SAE review
- Treatment/Procedural review
- Primary Wound Pain Questionnaire
  - FLACC-R (Subjects less than 6 years of age)
  - VAS (Subjects 6 years of age and older)
- Wound imaging of all selected wounds
- Assess Primary Wound Closure
- Assess Secondary Wound/s
- Collection of skin swabs for viral shedding and infectivity from all the selected Primary Wounds
- Collection of bandage swabs for viral shedding from all the Primary Wounds, if applicable
- IP administration

4.2.7 Week 23

- Medication review

- AE/SAE review
- Treatment/Procedural review
- Wound imaging of all selected wounds
- Assess Secondary Wound/s
- Collection of skin swabs for viral shedding and infectivity from all the selected Primary Wounds
- Collection of bandage swabs for viral shedding from all the Primary Wounds, if applicable
- IP administration

4.2.8 Week 24

- Medication review
- AE/SAE review
- Treatment/Procedural review
- Primary Wound Pain Questionnaire
    - FLACC-R (Subjects less than 6 years of age)
    - VAS (Subjects 6 years of age and older)
- Wound imaging of all selected wounds
- Assess Primary Wound Closure
- Assess Secondary Wound/s
- Collection of skin swabs for viral shedding and infectivity from all the selected Primary Wounds
- Collection of bandage swabs for viral shedding from all the Primary Wounds, if applicable
- IP administration

4.2.9 Week 25

- Medication review
- AE/SAE review
- Treatment/Procedural review
- Wound imaging of all selected wounds
- Assess Secondary Wound/s
- Vital signs will be collected
- Collection of skin swabs for viral shedding and infectivity from all the selected Primary Wounds
- Collection of bandage swabs for viral shedding from all the Primary Wounds, if applicable
- IP administration

4.2.10 Week 26

- Medication review

- AE/SAE review
- Treatment/Procedural review
- Primary Wound Pain Questionnaire
    - FLACC-R (Subjects less than 6 years of age)
    - VAS (Subjects 6 years of age and older)
- Quality of Life Questionnaire (Subjects 12 years of age and older)
- Skindex Questionnaire (Subjects 12 years of age and older)
- Wound imaging of all selected wounds
- Assess Primary Wound Closure
- Assess Secondary Wound/s
- Abbreviated Physical Exam
- Collection of skin swabs for viral shedding and infectivity from all the selected Primary Wounds
- Collection of bandage swabs for viral shedding from all the Primary Wounds, if applicable
- Collection of urine for a pregnancy test, if applicable as determined by the Investigator
- Collection of urine for viral shedding
- Collection of blood for clinical laboratory tests:
    - Complete Metabolic Panel with Direct Bilirubin
    - Complete Blood Count with Differential and Platelets
    - HSV and COL7 Serum ADA
    - Whole blood for viral shedding
- IP administration

4.2.11 Safety Follow-up/ Early Termination

- Roll-Over into OLE or LTFU Protocol
- Medication review
- AE/SAE review
- Treatment/Procedural review
- Wound imaging of all selected wounds
- Abbreviated Physical Exam
- Vital Signs

4.2.12 Safety Follow-Up

The Safety Follow-up will occur 30 days (±4 days) following the last dose of B-VEC. At the Safety Follow-up Visit, subjects may be asked to enroll into an OLE protocol to continue to receive treatment or a LTFU protocol where they will be monitored for an additional 5 years following the SFU visit.

4.2.13 Early Termination Scheduling

An early termination (ET) visit should be scheduled as soon as possible after the subject, Investigator or Sponsor decides to terminate study treatment. Subjects who prematurely discontinue treatment will be required to complete the Safety Follow-up Visit (ET) visit approximately 30 days (±4) after their last dose of Investigational Product.

4.3 Sites and Trial Duration

Approximately three (3) sites are planned for this study in the US.

The trial duration for each subject is about 6 months. A Safety Follow-up Visit occurring 30 days from the date of final treatment with the Investigational Product, B-VEC, will also occur.

4.4 Study Restrictions

Throughout the study assessments period, up to Week 26, topical administration of any medication (other than B-VEC and placebo) to a study target wound is prohibited, unless approved in advance by the Medical Monitor/Sponsor. Secondary wounds that are not naturally occurring, such as wounds that manifest after a surgical procedure are excluded from receiving the Investigational Product.

4.5 Concomitant Medications and Topical Treatments

Medications including prescriptions, herbal and dietary supplements, over the counter medications, injections, and topical treatments the subject has taken within three (3) months prior to the Visit 1 (Week 1) or Screening visit will be obtained and documented. At subsequent visits, medication reviews will occur, noting if the medication is continuing or if the subject has begun any new medication.

Topical concomitant medications or treatments deemed necessary to provide adequate supportive care to non-target wounds may be prescribed and will be documented on the concomitant medication log. Additionally, the Investigator may prescribe Tacrolimus, Clobetasol or Regranex, to be topically applied to all study target wounds, during the study.

4.5.1 Contraception

Women of childbearing potential must have a negative urine pregnancy test at the Visit 1 (Week 1) visit and must commit to using an acceptable form of contraception during the entire study period, up to three (3) months following the last dose of B-VEC. Acceptable forms of contraception include abstinence, intrauterine device, oral, implantable, or injectable contraception, or a combination barrier method, such as female or male condom, a diaphragm or cervical cap and a spermicide. Women using oral contraception must have consistently been taking their birth control for three (3) months prior to Visit 1 (Week 1) or utilize a combination barrier method, as stated above.

Male subjects must be surgically sterile, prepubescent or agree to use (you or your childbearing partner) an effective form on contraception from Visit 1 (Week 1) to three (3) months following study completion (last dose of B-VEC), such as abstinence, intrauterine device, oral, implantable or injectable contraception, or a combination barrier method, such as female or male condom, a diaphragm or cervical cap and a spermicide.

4.6 Subject Enrollment

Written protocol and informed consent approval are required from the IRB prior to enrollment. Assent form approval is required from the IRB prior to enrolling subjects below the age of consent. All subjects or their respective legal guardians must personally sign and date the relevant consent and/or assent form before

enrollment. Subjects who withdraw prior to the first B-VEC administration are considered a screen failure and are not considered a participant and can be re-screened.

4.6.1 Subject Identification and Number Assignment

Subjects who sign the informed consent form are assigned a 2-digit subject identification number within each study site. Subject identification numbers at each site begin with the specific 2-digit study site number (assigned by the Sponsor) followed by the subject's specific 2-digit subject number (XX-XX). This number identifies the subject throughout the study and must be used on all study documentation related to that subject.

5 B-VEC and Placebo Administration and Wound Selection

5.1 Dosing Regimen

Table 3. Maximum Weekly dose based on age at the visit

Age	Maximum Weekly Dose
≥ 6 months to < 3 years	1.6×10^9 PFU/week
≥ 3 years to < 6 years	2.4×10^9 PFU/week
≥ 6 years	3.2×10^9 PFU/week

Table 4. Unit dose based on wound area

Wound Area	Unit Dose
<20 cm^2	4×10^8 PFU/wound
20 to 40 cm^2	8×10^8 PFU/wound
40 to 60 cm^2	1.2×10^9 PFU/wound

At Visit 1 (Week 1) the wounds will be measured by an Investigator using a validated Canfield photography quantitation system. The unit dose will be determined based on this initial measurement, which is recorded in the CRF, for the Treatment Cycle and will not exceed the Maximum Weekly Dose based on the Subject's age at the time of the visit. Subsequent Secondary Wounds, not selected at Week 1, will have the wound area determined during their initial selection. If a Secondary wound selected, exceeds 60cm^2, split the wound, to allow it to meet the unit dose criteria above, and treat accordingly.

Two matched wounds (Primary Wound Pair) will be selected to evaluate the primary and key secondary end points. The Primary Wound Pair will be randomized, such that one wound in the pair will receive one-unit dose of B-VEC and the other will receive placebo for a Treatment Cycle. One unit of B-VEC or placebo weekly for 26 weeks, to evaluate durability and repeat dosing. During the study, the originally selected wound, as well as neighboring wounds in proximity (approximately 2-3cm) to the originally selected wound, may receive treatment and will receive treatment until both the originally selected wound and its neighboring wounds have closed. Avoid application if a neighboring secondary wound is near a primary wound or another primary wound. Weekly treatment on the wound will resume when that original wound or

neighboring wounds to the originally selected wound re-opens, as determined by the Investigator at a weekly visit.

Unmatched Secondary open wounds (up to four (4) maximum) may be treated if there is remaining Weekly Dose available. For example: if a 12 month old subject, presents with a primary wound pair of 24 cm^2 then the remaining weekly dose during a weekly visit = (1.6×10^9 PFU -8×10^8 PFU)= 8×10^8 PFU (i.e. there would be enough remaining weekly dose to treat one (1) 20cm^2 to 40cm^2 secondary wound). A neighboring wound in close proximately (approximately 2-3cm) to the originally selected wound may receive treatment. Treatment to the area will resume until the area is closed. However, avoid application to neighboring wounds in close proximity to the matched wounds.

5.1.1 Dosing Regimen Rationale

The proposed Maximum Weekly Dose of 3.2×10^9 PFU /subject (6 years of age and older) and the Unit Dose by Wound Area of 4.0×10^8 PFU/20 cm^2, are based on efficacy and safety data obtained from similar dosing regimens in the Phase II study. Out of the 9 subjects enrolled in the Phase II study, the maximum weekly dose per subject ranged from 1.2×10^9 PFU/week to 6.0×10^9 PFU/week (median 4.2×10^9 PFU/week, average 2.6×10^9 PFU/week) with no B-VEC related adverse events.

The proposed weekly dose of 3.2×10^9 PFU falls within the doses administered to patients in Phase II. Furthermore, robust efficacy as evident by wound healing supported by molecular correction was observed ("surrogate measurement") with no drug related safety events.

The dose and the weekly dosing regimen proposed is to demonstrate the safety and efficacy of B-VEC in subjects chronically open wounds. The unit dose is based on a wound area of ≤20 cm^2 because 80% of RDEB wounds are in the ≤20 cm^2 range and occasionally span 40 to 60 cm^2 or larger (Eng, et al. 2020).

In the Phase II study, 18 wounds ≤20 cm^2 were given a unit dose between (2.0×10^8 to 6.0×10^8) PFU for 5 consecutive treatments, daily or every other day. Therefore, a unit dose of 4.0×10^8 PFU to treat wounds ≤20 cm^2 is well within the unit dose range seen in the Phase II study.

Furthermore, the following Maximum Weekly dose is based off the average body surface area for pediatric subjects below the age of 6 (Center for Disease Control 2002) (Nelson, et al. 2006). A proposed fixed dose based on age group was determined to mitigate dosing error and allows for better compliance from the Investigator (Shi and Derendorf 2010).

The proposed unit dose by wound area and maximum weekly dose were both safe and efficacious based on the results of the Phase II trial.

5.2 Preparation and Dispensing

Investigational Product may be dispensed under the supervision of the Investigator or an authorized designee and only for the application/administration of study subjects. Further details on preparation and application can be found in the Pharmacy Manual.

5.3 Packaging and Labeling

Both the Methocel™ and the B-VEC will be packaged in vials. The labeling will be in compliance with applicable local and national regulations. Further details on packaging, dispensing, and labeling can be found in the Pharmacy Manual.

5.4 Storage and Handling

While at the clinical site, the Investigator, or an authorized designee, will ensure that all study products are stored in a secure location, under recommended storage conditions and in accordance with applicable regulatory requirements. For further instructions refer to the Pharmacy Manual.

5.5 Drug Accountability

The pharmacist or authorized unblinded designee will maintain information regarding the dates and amounts of study products received, Investigational Product dispensed to the individual subjects, and study products that may have been damaged in a shipment. These materials are retained by the site according to the Sponsor representative. The study products and Investigational Product will be monitored throughout the study by a designated monitor, who will review all records and inventory.

5.6 Drug Disposal, Returns, or Retaining Used Drug

The pharmacist and or unblinded authorized designee will retain all vials used to mix the Investigational Product as well as empty syringes, as applicable, for subject administration until the study monitor has performed accountability. The monitor will provide confirmation that the vials/syringes may be disposed of (both used and unused drug inventory). If authorization for onsite destruction is granted, the Investigator will ensure that the materials are destroyed in compliance with applicable policies and guidelines. Destruction will be documented.

5.7 Blinding and Unblinding

The subjects (including their caregivers) and Investigator as well as Sub-Investigator (conducting outcome related assessments and procedures) will be blinded to the identity of treatment for the Primary Wounds. The un-blinded staff, including the pharmacist or authorized designee, and the monitor will remain separate from the primary study team and will not be involved in any study conduct outside their functions of managing the receipt, storage, preparation, dispensing and reconciliation of all study products. All un-blinded material will be secured in a secondary locked location, that is not accessible to the primary study team.

The following precautions will be taken to ensure the integrity of the study blind to minimize potential impact on interpretation and of other efficacy and safety measurements:

- In order to maintain the blind, if a matched wound is determined to be closed at a weekly visit, the Remaining Dose will not be used to treat Secondary Wounds and Secondary Wounds will be capped at four (4).
- In addition, treatment may be unblinded in a medical emergency. Materials will be provided to the site for emergency unblinding and will be maintained in a secure location where study personnel access is limited.

In the case of a medical emergency necessitating unblinding, the Investigator or designee should, whenever possible, contact the Medical Monitor/Sponsor directly, prior to breaking the blind to discuss if unblinding needs to occur. If unblinding must occur, the designated unblinded staff may provide the information to the Investigator and this must be captured on the CRF. If unblinded for any reason this must be reported to the Sponsor.

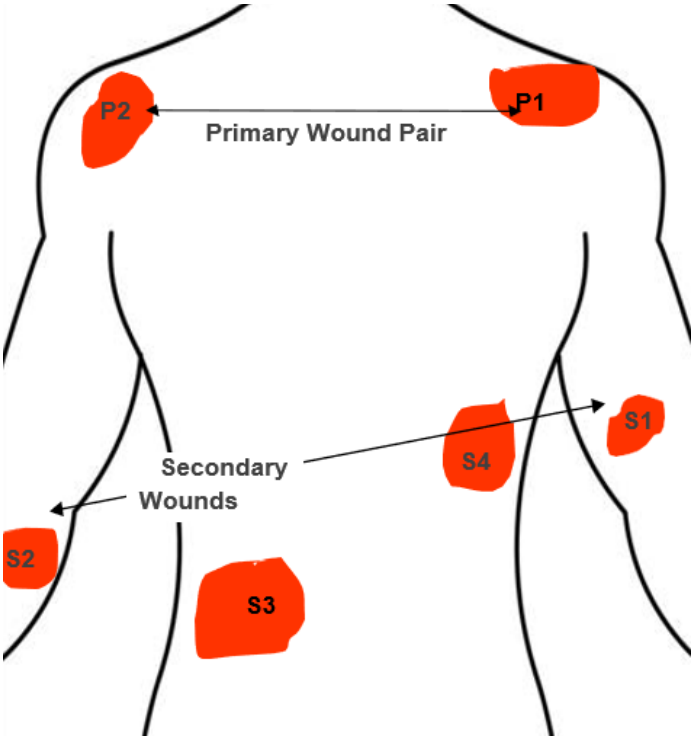
5.8 Wound Selection

One (1) matched wound pair will be selected to be part of the study, that meet the inclusion criteria (**Figure** 3).

Prior to randomization, wounds will be selected and labeled. The Primary Wound Pair will be labeled P1 & P2. For the Primary Wound Pair, one is randomized to B-VEC and one to Placebo.

Up to four (4) Secondary unmatched wounds may be chosen to receive the Remaining Weekly Dose of B-VEC. Secondary wounds will be labeled as they are selected starting with S1, S2, S3 and S4.

Figure 3. Wound Pairing, Labeling, and Selection Example



5.9 Wound Randomization

Using a pre-generated randomization schedule, the matched wounds are randomized to receive either B-VEC or Placebo gel.

5.10 Post-Administration Procedures

Following Investigational Product application, the subject will keep the treated wounds covered for roughly 24 hours.

6 Assessments

6.1 Timing of Assessments

Timing of assessments must be performed per the Schedule of Events (**Table 1**).

6.2 Efficacy Assessments

6.2.1 Wound Assessments

6.2.1.1 Wound Measurement and Imaging

Target wounds are imaged and measured on the study days outlined in the Schedule of Events (**Table 1**). Wound assessments should be performed by the PI. A trained, qualified Sub-I should only perform the wound assessments if the PI is unavailable. A validated Canfield tracing and imaging system will be used for the study. Trace where IP will be applied at each weekly visit, including the neighboring wounds and the originally selected wound, as applicable. Additional information about the Canfield system can be found in **Appendix 1**. Image the wounds in the same order and orientation at each visit.

6.2.1.2 Investigator Assessment of Complete Wound Closure

Investigator Assessment of Complete Wound Closure will be performed at the time points indicated in the Schedule of Events (**Table 1**) after removal of subject's dressings from target wounds prior to any potential disruption of the target wounds (i.e., markings, bacterial culture of wounds for clinical purposes, or B-VEC administration).

The Investigator Assessment of Complete Wound Closure of Primary and Secondary wounds should be performed by the PI. A trained, medically qualified Sub-I should only perform if the PI is unavailable. Evaluator information will be recorded on the applicable assessments.

In order to reduce inter-evaluator variability, it is important that the same evaluator assess complete wound closure for the same subject at all study visits, whenever feasible. If it is not possible for the same evaluator to continue performing the assessment, it is recommended that the primary and subsequent evaluator both examine and discuss their respective scoring during at least one visit.

Wound healing will be defined as complete closure of the originally selected wound surface identified at baseline, specified as skin re-epithelialization without drainage, as evaluated by the Investigator. If new neighboring wounds form during the key evaluation time periods at Weeks 8, 10 12, 22, 24 and 26 those wounds will not be included in the wound closure evaluation. Primary efficacy wound assessment occurring at two (2) consecutive weeks at Week 22 and 24 or 24 and 26 will be assessed live, followed by a review against the 2D and 3D images.

6.2.2 Pain Reported Outcome

6.2.2.1 Faces Legs Activity Cry Consolability Revised Scale (FLACC-R)

The Faces, Legs, Activity, Cry, Consolability- Revised Scale (FLACC-R) will be completed at the time points indicated in the Schedule of Events (**Table 1**) following the removal of the dressings on the matched wounds (Primary Wound Pair).

The FLACC-R Scale is used for children, under 6 years of age, who cannot accurately report their pain, due to being too young or not being able to understand what is being asked of them. A child is evaluated for each Primary Wound dressing change and will receive either a 0, 1 or 2 in each category based off of their behavior during the dressing removal. A total score is then calculated by study personnel, to determine

the overall pain and discomfort a subject is experiencing. The subject's caregiver will complete the scale at scheduled visits.

It is important that the same caregiver completes the assessment at all subject visits, whenever feasible, to reduce inter-evaluator variability. Additionally, this scale should continue to be used throughout the study even if the age of the subject changes during the study.

The FLACC-R is provided in **Appendix 2**.

6.2.2.2 Visual Analog Scale (VAS)

The Visual Analog Scale (VAS) will be completed at the time points indicated in the Schedule of Events (**Table 1**) following the removal of the dressings on the matched wounds. VAS uses a 10cm line with 1cm tick marks, where subjects indicate their level of pain by marking the appropriate tick mark on the scale from 0 cm (no pain) to 10 cm (the worst possible pain). VAS is used to provide indices of overall pain intensity during the dressing change.

VAS will be administered to subjects 6 years of age and older, who will complete assessment themselves (**Appendix 3**).

6.3 Safety Assessments

6.3.1 Medical and Medication History

The Investigator or delegated staff performs a complete medical history (from the time of birth), including a medication history and procedure and treatment history within the past (3) months. The Investigator or delegated staff must record all clinically or medically relevant information. Medical, procedure/treatment and medication history are reviewed and updated during the study. All medication taken within the past (3) three months from Screening or Visit 1 (Week 1) (including prescriptions, herbal and dietary supplements, over the counter medications, injections, and topical treatments) will be recorded on the CRF. The medical history includes respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases.

6.3.2 Physical/Skin Examination

A qualified individual performs a complete physical examination. Body systems evaluated include:

General appearance	Skin
HEENT (Head, Ears, Eyes, Nose, Throat)	Spine/Neck/Thyroid
Respiratory	Cardiovascular
Abdomen	Nervous System
Musculoskeletal	

Abnormalities or changes in severity noted during the exam should be reported in the source document and on the appropriate CRF page and recorded as an AE, if noted after the initial exam.

Abbreviated exams include evaluations of the general appearance; HEENT; abdomen; and skin will be compared against the original exam (i.e., if noted to be "abnormal skin" with erosions at the baseline, a subsequent visit exam would be considered "normal," if the findings are consistent to the baseline exam). At other visits, symptom-directed PEs can be performed at the discretion of the Investigator.

If at any point in the study a skin cancer occurs in the region of the B-VEC administration, attempts are made to collect samples of the skin cancer to evaluate cells for the presence of viral vector.

6.3.3 Vital Signs

Vital sign measurements include pulse, respiratory rate as well as temperature. Pulse and respiratory rate are taken after subjects are in a rested state. The method used for temperature measurement is at the discretion of the Investigator; however, the same method should be used throughout the study. Changes in vital signs that are reviewed and determined to be not clinically significant by the Investigator are not considered AEs.

On visits in which a blood draw occurs, vitals should be collected prior to the blood draw.

Vital signs are assessed monthly during the 26 weeks (i.e. Week 1; 5; 9; 13; 17; 21; 25; and SFU/ET). Symptom-directed vital sign assessments can be performed at the discretion of the Investigator.

6.3.4 Laboratory Evaluations

6.3.4.1 Complete Metabolic Panel with Direct Bilirubin & Compete Blood Count with Differential and Platelets

The amount of blood collected should be minimized. Reference ranges are used to assess the laboratory data for clinical significance. Abnormal laboratory values which are unexpected or not explained by the subject's clinical condition should be repeated as feasible until confirmed, explained, or resolved. Changes from baseline (Screening or Visit 1) are recorded as an AE if deemed clinically significant by the Investigator or qualified designee.

The following evaluations are conducted:

CMP14+ DBili	**CBC With Differential/ Platelet**
Glucose	White blood cells (WBC)
Blood Urea Nitrogen (BUN)	Red blood cells (RBC)
Creatinine	Hemoglobin
Sodium	Hematocrit
Potassium	Mean Corpuscular Volume (MCV)
Chloride	Mean Corpuscular Hemoglobin (MCH)
Carbon Dioxide	Mean Corpuscular Hemoglobin Concentration
Calcium	(MCHC)
Protein, Total	Red Cell Distribution Width (RDW)
Albumin	Platelets
Bilirubin, Total	Neutrophils
Bilirubin, Direct	Lymphocytes
Bilirubin, Indirect	Monocytes
Alkaline Phosphatase	Eosinophils
Aspartate Aminotransferase (AST)	Basophils
Alanine Aminotransferase (ALT)	

6.3.4.2 Urine and Pregnancy Test

A urine pregnancy test is performed for women of childbearing potential and must be negative prior to any invasive study related procedure and Investigational Product application, at the specified study visits, as determined by the Investigator.

6.3.4.3 HSV Antibody Assay

Serum is collected per the Schedule of Events (**Table 1**) for the purpose of screening for antibodies against HSV using a qualified Plaque Reduction Neutralization Test (PRNT).

6.3.4.4 Collagen VII Antibody Assay

Serum is collected per the Schedule of Events (**Table 1**) for the purpose of screening for antibodies against collagen VII using a commercially available CE IVD ELISA.

6.3.4.5 Viral Shedding

Whole blood, skin and bandage swabs and urine are collected per the Schedule of Events (**Table 1**) for evaluation of viral shedding by real time quantitative PCR.

6.3.4.6 Infectivity

Skin swabs are collected per the Schedule of Events (**Table 1**) for evaluation of viral infectivity by plaque titer analysis.

6.4 Principal Investigator

At each study site, a physician with expertise caring for patients with DEB will be designated as the Principal Investigator (PI). In close communication and coordination with the study monitor and Sponsor, the PI will have the following responsibilities in addition to overseeing all other study processes at their site.

6.4.1 Protocol Adherence

The Investigator will review deviations from the clinical protocol (e.g., lab results not within stated limits, additional clinical abnormalities not specified in protocol, exceptions to target wound criteria.) The PI or designee will consult with the study monitor and Sponsor as required. All deviations from the protocol must be documented and handled per institutional/Sponsor policies.

6.4.2 Treatments

The Investigator will determine treatments needed from complications that may arise, either due to the underlying disease (e.g., low hemoglobin or hematocrit, wound infection, other medical conditions) or B-VEC application (adverse events, wound infection, post-release criteria out of specification); Determine if the subject needs additional wound or systemic treatments; Determine which procedures will occur at unscheduled visits; Determine corrective actions for adverse events; and Determine whether to re-treat or perform additional treatment sessions post-adverse event.

6.4.3 Safety Assessments

The Investigator will review and assess all adverse events (e.g., severity, causality); Assess laboratory results for clinically significant abnormalities; and assess vital signs including blood pressure, temperature, and heart rate at every visit per the schedule of events (**Table 1**) and perform abbreviated physical examination for clinically significant abnormalities.

6.4.4 Adverse Events

Throughout the course of the study (following the initial IP application), all adverse events (AEs) will be monitored and reported on the AE Log. If an adverse event occurs, the first concern will be the safety of the study participants. All AEs occurring after administration will be followed throughout the study. All AEs related to study treatments or procedures will be followed until resolved or stabilized or until follow-up is no longer possible.

In general, even when not participating in a clinical trial, the study subjects and their caretakers communicate with their EB doctor on a regular basis via phone. Study subjects and their caretakers will be instructed to report via phone any adverse events that occur during the study while off-site. The events will then be transcribed to the AE Log. The Investigator is responsible for verifying that all serious and non-serious adverse event are reported to the appropriate regulatory bodies.

6.5 Definitions

6.5.1 Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a clinical investigation subject administered an investigational product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, disease or exacerbation of a pre-existing condition temporally associated with the use of a medicinal (investigational) product.

Subjects are asked a non-leading question in order to avoid bias in eliciting AEs. The question is asked in an open manner using language such as: “Have you experienced any change in your health or in your general condition since your last visit?”

It is important to question the subject in a non-leading way about changes in their health or concomitant medication usage since their last visit. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually.

Each AE requires a complete description including date of onset and corrective actions taken. The intensity of the AE, its relationship to the Investigational Product, as well as its outcome, must be recorded in the eCRF.

Symptoms of the disease under study/lack of efficacy should not be considered as AEs, as long as they are within the normal day-to-day fluctuation or expected progression of the disease. However, significant worsening of the symptoms should be recorded as an AE.

A change in the value of a safety laboratory evaluation can represent an AE if the change is clinically relevant (as determined by the Investigator) or if, during treatment with B-VEC, a shift of a parameter is observed from a normal value to a pathological value, or a further worsening of an already pathological value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with B-VEC, and the range of variation of the respective parameter within its reference range, should be taken into consideration. The Investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a laboratory parameter represents an AE. For pathological laboratory values that were not present at baseline, follow-up laboratory evaluations should be performed until the values return to within reference range or until a plausible explanation is found.

AEs should be recorded after the initial IP application through SFU/ET. AEs are to be recorded on the appropriate AE pages in the CRF and in source documents. Where possible, all AEs should be followed to resolution, or an outcome is reached.

Medical tests and examinations are performed, as appropriate, to document resolution of event(s). Where applicable and/or possible, AEs should be recorded as target wound specific.

Adverse events will be graded according to the National Cancer Institute’s (NCI’s) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 as applicable.

6.5.2 Immune Response Adverse Events

Observation of a severe immune response determined by the Investigator to be possibly, probably, or definitely related to B-VEC should be relayed to the Medical Monitor/Sponsor.

6.5.3 Serious Adverse Event

A Serious Adverse Event (SAE) is any untoward medical occurrence (whether considered to be related to B-VEC or not) that at any dose:

- Is fatal
- Is life-threatening (places the subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Is a persistent or significant disability/incapacity, or
- Is a congenital abnormality/birth defect

A hospitalization meeting the regulatory requirement for the “serious” criteria is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility, that was not planned.

Any event that does not exactly meet this definition, yet in the investigator’s opinion represents a significant hazard can be assigned the “other significant hazard” regulatory reporting serious criteria.

Additionally, important medical events that may not be immediately life threatening or result in death or hospitalization but that may jeopardize the subject or require intervention to prevent one of the outcomes listed above, or result in urgent investigation, may be considered serious. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

SAEs are collected and reported after the initial IP application through SFU/ET. If early termination of study treatment occurs, SAEs continue to be collected until the event resolves.

6.6 Severity

Definitions for classification of severity appear below. The Investigator will review these definitions with the subject. The Investigator will determine the severity classification based on these definitions, their clinical experience with DEB subjects, and/or the subject’s description of the event.

[Note: A “severe” AE is not the same as an “SAE” (serious adverse event), which is defined above.]

Mild (Grade 1): Symptoms are barely noticeable or do not make the subject uncomfortable. The AE does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).

Moderate (Grade 2): Symptoms are of sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) with prescription drugs or therapies may be needed.

Severe (Grade 3): Symptoms are of sufficient severity to cause the subject severe discomfort. Performance of daily activities is compromised. Treatment for symptom(s) with prescription drugs or therapies may be needed.

Life-threatening (Grade 4): Any adverse drug event that places the subject, in the view of the Investigator, at immediate risk of death

6.7 Relationship

The Investigator will categorize the subject’s adverse event as one of the following:

Not Related: No evidence of any causal relationship with the trial intervention. An alternative etiology will be documented in the subject's medical record.

Unlikely Related: Little evidence to suggest a causal relationship (e.g. the event did not occur within a reasonable time after administration of the Investigational Product) or another reasonable explanation for the event (e.g. another clinical condition or other concomitant treatment).

Possibly Related: Some evidence to suggest a causal relationship (e.g. occurrence within a reasonable time after administration of the Investigational Product), but other factors may have contributed to the event (e.g. another clinical condition or other concomitant treatment).

Related: Evidence that there is an association between the event and the administration of the trial medication. Causes other than the Investigational Product have been ruled out and/or the event re-appeared on re-exposure to the Investigational Product.

6.8 Study IP Action Taken

The Investigator will classify the study IP action taken as a result of the AE. The action taken will be one of the following:

Dose Not Changed: Study IP application was not changed in response to an AE

Drug Interrupted: Study IP application was interrupted in response to an AE

Drug Withdrawn: Study IP application was permanently discontinued in response to an AE

Not Applicable: Action taken regarding study IP application does not apply. Not applicable will be used in such circumstances such that the AE began after treatment completed.

6.9 Outcome

The AE will be followed until the Investigator determines and provides a final outcome. Adverse event outcomes are classified as one of the following:

Recovered/resolved: AE resolved with no residual signs or symptoms

Recovered/resolved with sequelae: AE resolved but symptoms remain, and a new baseline is established since full recovery is not expected (if Lyme's disease is the AE, the sequelae may be facial paralysis)

Not recovered/ resolved (continuing): AE has either no improvement or partial improvement, such that the AE remains ongoing

Fatal: Outcome of AE is death and may possibly be related to study IP as determined by the investigator

Unknown: The outcome of the AE is unknown (example lost to follow-up)

6.10 Reporting Procedures

All adverse events occurring after B-VEC administration observed by the Investigator or reported by the subject (whether or not attributed to B-VEC), are reported on the case report form.

Medically significant adverse events considered related to B-VEC by the Investigator or the Sponsor are followed until resolved or considered stable. The Investigator must assign the following attributes: description; dates of onset and resolution; severity; assessment of relatedness to B-VEC, and action taken. The Investigator may be asked to provide follow-up information.

All deaths occurring on study must be reported to the Sponsor; available autopsy reports and relevant medical reports may be requested.

The Investigator should notify the IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from the Sponsor, in accordance with local procedures.

It is left to the Investigator's clinical judgment whether or not an adverse event is of sufficient severity to require the subject's removal from study. A subject may also voluntarily withdraw from study due to what he or she perceives as an intolerable adverse event. If either of these occurs, the subject is asked to undergo an early termination assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable. If the subject was permanently withdrawn from the study due to a serious adverse event, this information must be included in either the initial or follow-up Serious Adverse Event Report Form, and in the End of Study Case Report Form.

6.10.1 SAE Reporting Procedures

All serious adverse events (SAEs) that occur after IP application must be reported to the Sponsor. All subjects with an SAE must be followed and the outcomes reported. The Investigator should supply the Sponsor and the IRB with any additional requested information (e.g., hospital discharge summary, autopsy reports and terminal medical reports). The Sponsor shall evaluate all SAEs and determine if they meet FDA reporting requirements. In the event of an SAE, the Investigator must:

1. Notify the Sponsor **within 24 hours** of the Investigator's awareness of the event.
2. Obtain and maintain all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject.
3. Provide the Sponsor with a complete, written case history, including copies of supporting reports (e.g., progress notes, laboratory reports) and a statement from the Investigator as to whether or not the event was related to the use of B-VEC.
4. Promptly inform the governing IRB/IEC of the event if it is related. For other SAEs, notify the governing IRB as required by the IRB, local regulations, and the governing health authorities.

Immediately report any SAE that meets the following to the Medical Monitor/Sponsor and suspend study intervention:

1. Occurrence of an SAE related or possibly related to the study intervention,
2. Systemic infection determined to be related to B-VEC,
3. Outside information is discovered that may affect the study and its participants.

6.10.2 Pregnancy

The Investigator must report all pregnancies to the Sponsor **within 24 hours** of their first knowledge of the pregnancy. If a subject become pregnant, they must be terminated from the study immediately. Pregnancies occurring up to three (3) months after the last application of B-VEC must be reported to the Investigator. The Investigator should counsel the subject on the potential risks of continuing the pregnancy and possible effects of the fetus. The female subject or their pregnant partner will be followed until the end of pregnancy. The infant will be followed for a year after birth if consent has been obtained to do so. Pregnancy itself is not considered an AE; however spontaneous abortion is.

6.11 Data Monitoring Board Review and Regulatory Reporting

A Data Safety Monitoring Board (DSMB) will be established for this study. The DSMB will be responsible for ensuring the safety of the subjects and to alert the Sponsor of any safety issues related to the conduct of the study. Members will be completely independent Investigators who have no financial, scientific, or

other conflicts of interest with the study. Details of DSMB membership requirements including potential conflicts of interest, as well as DSMB objectives, operational details and meeting scheduling are provided in the DSMB Charter.

The following will require reporting by the Investigator to the Sponsor for DSMB discussion:

- Occurrence of an unexpected SAE related or possibly related to the study intervention
- Systemic infection determined to be related to B-VEC
- Evidence of allergic reaction at B-VEC treatment site
- Evidence of malignancy at B-VEC treatment site
- Death of a study participant

The DSMB provides recommendations about stopping or continuing the trial and has the authority to recommend dose or regimen modifications for safety concerns. The DSMB may also make recommendations regarding the selection or retention of participants, their management, improving adherence to protocol-specified regimens, and the procedures for data management and quality control.

The end of the Data Safety Monitoring Board (DSMB) oversight is approximately six (6) months after the last subject is enrolled. More information can be found in the Data Safety Monitoring Plan and DSMB Charter.

6.12 Expedited Reporting and Safety Letters

Krystal Biotech, Inc. is responsible for reporting any suspected, unexpected, serious, adverse reactions and unexpected fatal or life-threatening suspected adverse reactions involving the Investigational Product to all regulatory authorities, IRB/IECs, and other participating Investigators in accordance with ICH GCP and local regulatory authorities as applicable.

Krystal Biotech, Inc. will be responsible for submitting Safety Letters to central IRB/IEC. It is the responsibility of the Investigator or designee to promptly notify local IRB/IEC of any of the events above, which involve risk to the human subject.

6.13 Safety Monitoring

The Medical Monitor/Sponsor will assess aggregate safety data across study sites on an ongoing basis. Routine meetings of the DSMB will be held every six (6) months at minimum or at the DSMB's request. Safety data, primary safety endpoints, all grade 3 and 4 adverse events, and all serious adverse events will be reviewed on a regular basis.

7 Study Completion

7.1 Long Term Follow-Up Protocol

The study will end after the last enrolled subject has completed the SFU/ET visit.

After the SFU/ET visit subjects will have the option to enroll in a long-term follow-up protocol under this IND, in which they will be followed for five (5) additional years after the SFU/ET Visit.

Any subject who completes the study, discontinues early, or withdraws from the study after receipt of B-VEC will be asked to participate in the Long-Term Follow-Ip protocol. The subject will have the option to not follow the Investigator's suggestions, but attempts will still be made to contact the subject. If a subject does not follow directions or refuses to return for follow-up, attempts will still be made to evaluate them or to have their local physician evaluate them.

7.2 Discontinuation, Withdrawal, Lost to Follow-Up, or Early Termination

Subjects who discontinue due to adverse events or protocol deviations/violations will be replaced at the discretion of the Sponsor. Subjects who withdraw prior to the first B-VEC administration are considered a screen failure and are not considered a participant and can be re-screened.

A subject is free to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Investigator or Sponsor may also withdraw the subject at any time in the interest of subject safety or for other reasons. Criteria for withdrawal include:

- Consent/assent is withdrawn
- The subject refuses treatment and/or procedures/observations
- Occurrence of unmanageable adverse events or pregnancy
- For other reasons (e.g., significant protocol violation, non-compliance)

The Sponsor may be contacted if clarification is required. The primary reason for withdrawal must be recorded on the CRF. Comments or complaints made by the subject must also be recorded on the CRF. Withdrawal should be discussed with the medical monitor prior to withdrawal when possible. This information will be communicated to the DSMB at each meeting in the enrollment update.

A subject may withdraw at any time but treated participants will be followed yearly for at least 5 years in a Long-Term Follow-up Protocol. The subject will have the option to not follow the Principal Investigator's suggestions, but attempts will still be made to contact the participant.

If the subject withdraws for other reasons, attempts will be made to contact them at least once per year to perform safety monitoring as described above. Subjects may be contacted more frequently if it is deemed necessary by the investigator. If a subject is lost to follow up, the attempts to contact the subject will be documented in an effort to show due diligence. If a subject is terminated early from the study, the same process as for "withdrawal" of a subject will be followed

The Sponsor reserves the right to terminate the study.

8 Statistical Considerations

Continuous variables will be summarized in tables and will include the number of subjects, mean, standard deviation (SD), percent of coefficient of variance (CV%), median, minimum, and maximum. Categorical variables will be presented in tables as frequencies and percentages. A statistical analysis plan (SAP) will provide additional details on the approach to the analysis and data displays.

8.1 Primary Efficacy Endpoint

The following hypothesis for the primary endpoint of the proportion of DEB wounds sites with complete wound healing (CWH) from baseline in B-VEC versus placebo treated intra-subject wound sites at Weeks 22 and 24 or 24 and 26 as determined by the Investigator will be tested:

Null Hypothesis	H0: %CWH in B-VEC = %CWH in Placebo
Alternate Hypothesis	H1: %CWH in B-VEC > %CWH in Placebo

Where % CWH is the percentage of primary wounds with a complete wound healing from baseline at Week 22 and 24 or 24 and 26. A two-sided significance level of 0.05 is considered.

The complete wound healing is defined as 100% wound closure from the exact wound area selected at baseline, specified as skin re-epithelialization without drainage. If new neighboring wounds form around the

original traced baseline wound during the primary evaluation time points, these areas will not be included in the evaluation.

The primary endpoint is defined as wounds that meet any of the following conditions:

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

Only wounds that are healed for at least two (2) consecutive weeks are counted as positive responses.

8.2 Key Secondary Efficacy Endpoint

The following hypothesis for the key secondary endpoint of the proportion of primary wound sites with complete wound healing from baseline, in B-VEC-treated versus baseline at Week 8 and 10 or 10 and 12 (as determined by the Investigator) will be tested:

Null Hypothesis	H0: %CWH in B-VEC = %CWH in Placebo
Alternate Hypothesis	H1: %CWH in B-VEC > %CWH in Placebo

Where % CWH is the percentage of matched wound sites with a complete wound healing from baseline at Week 8 and 10 or 10 and 12. A two-sided significance level of 0.05 is considered.

The complete wound healing is defined as 100% wound closure from the exact wound area selected at baseline, specified as skin re-epithelialization without drainage. If new neighboring wounds form around the original traced baseline wound during the secondary evaluation time points these areas will not be included in the evaluation.

The secondary key endpoint is defined as wounds that meet any of the following conditions:

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

Only wounds that are healed for at least two (2) consecutive weeks are counted as positive responses.

8.3 Number of Subjects

Per Agency's recommendation, a McNemar Test has been used for sample size calculation. In the Phase I/II study, the response rates for Weeks 8 through 12 were from 70-100% for wounds randomized to B-VEC and 0-33% for wounds randomized to placebo, respectively. Therefore, assuming a response rate of 75% among wounds randomized to B-VEC and a response rate of 25% among wounds randomized to placebo, with 90% power and a two-sided Type 1 error rate of 5%, 24 subjects (i.e., 24 wound pairs) are required.

8.4 Data Management

Pre-designed CRFs are used to collect information for safety and proof of mechanism analyses. An electronic CRF (eCRF) is managed and maintained by the Sponsor for this study. The eCRF is constructed based on the CRF data entry requirements of the protocol. Data queries are generated and resolved within the eCRF. In addition, range checks of the eCRF fields, plausibility and consistency checks across eCRF pages will be performed to assess consistency, accuracy and completeness of the data collected and entered into the eCRF. Standard SAS datasets are generated and provided for analysis.

8.5 Analysis Populations

Safety Population

This population is defined as all subjects who were administered with either B-VEC or placebo. Safety population will be used for all the safety analyses.

Intent-to-Treat Population

The intent-to-treat (ITT) population includes subjects whose primary wounds were randomized with or without either B-VEC or Placebo administration. ITT population will be used for all the primary and secondary efficacy sensitivity analyses and baseline summaries.

Modified Intent-to-Treat Population

The modified intent-to-treat (mITT) population includes subjects whose primary wounds were randomized and received B-VEC treatment with at least one post baseline primary endpoint assessment. The mITT population will be used for all the primary and secondary efficacy analyses.

Per Protocol Population

The per-protocol (PP) population includes all the safety population subjects who completed the study without major protocol deviations. PP population will be used for all the primary and secondary efficacy sensitivity analyses.

8.6 Demographic and Baseline Characteristics

The descriptive summaries of subjects' demographic and baseline characteristics are presented by treatment, where applicable, for the safety, ITT, mITT and PP populations. A detailed description of subject disposition is provided.

Subject characteristics include a summary of the following:

- Subject demographics
- Baseline disease characteristics
- Pre-existing medical conditions

Continuous variables are summarized using number of observations, mean and standard deviation, median, and minimum and maximum values. Categorical values are summarized using number of observations and percentages.

Medical History and AEs will be summarized by MedDRA System Organ Class and Preferred Term.

8.7 Efficacy Analyses

8.7.1 General Approach

The study has a complete randomized-block design in which each subject serves as a block to receive all of the treatment conditions. In this study, each subject provides at least one pair of target wounds with one wound from each pair being treated with B-VEC and the other wound from each pair with placebo in the primary target wound pair. Efficacy measurements are taken multiple times (or repeatedly) over the on-treatment period from each subject.

All data will be presented using summary statistics or frequency tables, as appropriate, and will be analyzed for superiority comparisons between B-VEC and placebo treatments. The description of the sample will be done using summary statistics (n, mean, standard deviation, median, and maximum/minimum) for continuous data and using frequency statistics (counts and percentages) for categorical data. Hypothesis

testing, unless otherwise indicated, will be performed at the 5% significance level (1-sided). All P-values will be rounded to four decimal places; P-values less than 0.0001 will be presented as '<0.0001' in all tables. Unless specifically stated, all confidence intervals will be two-sided with 95% coverage.

Efficacy measures collected pre-dosing at Screening or Visit 1 (Week 1) will be considered as the baseline measurement in this study.

The Sponsor, or their designee, will analyze the data using SAS® Statistical Analysis System Version 9.1.3 or higher. Detailed descriptions of the statistical analysis methods, data conventions, and sensitivity analysis, as well as handling of missing data for both efficacy and safety measures will be described in detail in the Statistical Analysis Plan (SAP).

8.7.2 Analysis of Primary Efficacy Endpoint

The primary endpoint of the proportion of DEB primary wound sites with complete wound healing from baseline will be analyzed using the McNemar Test at Weeks 22 and 24 or 24 and 26.

The complete wound healing is defined as complete wound closure from the exact wound area selected at baseline, specified as skin re-epithelialization without drainage. If new neighboring wounds form around the original traced baseline wound during the primary evaluation time points will not be included in the evaluation.

The primary endpoint is defined as wounds that meet any of the following conditions:

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

Only wounds that are healed for at least two (2) consecutive weeks are counted as positive responses.

The mITT population will be used for this primary efficacy analysis. The ITT and PP populations may also be used as part of the sensitivity analyses.

The primary endpoint results will be summarized by treatment and timepoints for all the subjects in mITT population. A listing of these results will also be presented for all the subjects in the ITT population.

8.7.3 Analysis of Key Secondary Efficacy Endpoint

The key secondary endpoint of the proportion of primary wound sites with complete wound healing from baseline, will be analyzed using the McNemar Test at Weeks 8 and 10 or 10 and 12.

The complete wound healing is defined as complete wound closure from the exact wound area selected at baseline, specified as skin re-epithelialization without drainage. If new neighboring wounds form around the original traced baseline wound during the secondary evaluation time points these areas will not be included in the evaluation.

The primary endpoint is defined as wounds that meet any of the following conditions:

- Healed on Week 8 and Week10, or
- Healed on Week 10 and Week 12.

Only wounds that are healed for at least two (2) consecutive weeks are counted as positive responses.

The ITT population will be used for this primary efficacy analysis. The PP populations may also be used as part of the sensitivity analyses.

The key secondary endpoint results will be summarized by treatment and timepoints for all the subjects in ITT population. A listing of these results will also be presented for all the subjects in the ITT population.

8.7.4 Analysis of Secondary Efficacy Endpoint

The following secondary endpoint will be analyzed using the Analysis of Covariance (ANCOVA) with treatment as the fixed effect and the baseline value as the covariate by the time points.

The mean change from baseline in pain severity VAS score per wound site associated with wound dressing changes at Weeks 22, 24 and 26 for each treated versus placebo for ages 6 and above on the primary wound pair. For ages below 6 years, the FLACC-R scale scores will be used instead of VAS scores.

The ITT population will be used for this primary efficacy analysis. The ITT and PP populations may also be used as part of the sensitivity analyses.

The secondary endpoint results will be summarized by treatment and timepoints for all the subjects in the ITT population. A listing of these results will also be presented for all the subjects in the ITT population.

8.8 Safety Analyses

The safety and tolerability of B-VEC based on the assessment of adverse events, physical examinations, vital signs, and clinical laboratory test results. All safety analysis results will be performed using the safety population.

Adverse events will be coded using the version of MedDRA System Organ Class and Preferred Term available at the start of the trial. Adverse events will be grouped into treatment-emergent adverse events and post-treatment adverse events and will be tabulated by preferred terminology and by body system. Each AE will be counted once for each subject unless it resolves and recurs, in which case it may appear as multiple AEs. Severity, frequency, and relationship of AEs to study intervention will be presented by System Organ Class (SOC) and preferred term. Incidence of target-wound-related adverse events will be summarized by treatment, respectively, for each wound pair.

Listings will be provided for discontinuations, deviations, compliance, AEs leading to discontinuation, and target-wound-related adverse events. AE listings will include severity and relationship to study medication, as well as actions taken.

Tables will be provided summarizing reasons for premature discontinuation, protocol deviations, subject compliance, treatment-emergent AEs (TEAEs), TEAEs of target wound, TEAEs by severity, SAEs, and TEAEs leading to discontinuation.

The prior and concomitant medications will be summarized and listed by treatment. Medications will be coded with WHO Drug and categorized as either prior medications (any medication that was started before the first application of B-VEC) or concomitant medications (medication continued or newly started on or after the date of first application of B-VEC).

Medical/procedural history data collected during Screening or Visit 1 (Week 1), will be summarized by MedDRA System Organ Class and Preferred Term.

Descriptive summary of physical examinations, vital signs, and clinical laboratory tests will be reported along with data listings.

Evaluations of viral shedding, infectivity, COL7 and HSV antibodies will be done descriptively.

Any abnormal lab tests obtained during the study will be listed for individual subjects. Any positive findings of the pregnancy test will be listed.

8.9 Missing Values and Imputations

Multiple imputation method will be used to handle missing data for primary efficacy analysis. For all the exploratory endpoints, the missing values will not be imputed.

8.10 Interim Safety Analyses

A Data Safety Monitoring Board (DSMB) as described in Section **6.11**, will be instituted for the interim analyses use in this study. They will operate under an approved charter describing their roles and responsibilities for the interim analysis Their main responsibility will be to review and adjudicate safety findings.

9 Regulatory Obligations

9.1 Informed Consent

Before a subject's participation in the trial, the Investigator (or designee) is responsible for obtaining written informed consent from the subject or legally acceptable representative (see note below) after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any investigational products are administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

The acquisition of informed consent should be documented in the subject's records, and the informed consent form should be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form must be retained in accordance with institutional policy, and a copy of the signed consent form must be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject or legally acceptable representative and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

9.2 Institutional Review Board

The protocol proposed informed consent form, other written subject information, and any proposed advertising material including the information letters must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol, informed consent form, and advertising material must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent changes to the above-named documents. The Investigator should notify the IRB/IEC of important deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from the Sponsor, in accordance with IRB/IEC procedures.

The Investigator is responsible for obtaining IRB/IEC approval/renewal throughout the duration of the study at the frequency specified by the IRB/IEC. Copies of the Investigator's reports and the IRB/IEC's written continuance of approval must be sent to the Sponsor.

9.3 Pre-Study Documentation Requirements

The Investigator is responsible for forwarding the following documents to the Sponsor for review before study initiation from the Sponsor can occur:

- Signed and dated protocol signature page (Investigator's Agreement)
- Copy of the IRB/IEC approval of the protocol, information letter, consent form, and assent form
- Up-to-date curricula vitae of Principal Investigator and all Sub-Investigators
- The IRB composition and/or written statement that IRB is in compliance with regulations
- Signed study contract
- Completed FDA form 1572. Laboratories providing primary and secondary endpoint data and any central laboratories for the study must be listed on the form
- For studies covered under 21 CFR Part 54.2(e), "Financial Disclosure," completed Financial Disclosure statements for the Principal Investigator, all Sub-Investigators, and their spouses (legal partners) and dependent children

9.4 Subject Confidentiality

The Investigator must take all reasonable measures to ensure that the subject's confidentiality is maintained. On the case report forms or other documents submitted to the study Sponsor and those working with the study Sponsor, subjects should be identified by their initials and a subject study number. Documents that are not for submission to the study Sponsor and those working with the study Sponsor should be kept in strict confidence by the Investigator.

In compliance with Federal regulations/ICH GCP Guidelines, the Investigator and Institution shall permit authorized representatives of the Sponsor and companies that work with the Sponsor, of the regulatory agency(s), and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the subject to permit such named representatives to have access to their study-related records without violating the confidentiality of the subject.

10 Administrative and Legal Obligations

10.1 Protocol Amendments and Study Terminations

Protocol amendments must be made only with the prior approval of the sponsor. Agreement from the sponsor must be obtained for all protocol amendments and amendments to the informed consent document. The IRB/IEC must be informed of all amendments and give approval for any amendments likely to affect the safety of the subjects or the conduct of the trial. The Investigator must send a copy of the approval letter from the IRB/IEC to the Sponsor.

The Sponsor reserves the right to terminate the study, according to the study contract. The Investigator should notify the IRB/IEC in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor.

10.2 Study Documentation and Storage

10.2.1 Delegation Log

The Investigator should maintain a list of appropriately qualified persons to whom he/she has delegated trial duties. All persons authorized to make entries and/or corrections on case report forms are included on the Delegation of Authority Form. The Delegation of Authority Form must be continuously updated as needed, and those delegated specified tasks, should have appropriate and up-to-date training.

10.2.2 Source Documents

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

10.2.3 Study File

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, in a complete, accurate, and legible manner, suitable for inspection at any time by representatives from the sponsor, companies that work for and with the Sponsor, and/or applicable regulatory authorities. Elements should include but are not limited to the following:

- Subject files containing completed case report forms, informed consents, and supporting copies of source documentation.
- Study files containing the protocol with all amendments, investigator's brochure, copies of pre-study documentation, training documentation and all correspondence to and from the IRB and the sponsor.
- Proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement, and all drug-related correspondence.

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.

No study document should be destroyed, moved to another location, or assigned to another party without prior written consent of the sponsor.

10.3 Study Monitoring and Data Collection

Representatives of the Sponsor, following ICH Guidelines for GCP (E6), will monitor the conduct of this study at regular intervals to verify adherence to the protocol; completeness, accuracy, and consistency of the data entered into the eCRFs; and adherence to Federal and local regulations on the conduct of clinical research. In addition, audits or inspections may be carried out by the Sponsor's or its designee's independent Quality Assurance Department, the FDA, local regulatory authority or the IRB. In accordance with ICH Guidelines for GCP, the Investigator must provide direct access to all study records including subject's source data/documents (e.g., subject's medical records), eCRFs, and other study related documents (e.g., Investigator Study File, investigational product drug accountability records). In addition, the Investigator agrees to provide to representatives of the Sponsor, regulatory agency or IRB/IEC access to facilities and personnel necessary for the effective conduct of any inspection or audit.

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, authorized representatives of the Sponsor may conduct a quality assurance audit. The purpose of a Sponsor audit is to systematically and independently examine all study-related activities and documents to determine

whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol and any supporting documentation, ICH Guidelines for GCP, and any applicable regulatory requirements.

The Investigator agrees to cooperate with the Sponsor's representatives to ensure that any problems detected in the course of monitoring and/or audit visits, including delays in completing eCRF data entry and answering queries, are resolved in a timely manner.

In addition, authorized representatives of regulatory agencies and/or an IRB may visit the site to perform audits or inspections. If the Investigator is notified of an inspection by a regulatory authority the Investigator agrees to notify the Sponsor immediately.

For this study, subject data will be entered into the Sponsor-defined eCRFs and combined with data provided from other sources, as applicable, in a validated data system. Data will be appropriately documented in the subject's source documents and entered into the eCRF when the information is available. Applicable data from the subject's source documents should be recorded in the eCRFs completely and promptly. Completed eCRFs should be ready for review by the Sponsor or its designee within 3 business days of each study visit for any given subject.

Management of clinical data will be performed in accordance with the Sponsor's standards and data cleaning procedures, and will be used to ensure the integrity of the data, e.g., inconsistencies and errors queried in the data per the study specific Data Management Plan (DMP) and the eCRF Completion Guidelines (CCGs).

Adverse events and relevant medical history will be coded using MedDRA System Organ Class and Preferred Term. Concomitant medications will be coded using the World Health Organization Drug Global Dictionary (WHO Drug Global).

Corrections of data entered into the eCRF must be made in the eCRF and supported by source documents, as appropriate. Corrections to the eCRF through queries and comments will be tracked by the eCRF internal audit trail.

The Investigator is responsible for all information collected on study subjects enrolled in this study. The data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. After a full review of the eCRFs by the Sponsor or its designee and resolution of any data clarifications, the Investigator will review, sign, and approve the subject's eCRF.

Copies of the final completed eCRFs will be provided on a data storage device (e.g., USB flash drive) for archiving at the investigative site following database lock at or prior to study closure.

10.3.1 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the electronic data capture (EDC) system directly. Additional manual reviews are done on a regular basis to ensure consistency and data quality. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

10.3.2 Retention of Records

All study documents (e.g., subject files, signed informed consent forms, copies of eCRFs, Investigator Study File notebook, etc.) must be kept secure and retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if

the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the Sponsor.

The Investigator must notify and receive prior written consent of the Sponsor before any study documents are destroyed, moved to another location, or assigned to another party.

10.4 Publication Policy

The information provided in support of or generated as a result of this study is confidential. Any use or reproduction thereof, including but not limited to publications or presentations by the Investigator or his associates, must be submitted to the Sponsor for review and approval prior to publication or presentation in any form. All publications must acknowledge the sponsorship.

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Appendix 1: Procedure for Digital Photography Using RUBI 3D Imaging

Canfield RUBI 3D Imaging System:

- iPad with Occipital Scanner and Canfield custom external flash
- Canfield Capture Mobile Application (software includes modules for capturing, viewing, measuring, and exporting 2D and 3D object data).

Proper Subject Preparation & Positioning:

For the duration of the study, the only variable that should change is the area of interest. Any extraneous objects (jewelry, makeup, clothing, etc.) should be eliminated from the field to be photographed.

For optimal imaging of the skin surface, the subject's photographic target wound area must be non-shiny/dry and clean (free of any extraneous items, e.g. lint). There must be no hair in the photographic target area field of view. Any hair within the target area field of view must be cut/trimmed (ideally shaved) from the region prior to imaging.

Careful preparation and positioning of the subject are critical to the accuracy of the image capture. Capture images in a well-lit room with the same lighting, throughout the study.

Photographic Procedures:

1. Prior to capturing the subject images using the camera system, the photographer launches the Canfield Capture Mobile Application.
2. The photographer either creates a New Subject for an initial visit or, for a return subject, highlights the appropriate existing Subject ID listed in the Canfield Capture database. The visit name (as per the study schedule) is selected by the photographer and the image date is captured by the software.
3. Positioning the Subject correctly in relation to the camera system depends on where the target area is located on the body.
4. With the Subject's target area positioned correctly within the frame of the camera system, the Photographer adjusts the camera distance for accurate image capture. The initial reference image is a 2D image capture.
5. The Photographer then captures the 3D image following the model on the screen. Once complete, the photographer is prompted to review the 3D build of the data model for image acceptability. The Photographer either accepts the image and moves on to the next capture or does not accept and recaptures the image.
6. After the 3D image capture the image is displayed for measurement. The Investigator or assigned Designee, will annotate the involved wound area and the software will report the surface area measurement (cm^2). If the target area is considered closed, the healed checkbox may be marked.
7. Following the session, the Photographer submits the images to Canfield. Upon exiting, the software automatically reads, checksums, encrypts, packages, and duplicates the data to submit to Canfield via internet submission.

A secure, validated, compliant web server set up at Canfield is used for secure transfer of study images by study sites. Images are to be transferred the day they are recorded. Only approved individuals by the Sponsor have access to the website.

The application logs a record of this action to a local database and prompts the Photographer when completed.

8. Trained Canfield staff review the data files for technical quality and acceptability and communicate any technical comments to the site.
9. Data Transfers are provided to sponsor as per the data transfer specifications. At the end of the study, a copy of site-specific subject images will be provided to each site. This is in addition to the Photography Result Reports available for printing from the Clinical Services Website after each session. Remote access to all images by the Sponsor is also provided.
10. Canfield will provide each study site with the necessary hardware as well as technical support as needed. All supplied photographic equipment remains the property of Canfield. Any questions regarding the photographic portion of this study are to be forwarded to the assigned Project Manager at Canfield Scientific.

Appendix 2: Face, Legs, Arms, Cry, Consolability Revised (FLACC-R)

Categories	0	1	2	Participant's Score
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested, sad, appears worried	Frequent to constant quivering chin, clenched jaw, distressed looking face, expression of fright/panic	
Legs	Normal position or relaxed, usual tone & motion to limbs	Uneasy, restless, tense occasional tremors	Kicking, or legs drawn up, marked increase in spasticity, constant tremors, jerking	
Activity	Lying quietly, normal position, moves easily, regular, rhythmic respirations	Squirming, shifting back and forth, tense, tense/guarded movements, mildly agitated, shallow/splinting respirations, intermittent sighs	Arched, rigid or jerking, severe agitation, head banging, shivering, breath holding, gasping, severe splinting	
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint, occasional verbal outbursts, grunting	Crying steadily, screams or sobs, frequent complaints, repeated outburst, constant grunting	
Consolability	Content, relaxed	Reassured by occasional touch, hugging or being talked to, distractible	Difficult to console or comfort, pushing caregiver away, resisting care or comfort measures	

Appendix 3: Visual Analog Scale (VAS)