# Statistical Analysis Plan

Protocol #: B-VEC-03

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|---|---|
| **Study Title:** | A Phase III Efficacy and Safety Study of Beremagene Geperpavec (B-VEC, previously KB103) for the Treatment of Dystrophic Epidermolysis Bullosa (DEB) |
| **Study Number:** | B-VEC-03 |
| **Study Phase:** | III |
| **Sponsor:** | Krystal Biotech, Inc.<br>2100 Wharton St.<br>Suite 701<br>Pittsburgh, PA 15203 |
| **Version:** | 1.3 Final |
| **Date:** | 25-August-2021 |

# Table of Contents

Table of Contents ..... 2
List of Tables ..... 4
List of Figures ..... 4
List of Abbreviations and Definitions of Terms ..... 5
1 Introduction ..... 6
2 Study Objectives and Endpoints ..... 6
2.1 Study Objective ..... 6
2.2 Study Endpoints ..... 6
2.2.1 Overview ..... 6
2.2.2 Primary Endpoint ..... 7
2.2.3 Key Secondary Endpoint ..... 8
2.2.4 Secondary Endpoints ..... 8
2.2.5 Safety Endpoints ..... 8
3 Study Implementation ..... 8
3.1 Study Design ..... 8
3.1.1 Study Design Rationale ..... 9
3.1.2 Treatment Period ..... 9
3.1.3 Number of Subjects and Interim Analysis ..... 9
3.1.4 Randomization and Blinding ..... 10
4 Study Populations ..... 12
4.1 Analysis Populations ..... 12
4.1.1 Intent-to-Treat (ITT) Population ..... 12
4.1.2 Safety Population ..... 12
4.1.3 Modified ITT Population ..... 12
4.1.4 Per-Protocol Population ..... 12
5 Overall Statistical Considerations ..... 12
5.1 General Conventions ..... 12
5.2 Baseline Definition ..... 12
5.3 Handling of Missing Data ..... 13
6 Statistical Analysis Methods ..... 13
6.1 Subject Disposition ..... 13

6.2 Demographics and Baseline Characteristics ..... 13
6.3 Treatment Compliance and Exposure ..... 13
7 Efficacy Analyses ..... 14
7.1 Analysis and Data Conventions ..... 14
7.1.1 Multi-center Study ..... 14
7.1.2 Adjustments for Covariates ..... 14
7.1.3 Handling of Dropouts or Missing Data ..... 14
7.1.4 Multiple Comparisons/Multiplicity ..... 14
7.1.5 Examination of Subgroups ..... 14
7.1.6 Analysis Methods – Multiple imputation ..... 15
7.2 Primary Efficacy Analysis ..... 16
7.2.1 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint ..... 17
7.3 Key Secondary Efficacy Analysis ..... 17
7.3.1 Sensitivity and Supplementary Analyses of the Key Secondary Efficacy Endpoint ..... 18
7.4 Secondary Efficacy Analyses ..... 18
7.4.1 Sensitivity Analyses of the Secondary Efficacy Endpoints ..... 18
7.5 Additional Analysis ..... 18
8 Safety and Tolerability ..... 18
8.1 Adverse Events ..... 18
8.2 Vital Signs ..... 19
8.3 Physical/Skin Examination ..... 19
8.4 Laboratory Values ..... 20
9 Other Relevant Data Analyses/Summaries ..... 21
9.1 Protocol Deviations ..... 21
9.2 Medical/Procedural History ..... 21
9.3 Prior and Concomitant Medications ..... 21
10 References ..... 22
11 Appendices ..... 23
Appendix 1: Schedule of Assessments and Procedures per Visit ..... 24
Appendix 2: Adverse Event and Prior/Concomitant Medication Date Imputations ..... 1

# List of Tables

Table 1. Primary Weekly Unit Dose (varied by wound area) ..... 6

Table 2. Maximum Weekly Dose (varied by age of subject) ..... 7

# List of Figures

Figure 1. B-VEC-03 Study Design ..... 8

Figure 2. Wound Pairing, Labeling, and Selection Example ..... 11

# List of Abbreviations and Definitions of Terms

| | |
|---|---|
| AEs | adverse events |
| ALT (SGPT) | alanine aminotransferase, included in metabolic panel |
| AST (SGOT) | aspartate aminotransferase, included in metabolic panel |
| B-VEC | Beremagene Geperpavec |
| CBC | complete blood count |
| CFR | Code of Federal Regulations |
| CM | centimetre |
| CMH | Cochran-Mantel-Haenszel test |
| COL7 | collagen VII |
| CRF | case report form |
| CWH | complete wound healing |
| DEB | dystrophic epidermolysis bullosa |
| DSMB | data safety monitoring board |
| EB | epidermolysis bullosa |
| FDA | Food and Drug Administration |
| HEENT | head, ears, eyes, nose, throat |
| HSV | herpes simplex virus |
| DSMB | Independent data monitoring committee |
| IEM | immunoelectron microscopy |
| IND | Investigational New Drug application |
| ITT | Intent-to-treat |
| LTFU | long-term follow-up |
| MCH | mean corpuscular hemoglobin |
| MCHC | mean corpuscular hemoglobin concentration |
| MCV | mean cell volume |
| NC1 | noncollagenous 1 domain |
| NC2 | noncollagenous 2 domain |
| PFU | plaque-forming units |
| 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 |

# 1 Introduction

This document presents the Statistical Analysis Plan (SAP) for the protocol 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)." The statistical plan described is an *a priori* plan and no analysis prior to the preparation of this plan has been conducted. This SAP summarizes the study design and objectives and provides details on the outcome definitions and statistical methods that will be used to analyze the data from protocol B-VEC-03.

# 2 Study Objectives and Endpoints

## 2.1 Study Objective

The primary objective of the Phase III study 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 subject served as their own control. Each site had a designated Principal Investigator.

Primary Wound Pair: Two (2) wounds in each Subject that were similar in size, located in similar anatomical regions and had similar appearance (Matched Wounds) will be selected to evaluate the Primary and the Key Secondary End points in the Phase III study.

The Primary Wound pair will be selected and labeled by the Investigator, prior to the randomization conducted by the unblinded designee using the sealed pre-generated Randomization Form. The pre-generated Randomization Form will assign one wound to receive a unit dose of B-VEC and the other wound will receive a unit dose of Placebo. The unit dose administered to the Primary Wound Pair (Primary Weekly Unit Dose) will be determined based on the wound area as shown in the Table 1 below. If one wound in the Primary Wound Pair and its neighboring wounds are assessed as closed by the Investigator during the visit, only then that wound will not be treated at the scheduled visit and treatment will resume when the wound area is assessed as open by the Investigator.

**Table 1. Primary Weekly Unit Dose (varied by wound area)**

| Wound Area | Unit Dose |
|---|---|
| <20 $cm^2$ | $4\times10^8$ PFU/wound |
| 20 to 40 $cm^2$ | $8\times10^8$ PFU/wound |
| 40 to 60 $cm^2$ | $1.2\times10^9$ PFU/wound |

The maximum dose a subject will receive during a weekly visit (Maximum Weekly Dose) is provided in Table 2.

**Table 2. Maximum Weekly Dose (varied by age of subject)**

| Subject Age | Maximum Weekly Dose |
|---|---|
| ≥ 6 months to < 3 years | $1.6\times10^9$ PFU/week |
| ≥ 3 years to < 6 years | $2.4\times10^9$ PFU/week |
| ≥ 6 years | $3.2\times10^9$ PFU/week |

The difference between the Maximum Weekly Dose and the Primary Weekly Unit Dose for each subject (Remaining Weekly Dose) will be calculated by the Investigator at baseline. This Remaining Weekly Dose for each subject was fixed at baseline and did not change during the duration of the Study.

In addition to the Primary Wound Pair, the Investigator will select up to four (4) Secondary Wounds in each subject to receive B-VEC. The total dose applied weekly to the selected Secondary Wounds will not exceed the Remaining Weekly Dose. As with the Primary Wound Pair, the unit Dose of B-VEC received by the Secondary Wounds will depend on the area of the wound (Table 1).

Example: If a subject 7 years of age, presents with the primary wound pair $\leq 20cm^2$ then the

- Primary Weekly Unit Dose for Subject = $4\times10^8$ PFU (see Table 1)
- Maximum Week Dose for Subject = $3.2\times10^9$ PFU (see Table 2)
- Remaining Weekly Dose for Subject = ($3.2\times10^9$ PFU – ($4\times10^8$ PFU)) = $2.8\times10^9$ PFU/subject/week

Wound areas at Baseline, for Primary and Secondary Wounds will be determined by the Investigator using the validated Canfield photography quantitation.

Re-dosing regimen: During a weekly visit, if a wound area in the matched Primary Wound Pair and their neighboring wounds or a Secondary Wound and their neighboring wounds are determined by the Investigator to be completely closed, then that particular wound will stop receiving Weekly Treatment. Treatment on that wound area will resume when that particular wound area is determined to be open by the Investigator during a subsequent weekly visit. The re-dosing regimen will be followed throughout the study.

### 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-treated and placebo-treated intra-subject wound sites at Weeks 22 and 24 or Weeks 24 and 26, as determined by the Investigator, to evaluate durability of response and repeat dosing. 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 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.

### 2.2.3 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 Weeks 10 and 12 (as determined by the Investigator). 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.

### 2.2.4 Secondary Endpoints

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.

### 2.2.5 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.

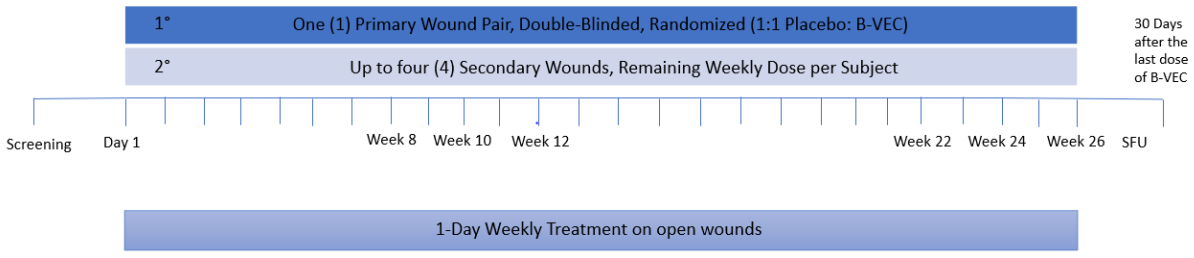
# 3 Study Implementation

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 (Appendix 1).

## 3.1 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 1 below.

**Figure 1. 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.

### 3.1.1 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.

### 3.1.2 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 another 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.

#### 3.1.2.1 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.

### 3.1.3 Number of Subjects and Interim Analysis

With 90% power and a two-sided Type 1 error rate of 5%, 24 subjects (i.e., 24 wound pairs) are required for a McNemar's test, assuming a response rate of 75% among wounds randomized to B-VEC and a response rate of 25% among wounds randomized to placebo. These response rates are supported by the results of a Phase 1/2 study in which the response rates for weeks 10 and 12 were 71% and 83% for active and 33% and 14% for placebo, respectively. Because the sample size calculation assumes no correlation within subjects, the estimate is conservative. Any positive correlation will cause an increase in power for the sample size of 24. PASS 2020, "Tests for Two Correlated Proportions (McNemar Test)", was used to calculate the sample size. Because of the small n, the multinomial enumeration was used instead of the normal approximation.

If we assume a 75% response rate among wounds randomized to B-VEC and a 25% response rate among wounds randomized to placebo and we assume independence among the wounds within a subject, we expect a total of 62.5% discordant pairs. Under this scenario, 18.75% of the subjects will have positive responses for both wounds and 18.75% will have negative responses for both wounds:

*Expected rates of response and non-response, assuming a 75% response rate for B-VEV treated wounds, a 25% response rate for placebo-treated wounds and no correlation between wounds. The off-diagonals correspond to discordant pairs.*

| | | **Placebo** | | |
|---|---|---|---|---|
| | | **Response** | **Non-response** | **Total** |
| **B-VEC** | **Response** | 18.75% | 56.25% | 75.00% |
| | **Non-response** | 6.25% | 18.75% | 25.00% |
| | **Total:** | 25.00% | 75.00% | 100% |

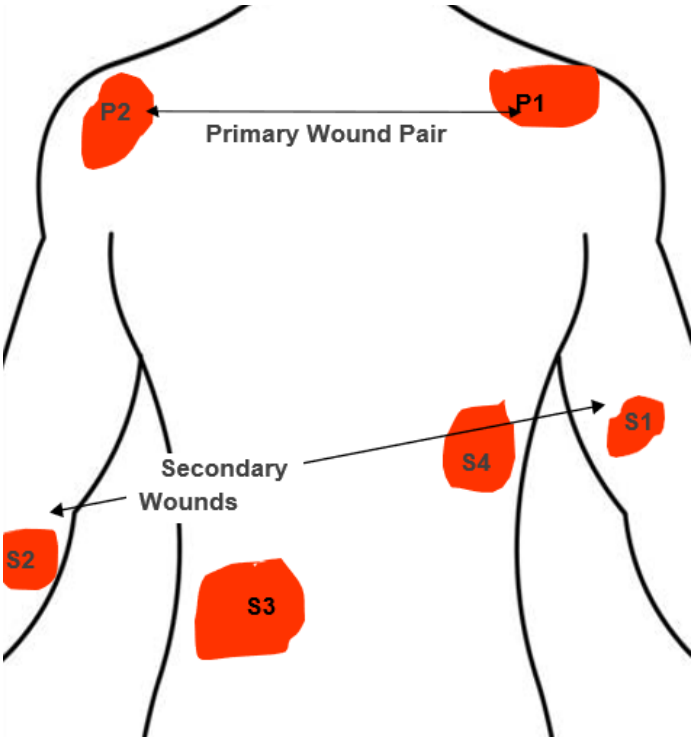
Interim analyses will not be performed for this study.

### 3.1.4 Randomization and Blinding

#### 3.1.4.1 Wound Selection

One (1) matched wound pair that meets the inclusion criteria (Figure 2) will be selected to be part of the study. Prior to randomization, wounds will be selected and labeled. The Primary Wounds will be labeled P1 & P2. For each subject, one Primary Wound is randomized to B-VEC and the other Primary Wound is randomized 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 2. Wound Pairing, Labeling, and Selection Example**




#### 3.1.4.2 Wound Randomization

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

#### 3.1.4.3 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 unblinded staff, including the pharmacist or authorized designee, and the monitor will remain separate from the primary study team. The unblinded staff will not be involved in any evaluation of the primary outcomes. 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, the Remaining Weekly Dose is determined by the Investigator at baseline and is fixed for the duration of the study. Even if a primary wound pair is determined to be closed at a weekly visit, the Remaining Weekly Dose will not change.
- 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.

# 4 Study Populations

## 4.1 Analysis Populations

### 4.1.1 Intent-to-Treat (ITT) Population

The intent-to-treat (ITT) population includes subjects whose primary wounds were randomized, regardless of whether they received randomized treatment or not. The ITT population will be used for all the primary and secondary efficacy analyses and baseline summaries.

### 4.1.2 Safety Population

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

### 4.1.3 Modified ITT Population

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

### 4.1.4 Per-Protocol Population

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

# 5 Overall Statistical Considerations

## 5.1 General Conventions

The following general comments apply to all statistical analyses and data presentations:

- Summaries will include frequency and percentages for categorical data; frequency and median for ordinal data; and frequency, mean, standard deviation, and median, minimum, and maximum for quantitative data.
- Duration variables (in days) will be calculated using the general formula (end date − start date) +1.
- Change from baseline will be calculated for each subject at the specified time point as the value at the specified time point minus the baseline value.
- Individual subject listings of all data represented on the eCRFs will be provided to facilitate the investigation of tabulated values and to allow for the clinical review of all efficacy and safety parameters.
- Version 9.4 (or higher) of SAS® statistical software package will be used to provide all summaries, listings, graphs, and statistical analyses.

## 5.2 Baseline Definition

In general, baseline is defined as the value closest to but prior to administration with either B-VEC or placebo (Screening or Visit 1/ Week 1).

### 5.3 Handling of Missing Data

Missing data will be handled as outlined below:

- All missing and partial dates for adverse events or for medications received after randomization will be queried for a value. If no value can be obtained, substitutions will be made as detailed in Appendix 2. These substitutions will be used in calculations; however, the actual value recorded on the eCRF will be used in all listings.
- A multiple imputation approach, described in section 7.1.6, will be used to impute any primary and key secondary efficacy endpoint missing values. The severity and causality assessment for adverse events cannot be missing. Missing data will be queried for a value.

## 6 Statistical Analysis Methods

### 6.1 Subject Disposition

The number of subjects included in each of the analysis populations (ie, ITT, Safety, mITT, and PP) will be summarized. A listing will be provided that indicates each subject's inclusion /exclusion from the populations and the reason for exclusion from each of the populations.

The number and percentage of subjects completing the study (defined as receiving at least 1 administration of either treatment and returning for all of the weeks 1 through 26, and SFU Visits), not completing the study, missing each of the Visits, and prematurely discontinuing from treatment will be presented for the ITT, mITT, and PP populations. A listing of all subjects who prematurely discontinued from treatment or not completing the study will be presented, and the primary reason for discontinuation of treatment or not completing the study will be provided.

### 6.2 Demographics and Baseline Characteristics

The descriptive summaries of subjects' demographic and baseline characteristics are for the safety, ITT, mITT and PP populations. A detailed description of subject disposition will be provided.

The following subject characteristics will be summarized:

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

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

Medical History and AEs will be summarized by MedDRA System Organ Class and preferred term.

### 6.3 Treatment Compliance and Exposure

Exposure summary by treatment group (primary wounds only) will be presented for the Safety, mITT, and PP populations. The distribution of subjects by the total number of weeks on therapy (0 through 26) will be presented. For the Safety population, the summary of exposure will be based on the actual treatment received.

Treatment compliance is defined as the number of wound treatment doses (active and placebo) actually received divided by the number of doses expected (× 100) over the time period defined by the first and last treatment dose dates. Descriptive statistics for treatment compliance and the number and percentage of

subjects at least 90% compliant will be presented by treatment group (primary wounds only) for the Safety, mITT, and PP populations.

# 7 Efficacy Analyses

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 (2-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 9.4 or higher.

## 7.1 Analysis and Data Conventions

### 7.1.1 Multi-center Study

The statistical analysis for this multi-center study will use the set of subjects pooled across all centers. Center will not be used as a stratification factor or covariate in the statistical analysis models.

### 7.1.2 Adjustments for Covariates

No stratification factors were used for randomization and no adjustments for covariates will be used in the efficacy analyses.

### 7.1.3 Handling of Dropouts or Missing Data

The reason of early study treatment / study discontinuation will be identified, and the percentage of these subjects will be summarized by treatment group.

A multiple imputation approach, described in section 7.1.6, will be used to impute missing values.

### 7.1.4 Multiple Comparisons/Multiplicity

The primary efficacy endpoint is a single responder outcome during weeks 24 through 26 that will be compared between two treatment groups. Therefore, the primary analysis will not be adjusted for multiple comparisons.

### 7.1.5 Examination of Subgroups

The treatment effect for the primary and key secondary efficacy endpoints will be examined for the following subgroups:

- Age (≤ 12 years, >12 and ≤18 years, >18 years)
- Sex (Male, Female)
- Race (White, African American, additional groups must represent at least 25% of the population if not, will group as ‘All Other’)

Summaries of the primary and key secondary efficacy variables by treatment group and subgroups will be produced.

### 7.1.6 Analysis Methods – Multiple imputation

Multiple imputation methods will replace each missing primary efficacy endpoint value with a set of m=10 plausible values based on a model predicting values for a missing data point based on available data, assuming a Missing at Random (MAR) missingness mechanism.

This set of values represents the uncertainty about the correct value to be imputed. Each of the 10 complete datasets (generated by SAS PROC MI) will be analyzed by relevant statistical procedures (e.g., SAS PROC FREQ for McNemar Test, SAS PROC LOGISTIC, etc). The results for the 10 datasets will be combined using the method described on p. 115 of Schafer, J.L. (1997)

*Prediction model*

The prediction model predicts a missing endpoint value based on available data (variables) that may have an influence on that endpoint. The prediction model for the binary primary efficacy endpoint will be a logistic regression model with the following covariates:

- randomized study treatment: B-VEC or placebo
- sex: male or female
- age at baseline (continuous covariate)
- body weight at baseline (continuous covariate)
- race (White, African American, additional groups must represent at least 25% of the population if not, will group as 'All Other')

*Algorithm for the multiple imputation of missing values*

Within the Bayesian framework, the task of imputing missing values is achieved by drawing random values from the posterior predictive distribution of the missing primary efficacy endpoint data (predicted by the logistic regression prediction model specified above). This posterior predictive distribution is a function of the observed data and regression parameters (or function of regression parameters).

As non-monotone missing pattern may be observed, the fully conditional specification (FCS) method will be used for dealing with arbitrary non-monotone missing data patterns. The FCS is based on an iterative algorithm; at each iteration and for each variable of the prediction model, there is a

- prediction step (P-step): the current (iteration) values of the observed and imputed values are used to derive the predictive distribution of the missing values
- and an imputation step (I-step): updated imputations are generated by draws from the predictive distribution defined by the updated regression model.

When the last variable in the sequence (e.g., the primary efficacy endpoint) has been imputed, the algorithm cycles again through each variable, repeating the chain of regression estimation and imputation draw steps. These cycles are repeated and finally there will be $m$=10 draws from the predictive distribution for each missing primary efficacy endpoint value.

*Analyzing multiply imputed datasets*

Individual statistical analysis will be performed using the McNemar Test for each of the $m$=10 imputed complete datasets and the results (point estimates and associated standard errors for the study treatment effect) will be stored in a single output file.

*Estimation and inference for multiply imputed datasets*

As a final step, the $m$=10 estimates and associated standard errors will be combined using the method described on p. 115 of Schafer, J.L. (1997). The chi-square statistics can be either Wald statistics or

likelihood ratio statistics. The chi-square values and the degrees of freedom from all 10 imputed datasets will be used.

## 7.2 Primary Efficacy Analysis

The primary efficacy analyses will use the ITT population and the Primary Wound Pair.

The primary endpoint is the proportion of DEB primary wound sites with complete wound healing from baseline in B-VEC-treated and placebo-treated intra-subject wound sites at Weeks 22 and 24 or 24 and 26, as determined by the Investigator. Complete wound healing is defined as 100% wound closure from the exact wound area selected at baseline, specified as skin re-epithelialization without drainage:

The primary endpoint is defined as responder 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 primary endpoint response data will be summarized descriptively by the wound treatment.

A summary of the outcomes for each member of the Primary Wound Pair can be represented in the following 2×2 table, where each entry represents a subject. T is the total number of subjects in the ITT population and each cell entry is the number of subjects with the corresponding outcomes of the Primary Wounds.

| | | Placebo | | |
|---|---|---|---|---|
| | | Complete Wound Healing | No Complete Wound Healing | Row total |
| B-VEC | Complete Wound Healing | *A* | *B* | *N1* |
| | No Complete Wound Healing | *C* | *D* | *N2* |
| | Column total | *M1* | *M2* | *T* |

The null hypothesis of interest is the absence of a treatment effect on wound healing and the alternative hypothesis is the presence of a treatment effect on wound healing.

These hypotheses are equivalent to the following null and alternative hypotheses:

Null Hypothesis H0: Prob(B) = Prob(C)

Alternate Hypothesis H1: Prob(B) ≠ Prob(C)

Where Prob(B) and Prob(C) are the probability of the occurrence of discordant pairs B (B-VEC=Positive & PBO=Negative) and C (B-VEC=Negative & PBO=Positive).

The null hypothesis will be tested by a McNemar test statistic using a two-sided type I error rate of 0.05:

$$\chi^2_{McNemar} = (B - C)^2 / (B + C)$$

Under the null hypothesis of no difference between the proportions of the two possible types of discordant pairs, this test statistic follows a chi-square distribution with 1 degree of freedom. If the total number of discordant pairs (B+C) are sufficiently small (less than 6), the McNemar test with a continuity correction will be used. If the chi-square test result is significant, the null hypothesis of no treatment difference will be rejected in favor of the alternative hypothesis that a treatment difference exists.

In addition to testing the null hypothesis, the McNemar odds ratio and its 95% confidence interval will be summarized to indicate the magnitude of the treatment effect with B-VEC treatment. The McNemar odds ratio is the ratio of the counts of the discordant pairs B and C.

For subjects with missing primary endpoint data, a multiple imputation approach (details see section 7.1.6) assuming MAR will be used.

### 7.2.1 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint

Sensitivity analyses of the primary endpoint include:

- The primary analysis described in Section 7.2 for the primary efficacy endpoint will be repeated for the PP and mITT populations.
- The primary analysis described in Section 7.2 for the primary efficacy endpoint will be repeated with observed data without any imputations for missing values (i.e., if a subject is missing either a B-VEC or placebo outcome, the subject will be excluded from the analysis).

Supplementary Analysis:

- Common treatment risk difference will be obtained from conditional logistic regression with covariates age and gender and stratified by subject (matched pair) and multiple imputation approach described in section 7.1.6 assuming MAR.

## 7.3 Key Secondary Efficacy Analysis

The key secondary efficacy analyses will be based on the ITT population. The primary efficacy analyses will be repeated for responder 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. The key secondary endpoint response data will be summarized descriptively by the wound treatment.

The McNemar testing procedure used for the primary endpoint will repeated for this key secondary endpoint. A multiple imputation approach (details see section 7.1.6) assuming MAR will be used to impute missing endpoint data. If the primary endpoint is statistically significant at a type I rate of 0.05, the same full type I rate of 0.05 will passed on to evaluate the key secondary endpoint.

#### 7.3.1 Sensitivity and Supplementary Analyses of the Key Secondary Efficacy Endpoint

Sensitivity analyses of the key secondary endpoint include:

- The analysis described in Section 7.3 for the key secondary efficacy endpoint will be repeated for the PP and mITT populations.
- The key secondary efficacy analysis performed in Section 7.3 for the key secondary efficacy endpoint will be repeated with observed data without any imputations for missing values (i.e., if a subject is missing either a B-VEC or placebo outcome, the subject will be excluded from the analysis).

Supplementary Analysis:

- Common treatment risk difference will be obtained from conditional logistic regression with covariates age and gender and stratified by subject (matched pair) and multiple imputation approach described in section 7.1.6 assuming MAR.

### 7.4 Secondary Efficacy Analyses

The following secondary endpoints will be analyzed using Analysis of Covariance (ANCOVA) with treatment as the fixed effect, and the baseline value as the covariate. The analyses will be conducted in the ITT population for the matched Primary Wound Pair only.

1. The mean change in pain severity VAS score per wound site associated with wound dressing changes at Week 22 for each B-VEC-treated wound versus placebo-treated wound for ages 6 and above. For ages below 6 years, the FLACC-R scale scores will be used instead of VAS scores and will be summarized descriptively.
2. The analysis will be repeated for Week 24 and for Week 26.

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

#### 7.4.1 Sensitivity Analyses of the Secondary Efficacy Endpoints

Sensitivity analyses of the secondary endpoints include:

- The analyses described in Section 7.4 for the secondary efficacy endpoints will be repeated for the PP and mITT populations.

### 7.5 Additional Analysis

The wound healing data from wounds that are not from primary wound pair will be listed .

The change in patient reported outcomes such as Heath (EQ-5D-5L) and Skin Index (Skindex-29) before and after end of treatment will be summarized.

## 8 Safety and Tolerability

All safety analyses will be conducted in the Safety population. Safety measures include adverse events, physical examinations, vital signs, and clinical laboratory tests.

### 8.1 Adverse Events

Verbatim descriptions of AEs will be coded using MedDRA system organ class, version to be delineated in the CSR. Summary tables will be provided for all treatment-emergent adverse events (TEAEs), but all AEs will be provided in a listing. A treatment-emergent AE is defined as any AE that newly appeared, increased

in frequency, or worsened in severity on or after the initiation of active treatment. An AE is considered treatment emergent if the AE start date and time is on or after the start date and time of the first administration treatment dose. If time of the AE is missing and it occurred on the same date as the first administration treatment dose, the AE will be defined as treatment emergent. If the start date of the AE is partial or missing and it cannot be determined if the AE occurred prior to or after the first administration treatment dose, the AE should be defined as treatment emergent.

An overall summary of AEs will include the number of subjects who experienced at least one AE of the following categories: any AE, any TEAE, any drug-related TEAE, any severe TEAE, any serious TEAE, any drug-related SAE, any serious TEAE leading to death, any TEAE leading to premature discontinuation of treatment, any TEAE leading to premature discontinuation from the study, any TEAE leading to dose interruption of treatment, and any serious TEAE leading to premature discontinuation of treatment dose.

The number and percentage of subjects reporting a TEAE will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity (mild, moderate, and severe); and by system organ class, preferred term, and relationship (unrelated or related to treatment). The incidence of TEAEs will be summarized by preferred term, sorted by decreasing frequency in the B-VEC group, for all TEAEs, related TEAEs, serious TEAEs, and TEAEs leading to study drug discontinuation. The number and percentage of subjects reporting a TEAE of wound site reaction (based on the MedDRA higher level term) will be tabulated, preferred term and severity (mild, moderate, and severe). The incidence of serious TEAEs, TEAEs leading to premature discontinuation of treatment dose, and TEAEs leading to a dose interruption of treatment dose will be summarized by system organ class and preferred term. For all analyses of TEAEs, if the same AE (based on preferred term) is reported for the same subject more than once, the AE is counted only once for that preferred term and at the highest severity and strongest relationship to treatment.

In addition, all AEs (including non-TEAEs), serious TEAEs, TEAEs leading to discontinuation of treatment, and TEAEs leading to dose interruption of treatment will be provided in listings, study site, subject, verbatim term, MedDRA system organ class and preferred term, start and end date, seriousness, severity, relationship to the treatment, action taken with treatment and outcome.

Immune response adverse events due to a severe immune response determined by the Investigator to be possibly, probably or definitely related to B-VEC will be summarized by the number and percentage reporting such AEs along with a subject listing.

## 8.2 Vital Signs

Vital sign measurements include systolic and diastolic blood pressure, pulse, and respiratory rate as well as temperature. Vital signs data is collected during Visit 1, 5, 9, 13, 17, 21, 25 and at the safety follow-up (SFU)/ET.

Descriptive statistics of the absolute and change from baseline to each post-baseline time point values will be provided. Baseline is defined as the value closest to but prior to the initiation of treatment administration.

## 8.3 Physical/Skin Examination

Physical examination data is collected at Visit 1, Week 26, and safety follow-up (SFU)/ET. A full physical examination will be completed at Visit 1 (Week 1) of the body systems is included in the physical/skin examination:

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

Abbreviated Physical exams will be completed at Week 26, and the safety follow-up (SFU)/ET. Subsequent abbreviated exams will be compared to the baseline exam for abnormalities.

Subject listings of all physical examination results by body system will be provided. Physical examination results will be coded using MedDRA (version to be delineated in the CSR). Any abnormalities or changes in severity noted during the exam will provided in a subject listing.

## 8.4 Laboratory Values

Laboratory data is collected during Screening or Visit 1 (Week 1), and Week 26. 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 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 (MCHC) |
| Calcium | |
| 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) | |

Detailed subject listings of all laboratory data collected during the study will be provided. Laboratory values outside normal limits will be identified in the subject data listings with flags for low (L) and high (H). Actual and change from baseline laboratory values for hematology and serum chemistry will be summarized.

Data from the following other laboratory evaluations will be provided in subject listings:

- Urine and Pregnancy Test Results (positive or negative)
- HSV Antibody Assay
- Collagen VII Antibody Assay
- Viral Shedding
- Infectivity

# 9 Other Relevant Data Analyses/Summaries

## 9.1 Protocol Deviations

A listing of all protocol deviations will be provided. Deviations will also be reviewed by the Sponsor and categorized into general categories such as major and minor. Review of protocol deviations will be conducted and finalized prior to unblinding the database. The number of subjects with at least one protocol deviation, the number of subjects with a minor protocol deviation, the number of subjects with a major protocol deviation, and the number of subjects with at least one major deviation for the ITT population. A major deviation is defined as one that potentially affects the efficacy and/or safety analyses.

## 9.2 Medical/Procedural History

Medical/procedural history is collected during Screening or Visit 1 (Week 1). Medical/procedural history data will be summarized by MedDRA system organ class and preferred term, and a subject listing will be provided.

## 9.3 Prior and Concomitant Medications

The prior and concomitant medications will be summarized and listed. 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). A subject listing also will be provided for all prior and concomitant medications.

# 10 References

Schafer, J.L. (1997) Analysis of Incomplete Multivariate Data. London: Chapman and Hall, p.115.

# 11 Appendices

Appendix 1: Schedule of Assessments and Procedures per Visit

Appendix 2: Adverse Event Date Imputations

# Appendix 1: Schedule of Assessments and Procedures per Visit

| | 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 | | | | | | |
| 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).
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.

| | 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 6.3

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

# Appendix 2: Adverse Event and Prior/Concomitant Medication Date Imputations

**Adverse Event Start/Stop Date Imputation**

**Imputation Rules for Partial Dates (D = day, M = month, Y = year)**

| Parameter | Missing | Additional Conditions | Imputation |
|---|---|---|---|
| Start date for AEs | D | M and Y same as M and Y of first dose of study drug | Date of first dose of study drug |
| | | M and/or Y not same as date of first dose of study drug | First day of month |
| | D and M | Y same as Y of first dose of study drug | Date of first dose of study drug |
| | | Y prior to Y of first dose of study drug but same as Y of screening date | Date of screening date |
| | D, M, Y | None - date completely missing | Date of first dose of study drug |
| Stop date for AEs | D | M and Y same as M and Y of last dose of study drug | Date of last dose of study drug |
| | | M and/or Y not same as date of last dose of study drug | Use last day of month |
| | D and M | Y same as Y of last dose of study drug | Date of last dose of study drug |
| | | Y not same as Y of last dose of study drug | Use Dec 31 |
| | D, M, Y | None - date completely missing | No imputation, but assume ongoing |

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.
Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.
In all cases, if it cannot be determined if the adverse event occurred prior to or after the first dose of test article, the adverse event should be defined as treatment emergent.