# Statistical Analysis Plan

## Protocol #: KB103-001

| | |
|---|---|
| **Study Title:** | A Phase II Study of KB103, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB) |
| **Study Number:** | KB103-001 |
| **Study Phase:** | I/II |
| **Sponsor:** | Krystal Biotech, Inc.<br>2100 Wharton St.<br>Suite 310<br>Pittsburgh, PA 15203 |
| **Version:** | Final |
| **Date:** | 15-MAY-2020 |

# Table of Contents

# 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 |
| 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 |
| EB | epidermolysis bullosa |
| FDA | Food and Drug Administration |
| HEENT | head, ears, eyes, nose, throat |
| HSV | herpes simplex virus |
| 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 |
| PP | per protocol |
| RBC | red blood cell count |
| RDW | red blood cell distribution width |
| SAE | serious adverse event |
| SD | standard deviation |
| WBC | white blood cell |

# 1 Introduction

This document presents the Statistical Analysis Plan (SAP) for the protocol KB103-001, "A Phase I/II Study of KB103, a Non-Integrating, Replication-Incompetent HSV Vector Expressing the Human Collagen VII Protein, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)." The statistical plan described is prepared after an initial partial analysis was performed as the study is not a blinded study. This SAP summarizes the study design and objectives and provides details of the outcome definitions and statistical methods that will be used to completely analyze the data from Phase I through Phase II.

# 2 Study Objectives

## 2.1 Study Objectives Phase I

### 2.1.1 Primary

1) To evaluate safety through the incidence of adverse events (AEs) associated with KB103 post-administration.
2) To evaluate the expression of human collagen VII as determined by immunofluorescence (IF) and COL7A1 mRNA by RT qPCR post-administration
3) To evaluate the presence of anchoring fibrils as determined by immunoelectron microscopy (IEM) post-administration

### 2.1.2 Secondary

4) To assess proportion of complete wound closure of KB103 treated wounds to that of placebo treated wounds at weeks 8, 10 and 12.
5) To assess the duration of healing.
6) To access time to wound closure
7) To evaluate the safety of KB103 through
    a. Change in laboratory values:
        i. Collagen VII antibodies
        ii. HSV antibodies
        iii. Complete Blood Count with Differential
    b. Changes in vital signs: blood pressure, heart rate, respiratory rate, temperature
    c. Changes in physical exam

## 2.2 Study Objectives Phase II

### 2.2.1 Primary

8) To assess wound closure through post-administration imaging:
    a. To assess proportion of complete wound closure of B-VEC treated wounds to that of placebo treated wounds at weeks 8, 10 and 12.
    b. Time to wound closure of a KB103-administered wound relative to a placebo-administered wound
    c. Duration of wound closure of a KB103-administered wound relative to a placebo-administered wound

#### 2.2.2 Other

1) To evaluate the expression of human collagen VII as determined by immunofluorescence (IF)
2) To evaluate the presence of anchoring fibrils as determined by immunoelectron microscopy (IEM) post-administration

# 3 Overview

The Phase I/II studies were randomized placebo controlled intrasubject comparison of KB103-administered and placebo-administered wounds.

To date, KB103 has been administered to 12 patients enrolled onto 4 versions of the Phase I/II protocol. A summary of the protocols and patients enrolled are presented below.

| Phase | Protocol: | SN and Date: | # of pts | Wound size | # of wounds treated | Dose | Dosing days |
|---|---|---|---|---|---|---|---|
| 1 | v1.0, 19Apr2018 | SN0001, 4/20/2018 | 2, Pts 01-02<br>Adults | Up to 10cm$^2$ | 2: one KB103, one placebo | 1e8 PFU/wound/day | 0, 2, 14, 28, 30 |
| Following v1.0, the protocol was amended to increase the frequency and PFU level of the doses, and to administer to patients age 5 and older. | | | | | | | |
| 2a | v2.2, 08Oct2018 | SN0008, 10/09/2018 | 4, Pts 03-06<br>2 adults, 2 children age 13&14 | Up to 20 cm$^2$ | 3: two KB103, one placebo | 3e8 PFU/wound/day with the option to escalate to 6e8 PFU/wound/day | 1, 2, 3, 4, 5, 30, 60, 90 |
| Following 2.2, the protocol was amended to administer KB103 every two to three days to correspond with bandage changes. The potential number of doses increased, and the dose level was set at 2e8 PFU/wound/administration. | | | | | | | |
| 2b | v3.1, 12Mar2019 and v3.2*, 25Jun2019 | SN0016, 3/4/2019 | 5, Pts 07-11<br>3 adults, 2 children age 14&15 | Up to 20 cm$^2$ | 3: two KB103, one placebo | 2e8 PFU/wound/day | Every 2 to 3 days up to 15 per month |
| Following 3.2, the protocol was amended to administer KB103 in 2 cycles. The age of inclusion was reduced to 2 years old. Wound areas increase to up to 50cm$^2$, and with the increase in area the dose was increased to 6e8 PFU per area. | | | | | | | |
| 2c | v4.0, 01Aug2019 | SN0024, 8/5/2019 | 3, TBD | Up to 50 cm$^2$ | Up to 3; 2 KB103 and one placebo | 6e8 PFU/wound/day | Every 2 to 3 days until wound closure x 2 cycles |

*v3.2 clarified the long-term follow-up

# 4 Study Implementation

Detailed information for the protocol study visits, is provided in the sections below and in the Schedule of Events (**Appendix 1: Schedule of Events**).

## 4.1 Number of Subjects

A formal sample size calculation was not performed for this study. The sample size is based on what was considered an adequate number of subjects for a pilot study to obtain sufficient information on the safety and effectiveness of KB103. Enrolled up to 12 subjects (including Phase I and Phase II).

# 5 Study Populations

The primary population for an analysis of the proof of mechanism is the intent-to-treat (ITT) population. Study populations are defined in the following sections.

## 5.1 Analysis Populations

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

The intent-to-treat (ITT) population includes subjects who were administered KB103 who have had at least one paired assessment of the target wound area post-administration, i.e., at least one KB103 target wound and one placebo target wound.

#### 5.1.2 Safety Population

This population is defined as all subjects who were administered KB103.

#### 5.1.3 Per-Protocol Population

The per-protocol (PP) population is defined as all subjects in the ITT population who have had at least one paired assessment of the target wound area post-administration and completed the protocol as planned.

# 6 Overall Statistical Considerations

## 6.1 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 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 9.1.3 (or higher) of SAS® statistical software package will be used to provide all summaries, listings, graphs, and statistical analyses.

## 6.2 Baseline Definition

In general, baseline is defined as the value closest to, but prior to, administration with either KB103 or placebo.

## 6.3 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.
- Missing primary endpoints, values after the last non-missing value would be replaced by the last recorded observed value. This is analogous to a last observation carried forward (LOCF) strategy for study discontinuations. For all the other endpoints, the missing values will not be imputed.
- The severity and causality assessment for adverse events cannot be missing. Missing data will be queried for a value.

# 7 Statistical Analysis Methods

## 7.1 Subject Disposition

The number of subjects included in each of the analysis populations (ie, ITT, Safety and PP) will be summarized by treatment group. A listing will be provided that indicates each subject's inclusion in/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 (KB103 or placebo) and returning for weeks 8, 10, and 12, not completing the study, and prematurely discontinuing from treatment will be presented for the ITT, safety 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.

### 7.2 Demographics and Baseline Characteristics

The descriptive summaries of subjects' demographic and baseline characteristics are presented for the Safety, ITT, and PP populations.

Subject characteristics include a summary of the following:

- Subject demographics
- Baseline 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.

### 7.3 Treatment Compliance and Exposure

Exposure summary by treatment group will be presented for the Safety and PP populations. The distribution of subjects by the total number of weeks on therapy (baseline, 8, 10, and 12) 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 (KB103 and placebo) 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 for the ITT, Safety, and PP populations.

## 8 Efficacy (Proof of Mechanism) Analyses

The study has a complete randomized-block design in which each subject serves as a block to receive all of the treatment conditions. The Phase I/II studies provided at least one pair of target wounds, with one wound being treated with placebo and one wound being treated with KB103. Efficacy measurements are taken multiple times (or repeatedly) over the on-treatment period and off-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 KB103 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 will be considered as the baseline measurement (defined in **Section 6.2**) in this study. For all efficacy analyses, subjects will be analyzed in the group to which they were randomized.

The Sponsor, or their designee, will analyze the data using SAS® Statistical Analysis System Version 9.3 or higher.

## 8.1 Wound Efficacy Analyses:

### 8.1.1 Change in Wound Surface Area:

The efficacy analyses will be based on the observed ITT population.

The efficacy objective is the proportion of DEB wound sites with complete wound healing from baseline (≥90% reduction in wound surface from baseline) in KB103 versus placebo treated intra-participant wound sites at Weeks 8, 10 and 12 as determined by the Investigator.

The number and percentage of subjects in each treatment group defined as Complete Wound Healing (CWH) will be tabulated. The null and alternative hypotheses are as follows:

| | |
|---|---|
| Null Hypothesis | H0: %CWH in KB103 = %CWH in Placebo |
| Alternate Hypothesis | H1: %CWH in KB103 > %CWH in Placebo |

Where %CWH is the percentage of wounds with a complete wound healing from baseline at week 8, 10 and 12. A one-sided significance level of 0.05 is considered

The objective of the proportion of DEB wound sites with complete wound healing from baseline (≥90% reduction in wound surface from baseline) will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by the time points (weeks 8, 10 and 12). Under the null hypothesis of no association between complete wound healing and treatment, this test statistic follows a chi-square distribution with 1 degree of freedom. The CMH test provides test of independence for the repeated evaluations at weeks 8,10 and 12.

In addition to testing the null hypothesis, the CMH test also provides an estimate of the common odds ratio to summarize how large the treatment effect is when pooled across the different weeks of the treatment assuming the odds ratio is the same in the different weeks of treatment. This assumption will be tested using the Breslow-Day test and corresponding p-values will be provided. The null hypothesis of the CMH test is that the odds ratios within each week are equal to 1, indicating the complete wound healing proportions are the same.

A summary table with individual treatment proportions and the p-values treatment effect resulting from the chi-square test will be provided. In addition, p-values for independence of weekly evaluations (weeks 8, 10 and 12) using the Breslow-Day test will be provided.

#### 8.1.1.1 Sensitivity and Supplemental Analyses of the Change in Wound Surface Area:

- The analysis performed in Section 8.1.1 for the efficacy objective will be repeated for the PP and LOCF imputed ITT populations.
- The analysis performed in Section 8.1.1 for the efficacy objective will be repeated for weeks 8,10 and 12, separately with and without stratification by time points for observed, PP and LOCF imputed ITT populations.

Other Analyses of the of the Change in Wound Surface Area for observed and LOCF imputed populations Include:

- The analysis performed in Section 8.1.1 for the efficacy objective will be repeated for wound healing with ≥50% reduction in wound surface from baseline with and without stratification by time points.
- The analysis performed in Section 8.1.1 for the efficacy objective will be repeated for wound healing with ≥75% reduction in wound surface from baseline with and without stratification by time points.

- The analysis performed in Section 8.1.1 for the efficacy objective will be repeated for wound healing with 100% reduction in wound surface with and without stratification by time points.

All the efficacy wound healing responses will be summarized by treatment and timepoints for observed and LOCF imputed ITT populations. The percent reduction in wound surface from baseline will be summarized descriptively by treatment and timepoints and treatment comparisons will be performed using the Wilcoxon rank-sum test for observed and LOCF imputed ITT populations. A subject listing will be provided for these reductions in wound surface.

#### 8.1.2 Time to Wound Closure

The time to wound closure defined as the time from the first treatment to complete wound closure (≥90% reduction in wound surface from baseline for 2 consecutive weeks) will be summarized by treatment and compared using analysis of variance with treatment as the fixed effect. This analysis will be performed for both Observed and LOCF imputed ITT populations

#### 8.1.3 Duration of Wound Closure

The duration of wound closure, defined as the time from the complete wound healing to the first reduction in wound surface from baseline to a value below 90%, will be summarized will be summarized by treatment and compared using analysis of variance with treatment as the fixed effect. This analysis will be performed for both Observed and LOCF imputed ITT populations

### 8.2 Other Efficacy Analyses

No formal hypothesis testing will be done for the following exploratory objectives, but will be presented with descriptive statistical summaries, if applicable:

1. Summary results of the expression of human collagen VII as determined by immunofluorescence (IF) by treatment.
2. Summary results of the presence of anchoring fibrils as determined by immunoelectron microscopy (IEM) post-administration.

## 9 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.

### 9.1 Adverse Events

Verbatim descriptions of AEs will be coded using MedDRA, 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 test article. 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 test article, and any serious TEAE leading to premature discontinuation of treatment dose.

The number and percentage of subjects reporting a TEAE in each treatment group 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 test article). The incidence of TEAEs will be summarized by preferred term, sorted by decreasing frequency in the KB103 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 by treatment group, preferred term and severity (mild, moderate, and severe). The incidence of serious TEAEs, and TEAEs leading to premature discontinuation of treatment 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 test article.

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

Immune response adverse events due to a severe immune response determined by the Investigator to be possibly, probably or definitely related to KB103 will be summarized by the number and percentage reporting such AEs along with a subject listing.

## 9.2 Vital Signs

Vital sign measurements include systolic and diastolic blood pressure, pulse, and respiratory rate as well as temperature. Vital signs data is collected at on-site visits.

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.

## 9.3 Physical/Skin Examination

Physical examinations at screening and subsequent follow-up visits are displayed in tabular format displaying number of subjects examined and number and percentage of subjects with abnormalities by physical examination category. A full physical examination of the body systems is included in the physical/skin examination as follows:

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

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.

### 9.4 Laboratory Values

Laboratory data is collected during the study as outlined in the schedule of events (**Appendix 1: Schedule of Events**). 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:

Serum Chemistry / Metabolic Panel

- Albumin
- Alkaline Phosphatase Total
- Anion Gap
- ALT (SGPT)
- AST (SGOT)
- Urea Nitrogen
- Calcium
- Chloride
- Bilirubin, direct & indirect
- CO2
- Creatinine
- Glucose
- Globulin
- Potassium
- Sodium
- Total Bilirubin
- Total Protein

Hematology / Complete Blood Count with Differential

- WBC
- Hemoglobin
- Hematocrit
- Platelet Count
- MCV RDW
- RBC MCH
- MCHC
- Neutrophils, % and abs
- Lymphocytes, % and abs
- Monocytes, % and abs
- Eosinophils, % and abs
- Basophils, % and abs

The absolute and change from baseline laboratory data from the above evaluations will be summarized by treatment and evaluation timepoint. Baseline is defined as the lab value closest to and prior to the first dose of either treatment.

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).

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

- Urine and Pregnancy Test Results
- HSV Antibody Assay
- Collagen VII Antibody Assay
- Viral Shedding

## 10 Other Relevant Data Analyses/Summaries

### 10.1 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 analyzing 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 in each category will be presented by treatment group for the ITT population. A major deviation is defined as one that potentially affects the efficacy and/or safety analyses.

## 10.2 Medical/Procedural History

Medical/procedural history is collected during the baseline visit. Medical/procedural history data will be summarized by preferred term and a subject listing will be provided.

## 10.3 Prior and Concomitant Medications

The prior and concomitant medications will be summarized and listed by treatment. Medications will be coded with WHO and categorized as either prior medications (any medication that was started before the first application of KB103), or concomitant medications (medication continued or newly started on or after the date of first application of KB103). A subject listing also will be provided for all prior and concomitant medications.

# 11 Appendices

## 11.1 Appendix 1: Schedule of Events

### 11.1.1 Protocol Version 1.0

| | Visit | Prescreen | Screen | 1 | | 2 | 3[1] | | 4[2] | 5 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week | N/A | -2 | 0 | | 2 | 4 | | 6 | 12 | |
| | Day | N/A | -14 | 0 | 2 | 14 | 28 | 30 | 42 | 84 | |
| **Event** | Window | N/A | ± 2wk | N/A | N/A | ± 2d | ± 2d | N/A | ± 2d | ± 5d | LTFU |
| **KB103 Administration[3]** | | | | X | X | | X | X | | | |
| **Placebo Administration** | | | | X | X | | X | X | | | |
| Phone Screen | | X | | | | | | | | | |
| ICF / Assent / HIPAA | | | X | | | | | | | | |
| Inclusion / Exclusion Criteria | | X | X | X | | | | | | | |
| Demographics | | X | X | | | | | | | | |
| Medical / Medication History | | X | X | X | | | | | | | |
| Concomitant Medications | | | | X | X | X | X | X | X | X | |
| Adverse Events | | | | X | X | X | X | X | X | X | X |
| Physical Exam | | | X | X | | | | | | X | |
| Vital Signs | | | X | X | X | X | X | X | X | X | |
| Digital Imaging of Wounds[4] | | | X | X | X | X | X | X | X | X | |
| Wound Assignment | | | | X | | | | | | | |
| Pre-dose tattoos | | | | X | | | | | | | |
| Bacterial Culture | | | | As Needed | | | | | | | |
| Blood and Urine Tests: Urine Pregnancy Test | | | X | X | | | | | | | |
| Blood and Urine Tests: Hematology & Chemistry | | | X | X | | X | | | X | X | |
| Blood and Urine Tests: HIV, Hep B, Hep C Testing | | | X | | | | | | | | |
| Blood and Urine Tests: RCV evaluation | | | | X | | X | | | | | X |
| Blood and Urine Tests: COL7 Antibody Assay[5] | | | X | | | X | | | | X | |
| Blood and Urine Tests: HSV Antibody Assay[5] | | | | X | | X | | | | X | |
| Blood and Urine Tests: Viral shedding assay, urine[6] | | | | X | X | X | X | X | X | X | |
| Blood and Urine Tests: Viral shedding assay, blood[6] | | | | X | X | X | X | X | X | X | |
| Blood and Urine Tests: Genetic Testing | | | X[7] | | | | | | | | |
| **Day** | | PS | S | 0 | 2 | 14 | 28 | 30 | 42 | 84 | |
| Wound Biopsies: IF for COL7 | | | | | X | X | | | X | X | |
| Wound Biopsies: qRT-PCR for mRNA and qPCR for viral vector DNA[8] | | | | | X | | | X | | | |
| Wound Biopsies: IEM for Anchoring Fibrils | | | | | | X | | | X | X | |
| Intact Skin Biopsies: IF for COL7 | | | X[7] | X | X | X | | X | X | X | |
| Intact Skin Biopsies: qRT-PCR for mRNA and qPCR for viral vector DNA[8] | | | X[7] | X | X | | | X | | | |
| Intact Skin Biopsies: IEM for Anchoring Fibrils | | | | X | | X | | | X | X | |

X = Perform the procedure before and after dosing.

X = Optional biopsy. Reference Section 7.2.

[1] If the target wound is closed at Day 28, do not administer KB103 topically.
[2] If the target wound is closed at Day 28 and then reopens by Day 42, topical KB103 is re-administered at this visit.
[3] Topical and intradermal KB103 administration. Skin must be tattooed prior to administration.
[4] On dosing days, image the KB103 and control wounds both pre- and post-dose.
[5] May be waived at Day 84 if prior results are negative.
[6] On dosing days, collect viral shedding samples both pre-dose and 2 hours post-dose.
[7] Only if needed for diagnosis.
[8] mRNA and DNA biopsies will minimized to the extent possible (based on previous knowledge) in children

### 11.1.2 Protocol Version 2.2

| Month | 1 | | | | | | 2 | 3 | 3+ |
|---|---|---|---|---|---|---|---|---|---|
| Visit | **Screen/BL[1]** | **1[2]** | | | | **2** | **3** | **4** | **-** |
| Day | **0** | **1** | **2** | **3** | **4** | **5** | **30** | **60** | **90** | **91-180** |
| Window | n/a | | | | | | +/-7d | +/-7d | +/-7d | n/a |
| Genetic Testing | X | | | | | | | | | |
| Bacterial Culture[3] | -- -- -- -- -- | -- | -- | -- | -- | -- | -- -- -- | -- -- -- | -- -- -- | -- -- -- |
| Urine Pregnancy Test[3] | X | -- | -- | -- | -- | -- | -- -- -- | -- -- -- | -- -- -- | -- -- -- |
| HIV, Hep B, Hep C Testing[3] | X | -- | -- | -- | -- | -- | -- -- -- | -- -- -- | -- -- -- | -- -- -- |
| Hematology & Chemistry[4] | X | | | | | | X | | | |
| COL7 Antibody Assay[4] | X | | | | | | X | | | |
| HSV Antibody Assay[5] | X | | | | | | X | | | |
| Wound Assignment | X | | | | | | | | | |
| Pre-dose tattoos | X | | | | | | | | | |
| Concomitant Medications | | X | X | X | X | X | X | X | | |
| Adverse Events | | X | X | X | X | X | X | X | | |
| Viral shedding (skin swab) | | | | | | X | X | X[6] | | |
| Physical Exam | X | | | | | | | | X | |
| PRO Assessment | X | | | | | X | X | X | X | |
| Global Wound Assessment | X | | | | | X | X | X | X | |
| Vital Signs | X | X | X | X | X | X | X | X | X | |
| At-home wound imaging[7] | | | | | | | X | X | X | X |
| On-site wound imaging | X | X | X | X | X | X | X | X | X | |
| KB103 and Placebo Administration | | X | X | X | X | X | X | X | X | |
| Wound biopsy[8] | | | | | | | X | X | X | |

[X] = Optional visit for subjects whose wounds have opened.

[1] See Section 5.2.2 for a full list of screening procedures

[2] Diagnostic screening procedures can be performed prior to the visit as indicated below

[3] Conducted as clinically indicated

[4] After screening, except for Day 30, performed only as clinically indicated to minimize blood draws

[5] May be waived after Day 4 if prior results are negative.

[6] Viral shedding at Day 60 will only be performed if positive at Day 30

[7] Subjects will be instructed to image the target wounds during bandage changes (approximately twice per week).

[8] Biopsies are performed at the discretion of the Investigator and Sponsor. One of the two target wounds should be designated to receive all of the biopsies

### 11.1.3 Protocol Version 3.1

| Visit | 1 | | | | 2 | 3 | 4 | |
|---|---|---|---|---|---|---|---|---|
| Day | 0/Screen/BL[1] | 1 | 3 | 15 | 30 | 60[2] | 90 | 91-180[3] |
| Genetic Testing | X | | | | | | | |
| Bacterial Culture[4] | X | X | | X | X | X | X | X |
| Urine Pregnancy Test[3] | X | X | | | | | X | |
| HIV, Hep B, Hep C Testing[3] | X | X | | | | | X | |
| Hematology & Chemistry[5] | X | | | | X | | X | X |
| COL7 Antibody Assay[4] | X | | | | X | | X | |
| HSV Antibody Assay[6] | X | | | | X | | X | |
| Wound Assignment | X | | | | | | | |
| Pre-dose tattoos | X | | | | | | | |
| Concomitant Medications | | X | X | X | X | X | X | X |
| Adverse Events | | X | X | X | X | X | X | X |
| Viral shedding (skin swab) | X | X | X | X | X | X | X | X |
| Physical Exam | X | | | | | | X | |
| PRO Assessment | X | | X | X | X | X | X | X |
| Global Wound Assessment | X | | X | X | X | X | X | X |
| Vital Signs | X | | X | X | X | X | X | X |
| At-home wound imaging[7] | | | | X | | | | |
| On-site wound imaging | X | X | X | X | X | X | X | |
| At-home topical IP administration | | | | X | | | | |
| On-site topical IP Administration | | X | | | X | X | X | |
| ID KB103 admin to intact skin[8] | | X | | | | | | |
| Intact skin biopsy[9] | | | X | X | X[9] | X | | |
| Wound biopsy[10] | X | | | X | X | X | X | X |

| | |
|---|---|
| X | Optional procedures. Early results may negate the need for ID injection and biopsies to intact skin in later patients. |

[1] Diagnostic screening procedures can be performed prior to the visit as indicated below

[2] Day 15 and 60 visits are required for patients that receive ID injections to intact skin at Day 1.

[3] Follow-up visits after Day 90 are conducted as the subject is able at the discretion of the Investigator

[4] Conducted as clinically indicated

[5] After screening/baseline, performed only as clinically indicated to minimize blood draws

[6] May be waived after the first follow-up visit if prior results are negative.

[7] Subjects will be instructed to image the target wounds during bandage changes (approximately twice per week). [8] Optional ID administration for subjects at least 13 years old. Performed at the discretion of the Investigator. Early results may negate the need for ID injection and biopsies to intact skin in later patients.

[9] Two intact skin locations will be biopsied on Day 30

[10] Biopsies are performed at the discretion of the Investigator and Sponsor.

### 11.1.4 Protocol Version 4.0

| | | Cycle #1 | | OP[1] #1 | Cycle #2 | | OP #2 | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Dosing every 2-3 days | | Home images | Dosing every 2-3 days | | At-home monitoring and monthly on-site visits | | | |
| | | ≤ 3 months | | Variable | ≤ 3 months | | 3 months after C2[2] | | | |
| **Procedures** | **Screen/ BL** | **Dose days** | **Last dose** | **OP 1** | **Dose days** | **Last dose** | **C2 +1mo** | **C2 +2mo** | **C2 +3mo** | **LTFU** |
| Urine Pregnancy Test | X | | | | | | | | | |
| HIV, Hep B, Hep C Testing | X | | | | | | | | | |
| Hematology & Chemistry[3] | X | | X | | | X | X | X | X | |
| COL7 Antibody Assay | X | | X | | | X | X | X | X | |
| HSV Antibody Assay | X | | X | | | X | X | X | X | |
| Wound Area Assignment | X | | | | | | | | | |
| Pre-dose Tattoos | X | | | | | | | | | |
| Concomitant Medications | X | X | X | | X | X | X | X | X | X |
| Adverse Events | X | X | X | | X | X | X | X | X | X |
| Viral shedding (skin swab) | X | X | X | | X | X | X | X | X | |
| Viral shedding (blood and urine) | X | | X | | | X | X | X | X | |
| Physical Exam | X | | | | | | | | X | |
| PRO Assessment | X | X | X | | X | X | X | X | X | |
| Global Wound Assessment | X | X | X | | X | X | X | X | X | |
| Vital Signs | X | X | X | | X | X | X | X | X | |
| At-home wound imaging[4] | | X | X | X | X | X | X | X | X | |
| On-site wound imaging | X | X | X | | X | X | X | X | X | |
| Wound stenciling | X | X | X | | X | X | X | X | X | |
| IP Administration | X | X | X | | X | X | X | X | X | |
| Wound biopsy[5] | X | | X | | | X | X | X | X | |

[1] OP = Observation Period

[2] Visit windows for the OP2 visits are +/- 1 week

[3] After screening/baseline, performed only as clinically indicated to minimize blood draws

[4] At-home wound imaging occurs throughout the study during bandage changes

[5] Biopsies are performed at the discretion of the Investigator and Sponsor.

## 11.2 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.