Protocol SD-004

An Open Label Extension, Multi-Center, Study to Evaluate the Safety of SD-101 Cream in Subjects with Epidermolysis Bullosa

Statistical Analysis Plan

Final Version 2.0

Date 20Dec2018

Confidential

Sponsor:
Scioderm, Inc.
An Amicus Therapeutics Company
4601 Creekstone Drive
Suite 160
Durham, NC 27703

REVISION HISTORY

Version	Date	Revision Author	Comments
Draft 0.2	30June2016	Amicus	Initial release
Final 1.0	26July2017		Updates based on protocol amendment 3 and standard safety text. Updates of safety section for consistency with pivotal study SD-005.
Final 2.0	20December2018		Updates based on Dear Doctor Letter of June 4, 2018. Deletion of analysis of skin reactions and concomitant medication of interest.

SIGNATURE PAGE

Author:			
	Amicus		Date
			9/JAN/2019
	Amicus Therapeutics, Inc.		
Approved by:			

Amicus

Date: 9 /JAN/ 2019

Amicus Therapeutics, Inc.

Amicus

Date: 14 / JAN 2019

Amicus Therapeutics, Inc.

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
BSA	Body surface area
BSAI	Body surface area index
EB	Epidermolysis bullosa
ITT	Intent-to-treat
Placebo	Contains 0% allantoin
PT	Preferred term
SAE	Serious adverse event
SD-101	Drug Product formulation
SD-101-3.0	Contains 3% allantoin
SD-101-6.0	Contains 6% allantoin
Placebo –> SD-101-6.0	Rolled over from 003 study placebo group (referred to as SD-101-0.0) in the protocol)
SD-101-3.0 –> SD-101-6.0	Rolled over from 003 study SD-101-3.0 group
SD-101-6.0 –> SD-101-6.0	Rolled over from 003 study SD-101-6.0 group
SOC	System organ class
TEAE	Treatment-emergent adverse event

2. INTRODUCTION

This statistical analysis plan (SAP) defines the methodology and strategy for performing safety and efficacy analysis for subjects with epidermolysis bullosa (EB) in the study SD-004. This SAP is based on the protocol amendment 3, version 4 dated 25 January 2017.

3. STUDY OBJECTIVE

The primary objective is to demonstrate the long-term safety of SD-101-6.0 in subjects with Simplex, Recessive Dystrophic, and Junctional non-Herlitz epidermolysis bullosa.

The secondary objectives are to assess the efficacy of SD-101-6.0 in terms of the change in body surface area index (BSAI) of lesional skin in subjects rolling over from the SD-003 study.

4. STUDY DESIGN

4.1. General Design

This is an open label extension, multi-center study to assess the continued safety of SD-101-6.0 cream (containing 6% allantoin) in treating subjects with epidermolysis bullosa simplex (EBS), recessive dystrophic epidermolysis bullosa (RDEB), and junctional non-Herlitz epidermolysis bullosa (JEB).

SD-101-6.0 cream has been applied topically, once a day to the entire body for the duration of the study. Subjects who successfully completed the SD-003 study have been eligible to roll over into the SD-004 study. The Baseline Visit 1 occurred at the final visit date for SD-003. The body surface area (BSA) assessment from the final SD-003 study was used as the baseline information at Visit 1 for the SD-004 study. The subject has returned to the study site once every 3 months for Visit 2 (14 days ± 7 days from baseline) through Visit 14 (1080 days ± 7 days from baseline) to have BSA assessed. Body surface area has been assessed at all subsequent scheduled study center visits. Scheduled study center visits has occurred every 6 months after Visit 14 (Visits 16, 18, 20, etc.). After completion of Visit 14, the next subject visit (Visit 15) is to be a phone call from the site to the subject. Telephone visits are to occur every 6 months thereafter (Visits 17, 19, 21, etc.) and include assessment of adverse events (AEs) and concomitant medications only. At the Investigator's discretion, the subject may be asked to complete a study center visit in place of a phone call visit. If a study center visit is requested, no additional assessments (other than collection of information on AEs and concomitant medications) will be required (see Section 6.1 – Schedule of Evaluations for details).

4.2. Method of Assignment of Subjects to Treatment Groups

There will only be one treatment group so subjects will not be randomized to treatment. All subjects will receive SD-101-6.0.

4.3. Blinding

This was an open label trial; therefore, blinding was not performed.

4.4. Determination of Sample Size

All subjects who complete the protocol SD-003 (on study drug at Visit 5) and who meet all eligibility criteria, may be eligible to enter this open label extension. Up to approximately 48 subjects are expected to roll over from Study SD-003 into this open label extension.

5. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

5.1. Changes in the Conduct of the Study

There were three amendments to the SD-004 protocol. The first amendment was finalized on 27 February 2015, the second amendment was finalized on 2 December 2015, and the third amendment was finalized on 25 January 2017. The latest amendment extended the study duration and introduced intermittent 3 month phone call visits every 6 months starting at Month 36. On June 4, 2018, a Dear Doctor Letter was sent instructing all sites to discontinue the applications of SD-101 cream immediately, bring the subjects back to the sites for the end of study visit, and collect all the remaining tubes of SD-101. This was because the manufacturer of SD-101 had received a warning letter from the FDA for several violations of GMP regulations that, although not mentioning SD-101, may have resulted in the adulteration of SD-101.

5.2. Changes from the Analyses Planned in the Protocol/CIP

There were no changes in the analysis planned in the protocol of the study at the time of preparing this SAP.

6. BASELINE, EFFICACY, AND SAFETY EVALUATIONS

6.1. Schedule of Evaluations

Table 1: Assessments Conducted at Each Scheduled Visit

Procedure Visit	**1 Screening/ Baseline**	**2 Week 2**	**3 Month 3**	**4 Month 6**	**5 Month 9**	**6 Month 12**	**7, 9, 11, and 13 Months 15, 21, 27, and 33**	**8, 10, 12, and 14 Months 18, 24, 30, and 36**	**15 (odd visits) Month 39 Phone Call**	**16 (even visits) Month 42 Site Visit**	**Alternate Phone Call and Site Visit until Final Study Visit/Early Termination[a]**	**Final Study Visit/Early Termination**
Study Day (± 7 Days)	**0**	**14**	**90**	**180**	**270**	**360**	**450, 630, 810, and 990**	**540, 720, 900, and 1080**	**1170**	**1260**	**-**	**-**
Informed consent/ assent signed	X											
Inclusion/ Exclusion assessment	X											
Demographic, medical, and medication history	X								X	X		X
Physical examination[b]	X											X
Height, weight, and temperature	X											X

Table 1: Assessments Conducted at Each Scheduled Visit (Continued)

Procedure Visit	**1 Screening/ Baseline**	**2 Week 2**	**3 Month 3**	**4 Month 6**	**5 Month 9**	**6 Month 12**	**7, 9, 11, and 13 Months 15, 21, 27, and 33**	**8, 10, 12, and 14 Months 18, 24, 30, and 36**	**15 (odd visits) Month 39 Phone Call**	**16 (even visits) Month 42 Site Visit**	**Alternate Phone Call and Site Visit until Final Study Visit/Early Termination[a]**	**Final Study Visit/Early Termination**
Assess BSAI of lesional skin[c]	X	X	X	X	X	X	X	X		X		X
Urine pregnancy test (females of child-bearing potential only)[d]	X			X		X		X		X		X
Dispense SD-101-6.0[e]	X	X	X	X	X	X	X	X		X		X
Collect SD-101-6.0 for the purpose of drug accountability		X	X	X	X	X	X	X		X		X
Collect all SD-101-6.0												X
Monitor adverse events	X	X	X	X	X	X	X	X	X	X		X

Table 1: Assessments Conducted at Each Scheduled Visit (Continued)

Procedure Visit	1 Screening/ Baseline	2 Week 2	3 Month 3	4 Month 6	5 Month 9	6 Month 12	7, 9, 11, and 13 Months 15, 21, 27, and 33	8, 10, 12, and 14 Months 18, 24, 30, and 36	15 (odd visits) Month 39 Phone Call	16 (even visits) Month 42 Site Visit	Alternate Phone Call and Site Visit until Final Study Visit/Early Termination[a]	Final Study Visit/Early Termination
Monitor use of concomitant medications	X	X	X	X	X	X	X	X	X	X		X

Abbreviations: BSA = Body surface area; BSAI = Body surface area index

[a.] After completion of Visit 14, the subject will return to the site once every 6 months (Visits 16, 18, 20, etc.), with the intermittent 3 month visits conducted via telephone (Visits 15, 17, 19, etc.). Telephone visits will include assessment of adverse events and concomitant medications only. At the Investigator's discretion, the subject may be asked to complete a study center visit in place of a phone call visit. If a study center visit is requested, no additional assessments (other than collection of information on adverse events and concomitant medications) will be required.

[b.] A complete physical examination will be performed at the final visit. The physical examination performed at the final visit for SD-003 will be utilized as the baseline assessment for SD-004.

[c.] The BSA assessment will be performed at Visits 2 through 14 and at all subsequent scheduled study center visits. The BSA assessment performed at the final visit for SD-003 will be utilized as the baseline assessment for SD-004.

[d.] Urine pregnancy test will be performed at Visits 4, 6, 8, 10, 12, 14, and at all subsequent scheduled study center visits. The urine pregnancy test performed at the final visit for SD-003 will be utilized for entry into SD-004.

[e.] Re-dispense any unused SD-101 cream. Ensure the subject is dispensed sufficient SD-101 cream until the next study visit.

6.2. Time Point Algorithms

6.2.1. Study Day

The date of informed consent/assent (Visit 1), will be considered Study Day 0. Days prior to Study Day 1 will be negative. Study days will be calculated as follows only when the full assessment date is known (ie, partial dates will have missing relative days).

Study day will be calculated as follows:

Date of Assessment – Date of Informed Consent.

For relative day on study drug, the date of first study drug administration will be used. The first date of drug administration will be either the randomization day or the first day of study drug administration recorded on diary, if the study drug was not administered during the randomization office visit.

The relative day on study drug will be calculated as follows:

Date of Assessment – Date of the First Study Drug Administration + 1.

6.2.2. Windows

For analysis purposes, the visit numbers will be allotted into windowed visits, as illustrated in the following table:

Table 2: Analysis Windows

Week	Visit	Scheduled Study Day	Visit Window for Analysis (Days)
Screening/Baseline	Visit 1	0	Day -13 to Day 0
Week 2	Visit 2	14	Day 1 – Day 60
Month 3	Visit 3	90	Day 61 – Day 135
Month 6	Visit 4	180	Day 136 – Day 225
Month 9	Visit 5	270	Day 226 – Day 315
Month 12	Visit 6	360	Day 316 – Day 405
Month 15	Visit 7	450	Day 406 – Day 495
Month 18	Visit 8	540	Day 496 – Day 585
Month 21	Visit 9	630	Day 586 – Day 675
Month 24	Visit 10	720	Day 676 – Day 765
Month 27	Visit 11	810	Day 766 – Day 855
Month 30	Visit 12	900	Day 856 – Day 945

Table 2: Analysis Windows (Continued)

Week	Visit	Scheduled Study Day	Visit Window for Analysis (Days)
Month 33	Visit 13	990	Day 946 – Day 1035
Month 36	Visit 14	1080	Day 1036 – Day 1125
Month 39	Visit 15	1170	Day 1126 – Day 1215
Month 42	Visit 16	1260	Day 1216 – Day 1405
…..			
Final Visit			Up to Completion

If two visits fall within the window, then the closest one will be selected. If two visits are equal distance from the nominal visit day, then the first one is used.

6.3. Baseline Definition and Assessments

6.3.1. Baseline Definition

The baseline visit (Visit 1) will occur at Visit 5 for SD-003.

6.3.2. Baseline Assessments

The following screening and baseline assessments will be conducted prior to initial application of study treatment:

- Informed consent/assent signed and dated
- Inclusion/exclusion assessment
- Medical and medication history (including disease subtype) obtained from SD-003. Adverse events continuing in Study SD-003 and those originating within the gap between Studies SD-003 and SD-004 will be transcribed into Medical History. All AEs experienced in SD-003 and medical events occurring between the end of SD-003 and the enrollment into SD-004 after completion of SD-003 should be noted in the medical history for SD-004 at Visit 1 only.
- Demographics (date of birth, race, gender, ethnicity) obtained from SD-003
- Height/length, weight, and temperature obtained from final visit of SD-003
- Physical examination obtained from final visit of SD-003
- BSAI of lesional skin obtained from final visit of SD-003
- The urine pregnancy test performed at the final visit for SD-003 will be utilized for entry (Visit 1) into SD-004.
- Dispense sufficient SD-101-6.0 until next study visit

6.4. Efficacy Assessments

6.4.1. Change in Body Surface Area Index (BSAI)

Change in lesional skin based on BSA estimates at Week 2, and Month 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, and then every 6 months, as compared to baseline will be measured using the BSAI, where change is defined as the corresponding month value minus the baseline value.

The BSAI is a global measure of disease extent with weighting factors. The BSA affected with lesional skin will be calculated at baseline and at each visit to assess the total affected area before and after using the product. The BSAI of lesional skin will be assessed as listed in Section 11.1.

6.5. Safety Assessments

6.5.1. Extent of Exposure and Compliance to Study Treatment

SD-101-6.0 will be applied once a day to the entire body for the study duration. No daily use data are collected in this study.

6.5.2. Adverse Events

Treatment-emergent adverse events (TEAEs) are any untoward medical occurrence in a subject, administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Adverse events may include the onset of new illness and the exacerbation of pre-existing conditions. Adverse events will be collected after signing the informed consent/assent through the last study visit. If there is a gap between the completion of the Study SD-003 and the start of Study SD-004, AEs starting after the last study day or changing in severity or relationship to treatment within the gap will be recorded in the medical history for study SD-004. Continuing AEs will be also captured in medical history for the extension study SD-004. All AEs will be TEAEs unless they started or increased in severity or relationship to treatment between signing the informed consent and the first dose of study drug in Study SD-004.

The investigator's verbatim term of both serious and non-serious AEs will be mapped to system organ class (SOC) and preferred terms (PTs) using the 19.1 or later version of the Medical Dictionary for Regulatory Activities (MedDRA). Partial dates will be imputed as the following:

1. If year is not missing and is after the year of first application of study drug:
    a. If Month is missing, then Month will be imputed as January.
    b. If Day is missing, then Day will be imputed as the first of the month.

2. If year is not missing and is the same as the year of the first application of study drug:
    a. If Month is missing, then impute the Month as the month of the first application of study drug.
    b. If Day is missing but Month is on or after the month of first application of study drug, then impute Day as the first day of the month.
    c. If the Day and Month are missing then impute Day and Month as the Day and Month of the first study drug application.
3. If year is missing, then impute the year as the year of the first study drug application:
    a. If Month is missing, then impute the Month as the Month of the first study drug application.
    b. If Day is missing, then impute the Day as the day of the first study drug application.
4. If the start date is completely missing, but the AE is either ongoing or the stop date is after the first date of drug application, then impute the start date as the first date of study drug application.
5. If using the above rules, the stop date is before the start date, then leave the stop date missing and assume that AE is treatment-emergent for the purpose of the analysis.

Completely missing stop dates will not be imputed. The partial stop dates will be imputed as follows:

1. If the year is missing, the stop date will not be imputed.
2. If the month is missing, then the month will be imputed as December.
3. If the day is missing, then the day will be imputed as the last day of the month.

6.5.3. Clinical Laboratory Evaluations

The urine pregnancy test performed at the final visit for SD-003 will be utilized for entry (Visit 1) into SD-004 only if the visits occur on the same day, otherwise, urine pregnancy test will be performed at Visit 1. Urine pregnancy tests for female subjects of child bearing potential (sensitivity at least 25 mIU/mL) will also be performed every 6 months (Table 1) through final office visit.

6.5.4. Physical Examination Including Height/Length, Weight, and Temperature

The physical examination performed at the final visit for SD-003 will be utilized as the baseline assessment for SD-004. An additional physical examination will be done by a physician at the final office visit. The following sites will be examined: head, eyes, ears, nose, throat, neck, chest, lungs, heart, abdomen, skin, and lymph nodes; and the following systems will be assessed: musculoskeletal and neurological. Weight, height/length, and temperature will be recorded.

7. STATISTICAL METHODS

7.1. General Methodology

The final analysis after the study completion will be preceded by at least one interim analysis.

Data will be summarized by treatment groups (based on SD-003 study treatment: Placebo –> SD-101-6.0, SD-101-3.0 –> SD-101-6.0, and SD-101-6.0 –> SD-101-6.0) and overall (where appropriate). Summary and analysis tables will include number of subjects (n), mean, standard deviation, median, minimum, and maximum values for all continuous variables. When appropriate, two-sided 95% confidence intervals may be used.

In summary tables of categorical variables, counts and percentages will be presented. The denominator for each percentage will be the number of subjects within the population, treatment group, or subgroup as specified in table templates.

All analyses for efficacy will be performed using the intent-to-treat (ITT) population and all safety analyses will be performed using the safety population. No comparison between treatment groups will be performed. The comparison to baseline will be done by visit in Placebo –> SD-101-6.0 group, SD-101-3.0 –> SD-101-6.0, and SD-101-6.0 –> SD-101-6.0 group. All hypothesis testing will be two-sided. P-values less than 0.001 will be reported as < 0.001 in summary tables.

All statistical analysis will be performed using SAS® v9.2 or higher.

7.2. Adjustments for Covariates

No covariates are planned to be used in the analyses for this study.

7.3. Handling of Dropouts or Missing Data

Dropout subjects will not be replaced in this study. Missing data will not be imputed unless specified otherwise in the following section.

7.4. Multi-center Studies and Pooling of Centers

Data will be pooled across all study sites. The justification for pooling is made on the basis of three important factors: 1) all study sites use one common protocol, 2) sites are actively and adequately monitored to ensure protocol compliance, 3) all sites use a common data reporting method and data collection procedures. [(1)]

7.5. Multiple Comparisons/Multiplicity

No multiple comparisons and multiplicity adjustment will be used for this study.

7.6. Examination of Subgroups

Safety summaries will be presented by subgroups of gender, and age (0 to 27 days, 28 days to < 2 years, 2 years to < 12 years, 12 years to ≤ 18 years, > 18 years), , independently.

8. STATISTICAL ANALYSIS

8.1. Disposition of Subjects

The number and percentage of subjects who were enrolled, treated, and completed the study will be summarized. Similar summaries will be provided for those subjects who discontinued from the study prematurely. For those subjects who discontinue early, the reasons for discontinuing including general discontinuations at sponsor's request will also be summarized. The disposition of all subjects will be listed.

Data on screening failures (subjects who signed informed consent but were not entered into the trial) will be collected with a yes or no on the CRF and will be presented in a listing.

8.2. Protocol Deviations

Number and percentage of subjects with major protocol deviations will be summarized for each treatment group in the ITT population. A listing of subjects with major protocol deviations will also be provided.

8.3. Analysis Populations

8.3.1. Intent-to-Treat (ITT) Population

The ITT population will be defined as all subjects who have rolled over from SD-003.

8.3.2. Safety Population

The Safety population is defined as all randomized subjects who applied/were administered the study medication at least once.

The ITT population will be used for all efficacy analyses. The Safety population will be used for all safety analyses.

If the Safety population and ITT populations are identical, then the efficacy and safety analyses will be performed using the ITT population only.

8.4. Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented for the ITT population.

Continuous variables such as subject age, weight, height, body mass index (BMI), BSAI for lesional skin, and temperature will be summarized as described previously. Categorical variables

such as subject gender, race, ethnicity, age group (0 to 27 days, 28 days to < 2 years, 2 years to < 12 years, 12 years to ≤ 18 years, > 18 years), race, and EB type will be summarized using number of observations and percentages for each category.

Medical history, including disease history will be summarized and listed.

8.5. Prior and Concomitant Therapy

The World Health Organization (WHO) Drug Dictionary of March 2017 will be used to classify medications. The WHO Drug Dictionary version might be updated in the future analyses and if so it will be properly footnoted on all tables and listings. Any medication taken before and continuing after first application of SD-101-6.0 in the study SD-004 is considered a concomitant medication. Any medication given before first application but discontinued prior to first application is considered a prior medication. A medication can be considered both prior and concomitant. Medications missing both start and stop dates, or having a start date prior to the last dose of study drug and missing the stop date, or having a stop date after the start of study drug and missing the start date, will be considered concomitant. Medications will also be considered concomitant if partial start and stop dates are present but it cannot be determined if the medication ended prior to start of study drug.

A summary table will be provided in the safety population:

Number and percentage of subjects who had concomitant therapies/medications by ATC text and WHO drug name

Previous medications will be listed.

8.6. Analysis of Efficacy Parameters

8.6.1. Analysis of Body Surface Area Index (BSAI)

No comparison between treatment groups will be performed. The comparison to baseline will be done by visit in Placebo –> SD-101-6.0 group and in SD-101-3.0 –> SD-101-6.0 group using the paired t-test.

- Change in extent of lesional skin based on BSAI at each visit compared to baseline.

  To evaluate post-baseline BSAI of lesional skin, both change from baseline and percentage change from baseline will be explored using descriptive statistics. Change from baseline will be calculated as the post-baseline measurement minus the baseline value. Percentage change from baseline will be calculated as the change from baseline divided by the baseline value times 100.

  Graphs of the mean change and mean percentage change from baseline over time will also be presented.

8.7. Analysis of Safety

8.7.1. Extent of Exposure

The number of days on the study will be considered number of days of exposure. It will be summarized using descriptive statistics by treatment group and overall. Descriptive statistics will also be provided for duration of exposure into categorical summary of < 1 year, 1 to 2 years, and > 2 years.

8.7.2. Adverse Events by Preferred Term and System Organ Class

For the first interim analysis, serious AEs will be mapped to SOC and PTs using the 19.1 version of MedDRA.

If there is a gap between the completion of the study SD-003 and the start of the study SD-004, AEs starting after the last study day or changing the severity or relationship to treatment within the gap will be counted as medical history for the extension study SD-004. Continuing AEs will also be captured in medical history for the extension study SD-004. If the severity or relationship to treatment changed on or after the first dose of study medication, then that AE is considered a TEAE after that change.

8.7.3. Summaries of Adverse Event Incidence Rates for All Subjects

The number and percentage of subjects who experienced TEAEs will be presented by PT within SOC for each treatment group. Treatment-emergent AEs will be similarly presented by severity (mild, moderate, and severe), by relationship to study drug (unrelated, definite, probable, and possible) and by outcome of events. Additionally, the number of TEAEs (as opposed to the number and percentage of subjects) will be presented by treatment group.

The proportion of subjects with TEAEs will also be presented by the following subgroups of gender, and age (0 to 27 days, 28 days to < 2 years, 2 years to < 12 years, 12 years to ≤ 18 years, > 18 years); independently. Subgroups for age are defined based at the subject's age at Baseline.

To count the number of subjects who experienced each TEAE, a subject experiencing the same TEAE multiple times will only be counted once for the corresponding PT. Similarly, if a subject experiences multiple TEAEs within the same SOC, the subject will be counted only once for that SOC. If a subject experiencing more than one TEAE within different severity or relationship categories within the same SOC/PT, only the worst case (worst severity and related TEAE) will be reported. Treatment-emergent AEs will be sorted alphabetically by SOC, and within each SOC, the PT will be presented by decreasing order of total frequency.

For TEAE summary by outcome, if a subject experienced more than one TEAE, the worst outcome will be counted under that subject. If a subject experienced more than one outcome within a SOC (or PT), the subject is only counted once under worst outcome in that SOC (or PT).

In addition, all AEs will be provided by study site and by treatment group, in a listing, which will include the subject identifier, the PT, the reported term, the severity, the seriousness, the action taken, the outcome, the causality, the date onset, date of onset relative to the date of the first

study drug administration, date of resolution, date of resolution related to the first study drug administration, and the TEAE duration (resolution date –onset date + 1).

Additionally, the incidence and the number of non-serious TEAEs will be presented by treatment group.

Non-treatment-emergent AEs, if any, will be listed.

8.7.4. Missing Adverse Event Onset, Severity, and Relationship

8.7.4.1. Missing or Partial Adverse Event Dates

The following list describes how partially missing date information will be handled as it relates to partial or missing start dates. Partial dates will be imputed as follows:

1. If year is not missing and is after the year of first application of study drug:
    a. If Month is missing, then Month will be imputed as January.
    b. If Day is missing, then Day will be imputed as the first of the month.
2. If year is not missing and is the same as the year of the first application of study drug:
    a. If Month is missing, then impute the Month as the month of the first application of study drug.
    b. If Day is missing but Month is on or after the month of first application of study drug, then impute Day as the first day of the month.
    c. If the Day and Month are missing, then impute Day and Month as the Day and Month of the first study drug application.
3. If year is missing, then impute the year as the year of the first study drug application:
    a. If Month is missing, then impute the Month as the Month of the first study drug application.
    b. If Day is missing, then impute the Day as the day of the first study drug application.
4. If the start date is completely missing, but the AE is either ongoing or the stop date is after the first date of drug application, then impute the start date as the first date of study drug application.
5. If using the above rules, the stop date is before the start date, then leave the stop date missing and assume that AE is treatment-emergent for the purpose of the analysis.

Completely missing stop dates will not be imputed. The partial stop dates will be imputed as follows:

1. If the year is missing, the stop date will not be imputed.
2. If the month is missing, then the month will be imputed as December.
3. If the day is missing, then the day will be imputed as the last day of the month.

Imputed dates will be flagged in the individual supportive subject listings.

8.7.4.2. Missing Severity

If severity is missing for any AE, then its severity will be classified as missing in the summary tables.

8.7.4.3. Missing Relationship

If the assessment of relationship of the AE to study treatment is missing for any AE, then it will be presented as missing in the listings and in the summary tables.

8.7.5. Summaries of Adverse Incidence Rates for Serious Adverse Events (SAE), Adverse Event Dropouts, and Death

During the treatment period, the number and percentage of subjects who experienced treatment-emergent SAEs (TESAEs) and separately TEAEs leading to withdrawal from the study will be presented by PT within each SOC for each treatment. Treatment-emergent SAEs and separately TEAEs resulting in withdrawal from the study will be similarly presented by severity (mild, moderate, and severe), by relationship to study drug (related would include definite, probable, and possible) and by outcome of events. Additionally, the number of TESAEs (as opposed to the number and percentage of subjects) will be presented.

In case that there are non-treatment-emergent AEs observed, the number and percentage of subjects with all SAEs will be summarized by SOC and PT within each SOC. Additionally, the number of SAEs (as opposed to the number and percentage of subjects) will be presented.

A listing of all SAEs and discontinuations due to AEs will be included. Subject with deaths, SAEs, or subjects who withdraw due to AE will be listed separately and discussed with subject narratives.

8.7.6. Discontinuation from the Study

Number of subjects who discontinued from the study and reasons for discontinuation will be summarized.

8.7.7. Clinical Laboratory Evaluations

Pregnancy test results will be listed for all female subjects of child bearing potential only.

8.7.8. Other Observations Related to Safety

8.7.8.1. Weight, Height/length, and Temperature

Weight, height/length, and temperature conducted under the physical examination will be summarized using descriptive statistics for both actual results and change from baseline for each treatment group. Vital signs assessments will also be presented in a listing. All vital signs will be presented metric units.

8.7.8.2. Physical Findings

Physical examination findings will be summarized in shift tables that will be presented to display the shift in the normal range categories (normal vs. abnormal) from baseline to the final evaluation. Baseline is defined in Section 6.3.

9. COMPUTER SOFTWARE

All analyses will be performed by FMD K&L Inc. using Version 9.2 or later of SAS® software. All summary tables, data listings, and figures will be prepared utilizing SAS® software.

The standard operating procedures (SOPs) of FMD K&L Inc. will be followed in the creation and quality control of all data displays and analyses.

10. REFERENCES

1) Meinert, C. Clinical Trials: Design, Conduct, and Analysis. New York, NY: Oxford University Press; 1986.

11. APPENDIX

11.1. Body Surface Area Index (BSAI) of Lesional Skin

(Check only one box and complete the appropriate sections for each region)

1 ☐ Ages 1 month to 7 years[1]

Column 1	Column 2	Column 3	Column 4	Column 5
Region Number	**Region Description**	**Regional BSA % that is affected***	**Weighting Factor**	**Total BSA % that is affected ****
1	Head/Neck		x .2	
2	Upper Limbs		x .2	
3	Trunk (includes groin)		x .3	
4	Lower Limbs		x .3	
			TOTAL (BSAI)	

2 ☐ Age 8 years or greater

Column 1	Column 2	Column 3	Column 4	Column 5
Region Number	**Region Description**	**Regional BSA % that is affected***	**Weighting Factor**	**Total BSA % that is affected ****
1	Head/Neck		x .1	
2	Upper Limbs		x .2	
3	Trunk (includes groin)		x .3	
4	Lower Limbs		x .4	
			TOTAL (BSAI)	

* For each region, enter the % of BSA that is affected with lesional skin. Score each region separately from 0% - 100%.

** Multiply the value in Column 3 by the factor in Column 4. The Total value at the bottom of the table is the sum of Column 5 values for each region.