Protocol SD-006

An Open Label Multi-Center Extension Study to Evaluate the Long-term Safety of ZORBLISA™ (SD-101-6.0) in Patients with Epidermolysis Bullosa

Statistical Analysis Plan

Final Version 2.0

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CONFIDENTIAL

Sponsor:

Scioderm, Inc.

An Amicus Therapeutics Company

4601 Creekstone Drive

Suite 160

Durham, NC 27703

REVISION HISTORY

Version	Date	Revision Author	Comments
Draft 1.0	20Dec2016	Amicus	Initial Version based on Protocol Version 3.1, 10Nov2016
Draft 0.3	28Jun2017		Updates based on protocol amendment 2 and standard safety text
Draft 0.4	14Jul2017		Updates of safety section for consistency with pivotal study SD-005
Final 1.0	31Jul2017		Removal of time to wound healing analysis. Updates to safety section for consistency with SD-004.
Final 2.0	22Aug2018		Subgroup analysis deleted from efficacy analyses. Safety analysis limited to age subgroups.

SIGNATURE PAGE

Author:

Amicus

08/22/2018
Date

Amicus Therapeutics, Inc.

Approved by:

Amicus

Date: 08 / 23 / 2018

Amicus Therapeutics Inc.

Amicus

Date: 08 / 22 / 2018

Amicus Therapeutics Inc.

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
BSA	Body Surface Area
BSAI	Body Surface Area Index
CRF	Case Report Form
EB	Epidermolysis bullosa
EBS	Epidermolysis bullosa Simplex
EU	European Union
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
Placebo	Contains 0% allantoin
PP	Per Protocol
ROW	Rest of the world, including all other countries except US and Europe
SAE	Serious Adverse Event
SD-101	Drug Product Formulation
SD-101-6.0	Contains 6% allantoin – referred to as Zorblisa in the study protocol
Placebo –> SD-101-6.0	Rolled over from 005 study placebo group
SD-101-6.0 –> SD-101-6.0	Rolled over from 005 study SD-101-6.0 group
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TESAE	Treatment-emergent Serious Adverse Event
US	United States

2. INTRODUCTION

This statistical analysis plan (SAP) defines the methodology and strategy for performing safety and efficacy analysis for patients with epidermolysis bullosa (EB). This SAP is based on the protocol amendment 2, version 2 dated 10 November 2016.

3. STUDY OBJECTIVE

The primary objective is to demonstrate the long-term safety of SD-101-6.0 in patients 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 and BSAI of wound burden; as well as assessment of healing of unhealed target wounds in patients rolling over from the SD-005 study.

4. STUDY DESIGN

4.1. General Design

This is an open label, multi-center extension study to assess the long-term safety of SD-101-6.0 in treating patients with Simplex, Recessive Dystrophic, and Junctional non-Herlitz epidermolysis bullosa.

SD-101-6.0 will be applied topically, once a day, to the entire body for a period of 1440 days (48 months). This study may be further extended by amendment until either SD-101 becomes commercially available or the clinical development of SD-101 in EB is discontinued.

Patients who successfully completed Study SD-005 (on study drug at Visit 5) have had the option to roll over into the SD-006 study. The baseline visit (Visit 1) has occurred at Visit 5 for SD-005. The Body Surface Area Index (BSAI) assessments of lesional skin and wound burden performed at the final Visit for SD-005 are to be utilized as the baseline assessment for SD-006 unless Visit 1 is ≥14 days after the final SD-005 visit in which case the assessment are to be repeated. Patients return for follow-up visits at Months 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, and 48 after Visit 1. At each visit, assessments include BSAI of lesional skin and wound burden. The unhealed target wounds from SD-005 are assessed at each subsequent scheduled visit until the target wound is documented as closed. Closed wounds will be assessed for scarring.

4.2. Method of Assignment of Patients to Treatment Groups

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

4.3. Blinding

This is an open-label study; therefore, blinding was not performed.

4.4. Determination of Sample Size

All patients who complete the study SD-005 (on study drug at Visit 5) and who meet all eligibility criteria may be eligible to enter this open label extension. Up to approximately 150 patients are expected to roll over from Study SD-005.

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

5.1. Changes in the Conduct of the Study

There were two amendments in the protocol. The first amendment was finalized on 2 December 2015, the second amendment was finalized on 10 November 2016. The second amendment extends study period from 360 days to 1440 (48 months) days. On June 4, 2018, a Dear Doctor Letter was sent to all sites to discontinue the applications of SD-101 cream immediately, bring the patients back to the sites for the end of study visit and collect all the remaining tubes of SD-101, 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

Subgroup analysis deleted from efficacy analyses. Safety analysis limited to age subgroups.

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** **Month** **1**	**3** **Month** **3**	**4** **Month** **6**	**5** **Month** **9**	**6** **Month** **12**	**7 to 17** **Month** **15 to 45**[a] **(Every 3 months)**	**18** **Month 48** **Final Visit/ Early Termination**
Study Day **(± 7 Days for Visits 2 – 18)**	**0**	**30**	**90**	**180**	**270**	**360**	**450 to 1350**	**1440**
Informed consent /assent signed	X							
Inclusion/Exclusion assessment	X							
Demographic, medical and medication history[b]	X							
Physical examination[c]	X							X
Height, weight, and temperature[c]	X							X
Assess BSA of lesional skin[d]	X	X	X	X	X	X	X	X
Assess BSA of wound burden[d]	X	X	X	X	X	X	X	X
Assess target wound via ARANZ[e]	X	X	X	X	X	X	X	-
Bandage history	X		X	X	X	X	X	X
Urine pregnancy test (females of child-bearing potential only) [f]	X		X	X	X	X	X	X
Dispense SD-101-6.0[g]	X		X	X	X	X	X	

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

Procedure **Visit**	**1** **Screening/Baseline**	**2** **Month** **1**	**3** **Month** **3**	**4** **Month** **6**	**5** **Month** **9**	**6** **Month** **12**	**7 to 17** **Month** **15 to 45[a]** **(Every 3 months)**	**18** **Month 48** **Final Visit/ Early Termination**
Collect SD-101-6.0 for the purpose of drug accountability			X	X	X	X	X	X
Collect all SD-101-6.0								X
Monitor adverse events[h]	X	X	X	X	X	X	X	X
Monitor use of concomitant medications	X	X	X	X	X	X	X	X

a. Patients will return once every 3 months for Visit 7 (Month 15; day 450), Visit 8 (Month 18; day 540), Visit 9 (Month 21; day 630), Visit 10 (Month 24; day 720), Visit 11 (Month 27; day 810), Visit 12 (Month 30; day 900), Visit 13 (Month 33; day 990), Visit 14 (Month 36; day 1080), Visit 15 (Month 39; day 1170), Visit 16 (Month 42; day 1260), and Visit 17 (Month 45; day 1350).
b. Demographic, medical and medication history collected during SD-005 will be utilized as the baseline information for SD-006.
c. The physical examination, as well as, height, weight, and temperature performed at the final visit for SD-005 will be utilized as the baseline assessment for SD-006 unless Visit 1 is ≥ 14 days after the final SD-005 visit, in which case the assessment will be repeated. A complete physical examination, as well as, height, weight, and temperature will be performed at visit 18.
d. The BSA assessments of lesional skin and wound burden performed at the final visit for SD-005 will be utilized as the baseline assessment for SD-006 unless Visit 1 is ≥ 14 days after the final SD-005 visit in which case the assessment will be repeated. The BSA assessments of lesional skin and wound burden will be performed at visits 2 through 18.
e. If the target wound has not healed by the final visit of the SD-005 study, the target wound will be assessed in SD-006 using ARANZ until the wound has healed. The ARANZ picture and target wound area value determined at the final visit for SD-005 will be utilized as the baseline target wound area and picture for SD-006 unless Visit 1 is ≥ 14 days after the final SD-005 visit, in which case the assessment will be repeated. If target wound has healed, assess for scarring. Target wound data was not captured in the M48/EOS visit
f. The urine pregnancy test performed at the final visit for SD-005 will be utilized for entry into SD-006 if the visits occur on the same day. Otherwise, the urine pregnancy test will be performed at Visit 1 and at Visits 3 through 18.
g. Ensure the patient is dispensed sufficient SD-101-6.0 until the next study visit.
h. All AEs experienced in SD-005 should be noted in medical history for SD-006 at Visit 1 only.

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 0 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.

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 Table 2.

Table 2: Analysis Windows

Week	Visit	Scheduled Study Day	Visit Window for Analysis (Days)
Screening/Baseline	Visit 1	0	Day -13 to Day 0
Month 1	Visit 2	30	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
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 1305
Month 45	Visit 17	1350	Day 1306 – Day 1395
Month 48/Final Visit	Visit 18	1440	Day 1396 – 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

For most cases, the baseline visit (Visit 1) will occur at Visit 5 for SD-005. Exceptions are detailed below.

The Body Surface Area Index (BSAI) assessments of lesional skin and wound burden performed at the Visit 5 for SD-005 will be utilized as the baseline assessment for SD-006 unless Visit 1 is ≥ 14 days after the final SD-005 visit in which case the assessment will be repeated.

The urine pregnancy test performed at the final visit for SD-005 will be utilized for entry (Visit 1) into SD-006 only if the visits occur on the same day, otherwise, urine pregnancy test will be performed at Visit 1 as baseline assessment for SD-006.

The physical examination performed at the final visit for SD-005 will be utilized as the baseline assessment for SD-006 unless Visit 1 is ≥ 14 days after the final SD-005 visit, in which case a physical examination will be repeated and used as baseline assessment for SD-006.

The ARANZ picture that documents target wound status at the final visit for SD-005 will be utilized to determine target wound area unless Visit 1 is ≥ 14 days after the final SD-005 visit, in which case the assessment will be repeated on the same wound. For target wounds that are not closed by the end of Study SD-005, the ARANZ picture and calculation of target wound area at the final visit for Study SD-005 will be used as the baseline area size of the target wound for SD-006. The wounds that are closed at the end of study SD-005 will not be followed up and analyzed.

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-005. Adverse events continuing in study SD-005 and those originating within the gap between studies SD-005 and SD-006 will be transcribed into Medical History.

  Note: All Adverse Events (AEs) experienced in SD-005 and medical events occurring between the end of SD-005 and the enrollment into SD-006 after completion of SD-005 should be noted in the medical history for SD-006 at Visit 1 only.
- Demographics (date of birth, race, gender, ethnicity) obtained from SD-005.
- Vital Signs (height/length, weight, temperature) obtained from final visit of SD-005 unless Visit 1 is ≥ 14 days after the final SD-005 visit in which case the assessment will be repeated.
- Physical examination obtained from final visit of SD-005 unless Visit 1 is ≥ 14 days after the final SD-005 visit in which case the assessment will be repeated.
- BSAI of wound burden obtained from final visit of SD-005 unless Visit 1 is ≥ 14 days after the final SD-005 visit in which case the assessment will be repeated.
- BSAI of lesional skin obtained from final visit of SD-005 unless Visit 1 is ≥ 14 days after the final SD-005 visit in which case the assessment will be repeated.
- Assess target wound via ARANZ; if the target wound has not healed by the final visit of the SD-005 study, the same target wound will be assessed in SD-006 using ARANZ until the wound has healed. The ARANZ picture for target wound will be utilized as the baseline for SD-006 unless Visit 1 is ≥ 14 days after the final SD-005 visit in which case the assessment will be repeated.
- If target wound has healed, assess for scarring.
- Bandage history.

- The urine pregnancy test performed at the final visit for SD-005 will be utilized for entry (Visit 1) into SD-006 only if the visits occur on the same day, otherwise, urine pregnancy test will be performed at Visit 1 as baseline assessment for SD-006.
- 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 Month 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, and 48 compared to baseline will be measured using the Body Surface Area Index (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.
- Change in total body wound coverage based on BSAI estimates at Months 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, and 48 compared to baseline will be measured using the BSAI, where change is defined as the corresponding month value minus the baseline value. The BSAI of wounds will be assessed as listed in Section 11.2. Due to the termination of the study data at later time points will be limited.

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 a period of 1440 days. 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 patient, administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (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. AEs may include the onset of new illness and the exacerbation of pre-existing conditions. Treatment-emergent AEs 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-005 and the start of Study SD-006, adverse events 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-006. Continuing adverse events will be also captured in medical history for the extension study SD-006.

Medical review will take place to determine if any of AEs could be potentially related to the contamination of the study medication during the manufacturing process. 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 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-005 will be utilized for entry (Visit 1) into SD-006 only if the visits occur on the same day, otherwise, urine pregnancy test will be performed at Visit 1. Urine pregnancy tests for female patients of child bearing potential (sensitivity at least 25 mIU/ml) will also be performed at Visit 3 through Visit 18.

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

The physical examination performed at the final visit for SD-005 will be utilized as the baseline assessment for SD-006 unless Visit 1 is ≥ 14 days after the final SD-005 visit, in which case a physical examination will be repeated. An additional physical examination will be done by a physician at Visit 18. 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 005 study treatment: Placebo –> 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 patients (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 patients within the population (unless otherwise specified).

All analyses for efficacy will be performed using the Intent-To-Treat (ITT) population, 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. 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 patients 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, age (28 days to <2 years, 2 years to <12 years, 12 years to <= 18 years, >18 years).,

8. STATISTICAL ANALYSIS

8.1. Disposition of Patients

The number and percentage of patients who were enrolled, treated, and completed the study will be summarized. Similar summaries will be provided for those patients who discontinued from the study prematurely. For those patients who discontinue early, the reasons for discontinuing will also be summarized. The disposition of all patients will be listed.

Data on screening failures (patients 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 patients with major protocol deviations will be summarized for the ITT population. A final list of patients who have any major protocol deviations will be documented before interim and final database locks. A listing of patients with major protocol deviations will be provided.

8.3. Analysis Populations

8.3.1. Intent-to-Treat (ITT) Population

The intent-to-treat (ITT) population will be defined as all patients who have rolled over from SD-005.

8.3.2. Safety Population

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

The Intent-to-Treat (ITT) population will be used for all efficacy analyses. The Safety population will be used for all safety analyses. The Per Protocol (PP) population will be used for supportive analyses of the efficacy endpoints.

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 patient age, weight, height, body mass index (BMI), BSAI (for lesion and wound burden), and temperature will be summarized as described previously. Categorical variables such as patient gender, , age group (28 days to <2 years, 2 years to <12 years, 12 years to < 18years, 18 years to < 65 years, 65 years to <85 years, >=85 years), EB type, and baseline target wound size (=0, >0) will be summarized using number of observations and percentages for each category.

Enrollment by country will be summarized.

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

8.5. Prior and Concomitant Therapy

The World Health Organization (WHO) Drug Dictionary will be used to classify medications for the purpose of the first interim analysis. 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-006 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 for each of the following in the safety population:

1. Number and percentage of patients who had previous therapies/medications by Anatomical Therapeutic Chemical **(**ATC) code text and WHO drug name
2. Number and percentage of patients who had concomitant therapies/medications by ATC text and WHO drug name

8.6. Analysis of Efficacy Parameters

8.6.1. Analysis of 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 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.

- Change in total wound burden based on BSAI at each visit compared to baseline.

  This assessment will be analyzed using the same approach for lesional skin as the total body wound burden to both change from baseline and the percentage change from baseline.

  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

No diary data were collected on whether a patient used or did not use SD-101-6.0 on a given day. Therefore the number of days on the study will be considered number of days of exposure. It will be summarized using descriptive statistics by overall. Descriptive statistics will also be provided for duration of exposure into categorical summary of <30, >=30 to <90, >=90 to <180, >=180 to <1 year, >=1 year to <2 years, >=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 system organ class (SOC) and preferred terms (PTs) using the 19.1 version of MedDRA.

If there is a gap between the completion of the study SD-005 and the start of the study SD-006, adverse events 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-006. Continuing adverse events will also be captured in medical history for the extension study SD-006. 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.

If an AE stared after signing an informed consent/assent but before the first dose of study medication was taken in the study SD-006, then such an AE is non treatment-emergent.

8.7.3. Summaries of Adverse Event Incidence Rates for All Patients

The number and percentage of patients who experienced TEAEs will be presented by SOC and by PT within SOC for each treatment group. Treatment-emergent AEs (TEAEs) will be similarly presented by severity (mild, moderate, 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 patients) will be presented by treatment group.

The number of patients with TEAEs and number of TEAEs will also be presented by the following subgroups of Age (28 days to <2 years, 2 years to <12 years, 12 years to <=18 years, >18 years). Subgroups for age are defined based at the patient's age at Baseline.

To count the number of patients who experienced each TEAE, a patient experiencing the same TEAE multiple times will only be counted once for the corresponding PT. Similarly, if a patient experiences multiple TEAEs within the same SOC, the patient will be counted only once for that SOC. If a patient 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. TEAEs 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 patient experienced more than one TEAE, the worst outcome will be counted under that patient. If a patient experienced more than one outcome within a SOC (or PT), the patient is only counted once under worst outcome in that SOC (or PT).

In addition, all adverse events will be provided by study site and by treatment group, in a listing, which will include the patient 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 AE Onset, Severity, and Relationship

8.7.4.1. Missing or Partial AE 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.
3. 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.

4. 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.
5. 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.
6. 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.
7. 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 patient 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 patients who experienced TESAEs and separately TEAEs leading to withdrawal from the study will be presented by SOC and 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, 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 patients) and separately TEAEs leading to withdrawal will be presented.

Number of patients with TESAEs and separately TEAEs resulting in withdrawal as well as number of TESAEs and separately the number of TEAEs leading to withdrawal will also be presented by the following subgroups of Age (28 days to <2 years, 2 years to <12 years, 12 years to <=18 years, >18 years), EB type and independently. Subgroups for age are defined based at the patient's age at Baseline.

In case that there are non-treatment emergent serious adverse events, they will be listed.

A listing of all serious adverse events and discontinuations due to AEs will be included. Patient with deaths, SAEs or patients who withdraw due to AE will be listed separately and discussed with patient narratives.

8.7.6. Discontinuation from the Study

Number of patients 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 patients of child bearing potential only.

8.7.8. Other Observations Related to Safety

8.7.8.1. Vital Signs

Vital Signs (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. (1986). Oxford University Press. New York, NY

11. APPENDICES

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

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.

11.2. Body Surface Area Index (BSAI) of Total Wound Burden

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

1 ☐ Ages 1 month to 7 years

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 open wounds. 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.