# A Phase 3, Multi-center, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of SD-101 Cream in Patients with Epidermolysis Bullosa (ESSENCE Study)

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| **Unique Protocol ID:** | SD-005 |
| **NCT Number:** | NCT02384460 |
| **Date of Protocol:** | 20 March 2017 |

# A Phase 3, Multi-center, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of SD-101 Cream in Patients with Epidermolysis Bullosa (ESSENCE Study)

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Amendment 2: 19 September 2016
Amendment 3: 10 March 2017

**Sponsor:** Scioderm, INC.
An Amicus Therapeutics Company
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Durham, NC 27703

**Author(s):**
PPD

**Confidentiality Statement:**
This protocol contains information which is the property of Scioderm, INC. and therefore is provided to you in confidence for review by you, your staff, an applicable ethics committee / institutional review board and regulatory authorities. It is understood that this information will not be disclosed to others without written approval from Scioderm, INC.

**This study will be conducted in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments), in accordance with local legal and regulatory requirements and in compliance with the applicable parts of the United States Code of Federal Regulations.**

# 1. PROTOCOL SYNOPSIS

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| PROTOCOL TITLE | A Phase 3, Multi-center, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of SD-101 Cream in Patients with Epidermolysis Bullosa (ESSENCE Study) |
| PROTOCOL No. | SD-005 |
| VERSION No. | 4 |
| SPONSOR | Scioderm, INC.<br>An Amicus Therapeutics Company<br>4601 Creekstone Drive<br>Suite 160<br>Durham, NC 27703 |
| INVESTIGATIONAL PRODUCT | SD-101-6.0 cream administration (containing 6% allantoin) compared with placebo (SD-101-0.0 cream containing 0% allantoin). |
| PHASE OF DEVELOPMENT | Phase 3 |
| INDICATION AND RATIONALE | The aim is to assess the efficacy and safety of SD-101-6.0 cream vs. SD-101-0.0 (placebo) in the treatment of patients with Epidermolysis Bullosa. |
| STUDY DESIGN | This is a Phase 3, multi-center, randomized, double-blind, placebo-controlled, study to assess the efficacy and safety of SD-101-6.0 cream vs. placebo (SD-101-0.0) on lesions in patients with Simplex, Recessive Dystrophic, or Junctional non-Herlitz Epidermolysis Bullosa.<br><br>SD-101-6.0 cream or placebo (SD-101-0.0) will be applied topically, once a day to the entire body for a period of 90 days. Patients will be randomized on a 1:1 basis. Patients will have 1 target wound selected at baseline by the Investigator. Selected target wound must be at least 21 days old (size 10 to 50 $cm^2$). Photographic confirmation of the target wound location will be collected at baseline, and the picture saved from the first visit will be used to confirm location of the target wound at subsequent visits.<br><br>The patient will return to the study site for Visit 2 (14 days ±5 days from baseline), Visit 3 (30 days ±7 days from baseline), Visit 4 (60 days ±7 days from baseline), and Visit 5 (90 days ±7 days from baseline) to have the |

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| | target wound, previously identified at baseline, re-assessed for the level of healing. In addition, itching, pain, body surface area index (BSAI), and scarring of healed target wound will also be assessed at each visit. The ARANZ SilhouetteStar™ will be used to measure the target wound at all visits. |
| STUDY OBJECTIVE | The primary objective is to compare the efficacy and safety of SD-101-6.0 vs. SD-101-0.0 (placebo) in patients with Simplex, Recessive Dystrophic, or Junctional non-Herlitz Epidermolysis Bullosa. |
| STUDY EFFICACY ENDPOINTS | <u>Primary Efficacy Endpoints</u><br>The primary efficacy endpoints for this study are:<br>• Time to complete target wound closure within 3 months<br>• The proportion of patients experiencing complete closure of their target wound within 3 months<br><br><u>Key Secondary Efficacy Endpoints</u><br>The key secondary measures of efficacy include:<br>• Proportion of patients experiencing complete closure of their target wound within 2 months<br>• Proportion of patients experiencing complete closure of their target wound within 1 month<br>• Change in lesional skin based on BSAI at Month 3, compared to Baseline<br>• Change in Total Body Wound Burden based on BSAI at Month 3, compared to Baseline<br>• Change in itching assessed at Day 7, compared to Baseline<br>• Change in pain assessed at Day 7, compared to Baseline<br><br><u>Other Secondary Efficacy Endpoints</u><br>• Change in Total Body Wound Burden based on BSAI at Week 2 and Months 1 and 2, compared to Baseline<br>• Percent change from Baseline in Total Body Wound Burden based on BSAI at Week 2 and Months 1, 2, and 3<br>• Change in lesional skin based on BSAI at Week 2 and Months 1 and 2, compared to Baseline<br>• Percent change in lesional skin based on BSAI at Week 2 and Months 1, 2, and 3, compared to Baseline |

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| | • Presence of scarring of healed target wound at the visit where the complete closure is documented<br>• Change in target wound characteristics (ie, inflammation, blistering, granulation tissue, erythema, exudate) at Week 2 and Months 1, 2, and 3, compared to Baseline<br>• Change in itching and pain at Days 1 to 6, Week 2, Months 1, 2, and 3, compared to Baseline<br>• Proportion of patients experiencing target wound closure within Week 2 |
| PLANNED SAMPLE SIZE | Approximately 150 patients will be enrolled. |
| PATIENT POPULATION Inclusion Criteria | 1. Informed Consent form signed by the patient or patient's legal representative; if the patient is under the age of 18 but capable of providing assent, signed assent from the patient.<br>2. Patient (or caretaker) must be willing to comply with all protocol requirements.<br>3. Diagnosis of Simplex, Recessive Dystrophic, or Junctional non-Herlitz EB.<br>4. Patient must have 1 target wound (size 10 to 50 $cm^2$).<br>5. Patients 1 month and older.<br>6. Target wound must be present for 21 days or more. |
| PATIENT POPULATION Exclusion Criteria | 1. Patients who do not meet the entry criteria outlined above.<br>2. Selected target wound cannot have clinical evidence of local infection.<br>3. Use of any investigational drug within the 30 days before enrollment.<br>4. Use of immunotherapy or cytotoxic chemotherapy within the 60 days before enrollment.<br>5. Use of systemic or topical steroidal therapy within the 30 days before enrollment. (Inhaled steroids and ophthalmic drops containing steroids are allowed)<br>6. Use of systemic antibiotics within the 7 days before enrollment.<br>7. Current or former malignancy.<br>8. Arterial or venous disorder resulting in ulcerated lesions.<br>9. Pregnancy or breastfeeding during the study. (A urine pregnancy test will be performed at screening and every 30 days until the final visit for female patients of childbearing potential) |

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| | 10. Females of childbearing potential who are not abstinent and not practicing a medically acceptable method of contraception. |
| FORMULATION/DOSE | SD-101 cream will be applied topically, once a day to the entire body for a period of 90 days. Application will consist of blinded SD-101-6.0 or SD-101-0.0 (placebo). |
| ROUTE OF ADMINISTRATION | Topical administration of SD-101-6.0 dermal cream or SD-101-0.0 (placebo). |
| DURATION/FREQUENCY OF TREATMENT | Topical application of SD-101 once daily over the entire body surface for 90 days. |
| SAFETY ASSESSMENTS | The safety of SD-101-0.0 and SD-101-6.0 will be assessed by monitoring tolerability, adverse events (AEs), and physical examinations. |
| STATISTICAL METHODS | <u>Primary Efficacy Parameters:</u><br>The primary efficacy endpoints for this study are time to complete target wound closure within 3 months and the proportion of patients experiencing complete closure of their target wound within 3 months. These variables will be compared between SD-101-6.0 and SD-101-0.0 (placebo), and tested via a step-down procedure beginning with the time to complete target wound closure.<br><br>Time to event analyses will be performed using a Kaplan-Meier approach, where the event is target wound closure measured from the date of randomization (study day 0) to the date of wound closure. The two treatment groups will be compared with respect to the two primary endpoints using Cox Proportional Hazards model and Logistic Regression, respectively. Covariates will be included in the Cox Proportional Hazards and Logistic Regression models. The approach to evaluating these and secondary variables will be summarized in a fully detailed Statistical Analysis Plan.<br><br>Assumptions underlying the sample size estimation are that 35% of placebo patients will experience complete closure of their target wound at or before the 3-month follow-up visit and at least 60% of patients treated with SD-101-6.0 will experience complete closure of their target wound by this time (hazard ratio approximately 2.127, assuming exponential hazards over time). Using |

these assumptions and a 1-sided overall alpha of 0.025, approximately 150 patients will be required (75 in each group) to provide approximately 86% power for time to complete target wound closure. There is estimated 85% power for proportion of patients with complete target wound closure.

Safety Parameters:
Adverse events will be coded using MedDRA. The number of events, incidence, and percentage of treatment-emergent AEs (TEAE) will be calculated overall, by system organ class (SOC), and by preferred term. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, serious AEs (SAEs), and deaths will be summarized/listed.

Baseline and Month 3 physical examination results, together with changes during the study period, will be described using summary statistics.

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# 3. LIST OF ABBREVIATIONS

| | |
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| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| BSA | Body Surface Area |
| BSAI | Body Surface Area Index |
| CRF | Case Report Form |
| DMC | Data Monitoring Committee |
| EB | Epidermolysis Bullosa |
| EBS | Epidermolysis Bullosa Simplex |
| ET | Early Termination |
| FDA | Food and Drug Administration |
| FLACC | Face, Legs, Activity, Cry, Consolability |
| GCP | Good Clinical Practice |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| ISC | Independent Statistical Center |
| ITT | Intent-to-treat |
| IWRS | Interactive Web Response Services |
| MEDRA | Medical Dictionary for Regulatory Activities |
| PP | Per Protocol |
| RDEB | Recessive Dystrophic Epidermolysis Bullosa |
| SAE | Serious Adverse Event |
| SD-101-0.0 | SD-101 cream containing 0% allantoin (placebo) |
| SD-101-1.5 | SD-101 cream containing 1.5% allantoin |
| SD-101-3.0 | SD-101 cream containing 3% allantoin |
| SD-101-6.0 | SD-101 cream containing 6% allantoin |
| SD-101-9.0 | SD-101 cream containing 9% allantoin |
| TEAE | Treatment Emergent Adverse Event |
| U.S. | United States |
| WMA | World Medical Association |

# 4. ADMINISTRATIVE STRUCTURE

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| Medical Expert (Sponsor) | PPD<br>1 Cedar Brook Drive<br>Cranbury, NJ 08512<br><br>PPD<br>1 Cedar Brook Drive<br>Cranbury, NJ 08512 |
| Contract Research Organization Monitors | Chiltern Inc.<br>1016 West Ninth Ave.<br>King of Prussia, PA 19406-1221<br><br>QUINTILES<br>Suite 2, Level 10, 606 St Kilda Road<br>Melbourne, VIC 3004<br>Australia<br><br>HungaroTrial CRO<br>Fehérvári út 89 95<br>1119 Budapest, Hungary |

# 5. BACKGROUND INFORMATION

Epidermolysis Bullosa (EB) is a rare group of inherited disorders that typically manifest at birth as blistering and lesion formation on the skin and, in some cases, the epithelial lining of other organs, in response to little or no apparent trauma. In consequence, the skin is extremely fragile which can result in shearing of the skin, causing a high risk of infection. All forms of EB are both debilitating and life threatening. In some EB subtypes, high mortality occurs before the age of 1 (Junctional Herlitz), and others in adolescences to early adulthood, typically due to infection or failure to thrive. In addition, children surviving into their 20's and 30's are also at risk for development of a virulent form of squamous cell carcinoma, which is in many cases fatal.

There are no standard of care products available to treat the dermal manifestations of EB, and there is no approved drug for EB in either Europe or the United States. There have been numerous studies published on potential treatments for skin manifestations associated with EB, including vitamin E therapy, systemic phenytoin, topical nonsteroidal agents, cyproheptadine, tetracycline, and dapsone. No controlled studies showed clinical benefit of any therapy. Newer exploratory treatments including skin grafts, bioengineered skin products, and gene therapy have been unsuccessful to date.

## 5.1. Overview of Active Ingredient and Drug Product (SD-101)

**Pharmacology of Allantoin**

The precise mechanism of action of allantoin in wound healing has not yet been defined. There are many animal wound and EB models, however, no product to date effective in any of these models has demonstrated effectiveness in humans. SD-101 was tested in the current appropriate wound model in EB, which is EB patients, and is the first product that has produced beneficial effects in healing of lesional skin, and appears to reduce the outbreaks of blistering. Data from the literature suggest that allantoin does not work via a single activity, but rather appears to affect multiple aspects of the processes involved in wound healing. These include reduction of inflammation, induction of growth of healthy tissue, stimulation of collagen as well as stimulation of granulation in ulcers, including tissue differentiation and epithelialization. In addition, allantoin has demonstrated bacteriostatic and bactericidal effects, and appears to aid in removing necrotic tissue.

**Pharmacokinetics of Allantoin**

Allantoin is a compound that is found endogenously in rats, rabbits, pigs, dogs, monkeys, in addition to a lower extent in humans. Allantoin is the main end product of purine metabolism in most mammals, and is produced from metabolism of uric acid via the enzyme, uricase. In rats and other mammals, uricase is present within peroxisomes of liver parenchymal cells. In man and great apes, uricase is not present, so that the primary end product of purine metabolism is uric acid. However, small amounts of allantoin are produced in great apes and humans via non-enzymatic conversion of uric acid.

**SD-101 Topical Cream**

Allantoin is the active ingredient contained within SD-101 skin cream, which is a commercially viable formulation with demonstrated stability of allantoin for several years at concentrations up to 9%. The capability to deliver the active moiety to the target in skin is key in topical products, since the skin is an effective barrier to penetration. In a series of flux studies with SD-101 containing allantoin ranging from 0.5 to 9%, penetration across the various skin barriers was dose-related.

SD-101 has been developed to overcome the inherent limited solubility and stability of allantoin, allowing the ability to formulate allantoin at higher concentrations. In consequence, allantoin concentrations as high as 9% can be achieved in a topical product whereas the amount in existing cosmetics as an inactive excipient is typically less than 0.2%.

SD-101 cream is currently being developed as a new topical therapy for the treatment of lesional skin in patients with EB. The same product is foreseen for adult and pediatric patients.

## 5.2. Summary of Animal and Human Studies with SD-101

Toxicology studies assessing topical administration of SD-101-9.0 in multiple species demonstrated the lack of local or systemic effects with this active in the current formulation. The lack of systemic effects with allantoin in animals administered SD-101 topically was further supported by additional safety information obtained with intravenous administration of allantoin in the monkey. Peak intravenous blood levels in the monkeys were achieved that were approximately 700 times higher than endogenous levels measured in published healthy human subject pharmacokinetic studies, without any demonstrated clinical chemistry abnormalities or organ toxicity at either the macroscopic or microscopic level. Additional toxicology studies with SD-101-9.0 demonstrated that this product was non-sensitizing in the guinea pig and did not produce ocular irritation in the rabbit. Lastly, from examination of the excipients and the active ingredient, allantoin, for the ability to absorb light in the UV-A and / or UV-B ranges, there were no demonstrated concerns of potential phototoxicity with use of this product.

Studies in normal volunteers with topical use of SD-101 (SD-101-0.0, SD-101-3.0, SD-101-6.0, and SD-101-9.0), and in EB Patients with topical usage of SD-101 (SD-101-1.5, and SD-101-3.0) demonstrate to date that allantoin at these concentrations (in this formulation) has not produced any local or systemic adverse effects of concern. In addition, topical administration of SD-101 (SD-101-1.5) was found to be non-sensitizing in healthy subjects.

An open-label study using SD-101-3.0 was previously conducted. Eight EB patients with a diagnosis of EB (Simplex, Recessive Dystrophic, or Junctional) based on diagnostic immunomapping or electron microscopy, were treated with SD-101-3.0 cream once applied daily to their entire skin surface, for a period up to 3 months. Application of the

cream was non-irritating and did not produce any discomfort when applied to either unblistered areas or open lesions. The patients treated with SD-101-3.0 for three months showed significant improvements in the complete healing of lesions (typified by the results with the target wounds), clinically meaningful reductions in the extent of total skin surface involvement with active disease (body surface area [BSA]), and reduced pain and itching. Daily use of SD-101-3.0 cream in treatment up to 3 months was well tolerated by all patients in the study, with no related adverse events (AEs) noted. There were no serious AEs (SAEs) that occurred in any patient during the 3 month treatment period. In addition, there was good compliance on usage of the product on the entire skin surface, based on the soothing and non-irritating effects of the SD-101 creams.

A Phase 2B study (SD-003) was completed with two strengths of SD-101 (containing 3% and 6% allantoin: identified as SD-101-3.0 and SD-101-6.0) with a matching vehicle control (SD-101-0.0). The primary endpoint of this study was the complete closure of the patient's target chronic wound within one month. Secondary endpoints comprised effects on improvement in body coverage in lesional skin (including blistering), pain, and itching. In addition, patients from study SD-003 were offered to roll-over into an open-label extension study (Study SD-004) to continue treatment with SD-101-6.0 to collect long term safety data as well. The results of Study SD-003 support that SD-101-6.0 is the most efficacious concentration and provided good safety and will be the concentration used in this registration study (SD-005), and compared against the placebo group receiving SD-101-0.0.

The design of studies SD-003 (Phase 2B) and SD-005 (Phase 3) are essentially identical, with differences in number of treatment arms and sample size, and minor modification of the minimum target wound size at study entry. Patients completing SD-005 will also be offered a roll-over option (Study SD-006) to receive SD-101-6.0.

# 6. RATIONALE FOR STUDY

SD-005 is a Phase 3 study to evaluate the efficacy and safety of SD-101-6.0 relative to a placebo cream in the treatment of EB patients. This confirmatory study follows the demonstration in a Phase 2B study that SD-101-6.0 stimulated wound closure and had an acceptable safety profile.

The aim is to assess the safety and efficacy of SD-101-6.0 cream vs. placebo in the treatment of patients with Epidermolysis Bullosa.

# 7. STUDY OBJECTIVE AND PURPOSE

## 7.1. Objective

The primary objective is to compare the efficacy and safety of SD-101-6.0 vs. SD-101-0.0 (placebo) in patients with Simplex, Recessive Dystrophic, or Junctional non-Herlitz Epidermolysis Bullosa.

# 8. SELECTION AND WITHDRAWAL OF PATIENTS

## 8.1. Patient Numbers

Approximately 150 patients will be enrolled at study sites worldwide.

## 8.2. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study.

1. Informed Consent form signed by the patient or patient's legal representative; also, if the patient is under the age of 18 but capable of providing assent, signed assent from the patient.
2. Patient (or caretaker) must be willing to comply with all protocol requirements.
3. Diagnosis of Simplex, Recessive Dystrophic, or Junctional non-Herlitz EB.
4. Patient must have 1 target wound (size 10 to 50 $cm^2$).
5. Patients 1 month and older.
6. Target wound must be present for 21 days or more.

## 8.3. Exclusion Criteria

Patients with any of the following exclusion criteria will not be eligible for enrollment into the study.

1. Patients who do not meet the entry criteria outlined above.
2. Selected target wound cannot have clinical evidence of local infection.
3. Use of any investigational drug within the 30 days before enrollment.
4. Use of immunotherapy or cytotoxic chemotherapy within the 60 days before enrollment.
5. Use of systemic or topical steroidal therapy within the 30 days before enrollment. (Inhaled steroids and ophthalmic drops containing steroids are allowed)
6. Use of systemic antibiotics within the 7 days before enrollment.
7. Current or former malignancy.
8. Arterial or venous disorder resulting in ulcerated lesions.
9. Pregnancy or breastfeeding during the study. (A urine pregnancy test will be performed at screening and every 30 days until the final visit for female patients of childbearing potential)
10. Females of childbearing potential who are not abstinent and not practicing a medically acceptable method of contraception.

## 8.4. Withdrawal Criteria/Study Discontinuation

Patients may withdraw from the study at any time without stating a reason and without prejudice to further treatment. The Investigator may withdraw a patient from the study and discontinue study treatment and assessments at any time due to safety concerns or concerns about the patient's compliance with study requirements and procedures. Full skin examination will be performed at each visit. If SD-101 causes any significant rash that has not occurred previously in the patient, the Investigator should consider discontinuing the patient. In addition, if lesions appear to significantly worsen above the normal cycle seen in the patient, with use of SD-101, the Investigator should consider discontinuing the patient. If a patient discontinues treatment at any time after entering the study, the Investigator will make every effort to ensure the patient returns for all study visits.

Early discontinuation of any patient who has given informed consent/assent to participate will be recorded including the reason for discontinuation. The primary reason for a patient withdrawing prematurely will be selected from the following standard categories of early discontinuations.

1. Adverse Event (Adverse Reaction): Clinical events occurred or laboratory results are reported that in the medical judgment of the Investigator are grounds for discontinuation in the best interests of the patient.
2. Withdrawal of Consent: The patient desired to withdraw from further participation in the study. The patient is not obligated to provide any reason for withdrawal of consent, but where a reason is given this will be recorded on the eCRF.
3. Protocol Violation: The patient failed to adhere to the protocol requirements, at the Investigator's discretion.
4. Lost to Follow-Up: The patient stopped coming for visits and study personnel were unable to contact the patient.
5. Other: The patient was terminated for a reason other than those listed above, such as, termination of study by Sponsor or enrolled in the study by error when they did not meet inclusion/exclusion criteria.

## 8.5. Handling of Withdrawals

Although a patient is not obligated to give his/her reason for withdrawing prematurely, the Investigator will make a reasonable effort to obtain the reason while fully respecting the patient's rights. Every effort will be made to ensure the patient returns for all study visits, as a safety measure. If there is a medical reason for withdrawal, the patient will remain under the supervision of the study physician until in satisfactory health. In the case of withdrawal due to an AE the patient will be followed as per Section 11.3. Reasonable efforts will be made to contact a patient who fails to attend any follow-up appointments, in order to ensure that he/she is in satisfactory health.

# 9. STUDY DESIGN

## 9.1. Primary Efficacy Endpoints

The primary efficacy endpoints are:

- The time to complete target wound closure within 3 months
- The proportion of patients experiencing complete closure of the target wound within 3 months

Complete target wound closure is defined as skin re-epithelialization without drainage.

## 9.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are:

- Proportion of patients experiencing complete closure of their target wound within 2 months
- Proportion of patients experiencing complete closure of their target wound within 1 month
- Change in lesional skin based on BSAI at Month 3, compared to Baseline

  This change will be measured using the following:

  Body Surface Area Index (BSAI) is a global measure of disease "spread" 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.

  **Definition of Lesional Skin for Assessment and Calculation of BSA Coverage**

  - Consists of area(s) that contain any of the following: blisters, erosions, ulcerations, scabbing, bullae, and eschars, as well as areas that are weeping, sloughing, oozing, crusted, and denuded.
    - Percent of this area recorded for each defined body region (number from 0-100% assigned for each region) – BSA

    *Note: Coloration should not lead to misinterpretation of whether a lesion is active. Erythema and hyper- or hypo-pigmentation does not necessarily indicate that a lesion is active, and in fact can be found in healed or scarred skin that would not be added to BSAI calculation of lesional skin coverage, unless it meets the definition above.*
  - Other areas categorized as skin that is either healed or scarred are not considered lesional skin.

- The BSAI will be assessed per the definition above by a study physician. The same study physician will perform this assessment for each patient visit.

**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** | |

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** | |

*** 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.**

- Change in Total Body Wound Burden based on BSAI at Month 3, compared to Baseline

  Change in total body wound coverage based on BSAI estimates at each visit, compared to baseline will be measured using the following:

  A common measure is the Body Surface Area Index (BSAI). It is a global measure of disease "spread" with weighting factors. Using the same principles that underlie the BSAI estimates of lesional skin, the percentage of the total BSA affected by open wounds will be calculated at baseline and at each visit to assess the total wound area before and after using the product.

  **Calculation of Total Body Wound Burden**

  - The BSAI of wounds will be assessed by a study physician. The same study physician will perform this assessment for each patient visit.
  - A wound is defined as an open area on the skin (epidermal covering is disrupted).

**Body Surface Area Index (BSAI) of Total Body 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** | |

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** | |

*** 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.**

- Change in itching assessed at Day 7, compared to Baseline

  Change in itching assessed at Week 1 (Day 7), compared to baseline will be measured using the "Itch Man Pruritus Assessment Tool". For patients 1 month to 5 years of age itching will be assessed using caretaker's response and patients 6 years of age and older will self-report their itching assessments. See Section 17.2, Appendix 2 for the Itch Man Pruritus Assessment Tool.

- Change in pain assessed at Day 7, compared to Baseline

  Change in pain assessed at Week 1 (Day 7), compared to baseline will be measured using the "FLACC scale" for patients 1 month to 3 years of age and for patients 4 years of age and older the "Wong Faces Pain Scale" will be utilized. See Section 17.3, Appendix 3 for the FLACC Behavioral Scale and Section 17.4, Appendix 4 for the Wong Faces Pain Scale.

## 9.3. Other Secondary Efficacy Endpoints

- Change in Total Body Wound Burden based on BSAI at Week 2 and Months 1 and 2, compared to Baseline
- Percent change from Baseline in Total Body Wound Burden based on BSAI at Week 2 and Months 1, 2, and 3
- Change in lesional skin based on BSAI at Week 2 and Months 1 and 2, compared to Baseline
- Percent change in lesional skin based on BSAI at Week 2 and Months 1, 2, and 3, compared to Baseline
- Presence of scarring of healed target wound at the visit where the complete closure is documented
- Change in target wound characteristics (ie, inflammation, blistering, granulation tissue, erythema, exudate) at Week 2 and Months 1, 2, and 3, compared to Baseline
- Change in itching and pain at Days 1 to 6, Week 2, and Months 1, 2, and 3, compared to Baseline
- Proportion of patients experiencing target wound closure within Week 2

## 9.4. Study Design

This is a Phase 3, multi-center, randomized, double-blind, placebo controlled, study to assess the efficacy and safety of SD-101-6.0 cream vs. SD-101-0.0 (placebo) in the treatment of lesions in approximately 150 patients with Simplex, Recessive Dystrophic, or Junctional non-Herlitz Epidermolysis Bullosa.

Patients will be randomized on a 1:1 basis to either SD-101-6.0 cream or placebo (SD-101-0.0). SD-101-6.0 or placebo will be applied topically, once a day to the entire body for a period of 90 days.

Patients will have 1 target wound selected at baseline by the Investigator. The Investigator should identify a target wound per the ARANZ SilhouetteStar™ system manuals and training provided. At screening, multiple wounds on the subject can be assessed against study inclusion/exclusion criteria. The selected target wound must be at least 21 days old (size 10 to 50 $cm^2$). Photographic confirmation of the target wound location will be collected at baseline, and the picture saved from the first visit will be used to confirm location of the target wound at subsequent visits. Once the target wound is identified, it should be followed during the subsequent study visits 2, 3, 4 and 5. It should be ensured that only 1 wound is selected for the study and followed within the ARANZ system.

Patients who have an eligible target wound and meet all other inclusion/exclusion criteria will be randomized. Patients who screen fail may be rescreened. The first dose of treatment will be administered during the office visit. Patients randomized will initially be given one-month supply of study medication.

The patient will return to the study site for Visit 2 (14 days ±5 days from baseline), Visit 3 (30 days ±7 days from baseline), Visit 4 (60 days ±7 days from baseline), and Visit 5 (90 days ±7 days from baseline) to have the target wound, previously identified at baseline, re-assessed for the level of healing. In addition, itching, pain, body surface area index (BSAI), and scarring of healed target wound will also be assessed at each visit. The ARANZ SilhouetteStar™ will be used to measure the target wound area at all visits.

All females of childbearing potential must have a negative urine pregnancy test prior to enrolling in the study and must agree to use some form of birth control or agree to remain abstinent until the study is completed. In addition, a urine pregnancy test will be performed at the screening visit and every 30 days until the final visit.

Safety assessments will include monitoring of tolerability, AEs, and physical examinations.

Patients who complete the study will be eligible to enroll into an open-label study (SD-006).

### 9.4.1. ARANZ SilhouetteStar™:

The ARANZ measurement device is a portable device that easily allows capture of information about a patient's target wound. This information is analyzed, managed, and stored in a database on a secure device. Information captured includes photographic images, quantitative measures and other target wound assessment data input to the device by the clinician, all obtained with no contact with the patient's skin. ARANZ then builds that into an electronic record for printing and archiving. Information about the target wound's measurement history is available on this system so that the serial progression of the target wound status can also be calculated and presented.

The ARANZ measurement device has FDA 510(k) approval and is not being assessed for safety and efficacy in this study. The device is only being utilized to perform measurements.


**Figure 9-1 ARANZ SilhouetteStar™**

# 10. STUDY MEDICATION AND ADMINISTRATION

## 10.1. Study Medication and Administration

SD-101-6.0 or SD-101-0.0 (placebo) creams will be supplied in 8 ounce plastic tubes, to be reclosed after use and stored at room temperature.

SD-101-6.0 or SD-101-0.0 will be applied topically once a day to the entire body for a period of 90 days. The first dose of study treatment will be administered during the first study visit upon randomization and after completion of the physical examination, baseline BSAI, itching, and pain assessments.

The patient diary will be returned at visits 3, 4 and 5 to evaluate compliance.

Additional information on the composition of the SD-101 dermal cream is contained in the SD-101 Investigator's Brochure.

## 10.2. Selection of Doses in the Study

SD-101-6.0 dermal cream or SD-101-0.0 (placebo) will be applied topically once a day to the entire body.

## 10.3. Allocation to Treatment

Approximately 150 patients will be randomized using Interactive Web Response System (IWRS) to 1 of 2 dose-concentration groups: SD-101-0.0 (placebo) or SD-101-6.0.

## 10.4. Duration of Patient Participation

It is anticipated that each eligible patient will participate in the trial for approximately 90 days.

Patients who successfully complete the study will be eligible to enroll into an open-label study (SD-006).

## 10.5. Treatment Accountability and Compliance Checks

The Sponsor or Designee will be responsible for performing drug accountability for the dermal cream. The medication provided for this study is for use only as directed in the protocol. It is the Investigator/Institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, so as to ensure that:

- Deliveries of such products are correctly received by a responsible person
- Such deliveries are recorded
- Study treatments are handled and stored safely and properly as stated on the label
- Study treatments are only dispensed to study patients in accordance with the protocol
- Any unused products may be destroyed by the site or returned to the investigational product distribution center for destruction.

At the end of the study, it must be possible to reconcile delivery records with records of usage and destroyed stock. Records of usage should include the identification of the person to whom the study treatment was dispensed, the quantity of the study cream and date of dispensing. This record is in addition to any drug accountability information recorded on the electronic case report form (eCRF). Any discrepancies must be accounted for on the appropriate forms. Certificates of initial and any subsequent deliveries and destruction must be signed, preferably by the Investigator or a pharmacist, and copies retained in the Investigator Site File.

## 10.6. Treatment Blinding Code

The medical care of the trial subjects includes medical decisions such as whether to start or stop treatment or institute alternative treatment if required. In emergency situations, the Investigator may need to break the treatment code immediately, or as quickly as possible if he/she finds it is in the best interest of the trial subject. If the blinding is

prematurely broken, it is the responsibility of the Investigator to promptly document and explain any unblinding to the Sponsor.

## 10.7. Concurrent Therapy

Administration of the following medications is acceptable and will not result in the withdrawal of patient.

- Oral and topical antihistamines
- Topical antibiotics
- Systemic antibiotics
- Inhaled steroids and ophthalmic drops containing steroids
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Limited steroid use is acceptable for planned medical procedures, including but not limited to, esophageal dilatation
- Morphine or other narcotic pain relievers
- Vitamins

Medications considered necessary for the patient's welfare (intercurrent illness or AEs) may be given at the discretion of the Investigator. The Investigator should consider the necessity of any therapy before prescribing it to the patient. Subjects must be instructed not to take any medications without prior consultation with the Investigator, as feasible. The administration of all such medication / therapy must be recorded in the appropriate section of the eCRF and will be assessed at each visit.

### 10.7.1. Prohibited Medications

**The use of immunosuppressive agents or corticosteroids (oral, rectal, intravenous, and topical) are prohibited** (however, limited steroid use is acceptable for planned medical procedures, including but not limited to, esophageal dilatation). Use of prohibited medications during the trial may result in the withdrawal of the subject based on the assessment by the Investigator and medical monitor.

# 11. STUDY SCHEDULE

| **Procedure**<br>**Visit** | **1**<br>**Screening/ Baseline** | **2**<br>**Week 2** | **3**<br>**Month 1** | **4**<br>**Month 2** | **5**<br>**Month 3 Final Visit/ ET** |
|---|---|---|---|---|---|
| **Study Day** | **(-7) to (0)** | **14 (±5d)** | **30 (±7d)** | **60 (±7d)** | **90 (±7d)** |
| Informed consent /assent signed | X | | | | |
| Inclusion/Exclusion assessment | X | | | | |
| Demographic, medical and medication history | X | | | | |
| Physical examination [a] | X | | | | X |
| Height, weight, and temperature | X | | | | X |
| Identify and document location of one target wound. | X | | | | |
| Assess target wound with ARANZ. If healed, assess for scarring | X | X | X | X | X |
| Assess overall itching [c] | X | X | X | X | X |
| Assess overall pain with age-appropriate scale [c] | X | X | X | X | X |
| Assess BSA of lesional skin | X | X | X | X | X |
| Assess BSA of wound burden | X | X | X | X | X |
| Urine pregnancy test (females only) [b] | X | | X | X | X |
| Administer first dose of SD-101 cream | X | | | | |
| Dispense pain and itching scales for completion during next 7 days of at home treatment [c] | X | | | | |
| Collect and review pain and itching scales completed at home [c] | | X | | | |
| Dispense diaries | X | | X | X | |
| Collect and review diaries | | | X | X | X |
| Dispense SD-101 cream | X | | X | X | |
| Collect SD-101 cream for the purpose of drug accountability | | | X | X | |
| Collect all SD-101 cream for final drug accountability | | | | | X |
| Monitor adverse events | | X | X | X | X |
| Monitor use of concomitant medications | X | X | X | X | X |

a. A complete physical examination will be performed at Visits 1 and 5.
b. Urine pregnancy test will be performed at Visits 1, 3, 4, and 5.
c. Itching will be assessed using the "Itch Man Pruritus Assessment Tool". For patients up to 5 years of age itching will be assessed using caretaker's response and patients 6 years of age and older will self-report their itching assessments. Pain will be assessed using the "FLACC scale" for patients up to 3 years of age and for patients 4 years of age and older the "Wong Faces Pain Scale" will be utilized.

## 11.1. Efficacy Assessments

Time to complete target wound closure within 3 months and the proportion of patients experiencing complete target wound closure within 3 months are the primary measures of efficacy.

The key secondary measures of efficacy include:

- Proportion of patients experiencing complete closure of their target wound within 2 months
- Proportion of patients experiencing complete closure of their target wound within 1 month
- Change in lesional skin based on BSAI at Month 3, compared to Baseline
- Change in Total Body Wound Burden based on BSAI at Month 3, compared to Baseline
- Change in itching assessed at Week 1 (Day 7), compared to Baseline
- Change in pain assessed at Week 1 (Day 7), compared to Baseline

Other secondary measures of efficacy include:

- Change in Total Body Wound Burden based on BSAI at Week 2 and Months 1 and 2, compared to Baseline
- Percent change from Baseline in Total Body Wound Burden based on BSAI at Week 2 and Months 1, 2, and 3
- Change in lesional skin based on BSAI at Week 2 and Months 1 and 2, compared to Baseline
- Percent change in lesional skin based on BSAI at Week 2 and Months 1, 2, and 3, compared to Baseline
- Presence of scarring of healed target wound at the visit where the complete closure is documented
- Change in target wound characteristics (ie, inflammation, blistering, granulation tissue, erythema, exudate) at Week 2 and Months 1, 2, and 3, compared to Baseline
- Change in itching and pain at Days 1 to 6, Week 2, and Months 1, 2, and 3, compared to Baseline
- Proportion of patients experiencing target wound closure within Week 2

## 11.2. Safety Assessments

The safety of SD-101-0.0 and SD-101-6.0 dermal creams, applied daily to the entire skin surface, will be assessed by monitoring tolerability, AEs, and physical examinations.

For timing of individual measurements, refer to Section 11, Study Schedule.

**Physical Examination Including Height/Length, Weight, and Temperature**

Physical examinations will be done by a physician. 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.

**Urinalysis**

Urine pregnancy tests will be performed for female patients of child bearing potential (sensitivity at least 25 mIU/mL) at Visits 1, 3, 4, and 5.

## 11.3. Adverse Events

Adverse events (AEs) may be volunteered spontaneously by the patient or discovered as a result of general, non-leading questioning. All AEs should be recorded in the eCRF. Adverse events will be collected after signing the informed consent/assent through Visit 5 and these AEs will be followed up to 30 days after the last dose of study drug has been administered. This follow up is not required for subjects who enter the SD-006 study.

In the case of withdrawal due to an AE/SAE, the patient will be followed until resolution of the AE, or until in the opinion of the Investigator, the event has stabilized, or the Investigator does not expect any further improvement or worsening of the subject's condition, and the patient is referred to their primary physician for appropriate management of the ongoing event. Reasonable efforts will be made to contact a patient who fails to attend any follow-up appointments, in order to ensure that he/she is in satisfactory health.

## 11.4. Definitions

**Adverse Event (AE)**

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 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.

The routine evolution of the disease condition under treatment according to the protocol will be evaluated as part of the disease symptoms assessments. Changes in the disease condition may not qualify as AEs. However, if there is a clinically relevant worsening of a sign or symptom of the condition under treatment and the outcome fulfills the definition of an AE, it must be reported as directed in the protocol.

**Adverse Drug Reaction (ADR)**

All events considered to be noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out.

**Serious Adverse Event (SAE)**

An AE that at any dose:

- Results in death
- Is life-threatening (ie, the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- Results in hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly / birth defect
- Is considered to be an important medical event

Based upon medical and scientific judgment, important medical events that may not be immediately life-threatening, or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above may be considered an SAE.

Hospitalizations are defined as initial or prolonged admissions that include an overnight stay. Hospitalization or prolonged hospitalization for technical, practical, or social reasons, in the absence of an AE is not an SAE.

**Pregnancy**

Pregnancy itself is not considered an AE. Pregnancies will be reported and documented on a separate pregnancy report form provided to the sites. However, any pregnancy complication, spontaneous or elective abortion, still birth, neonatal death, or congenital anomaly will be recorded as an SAE.

**Unexpected Adverse Drug Reaction**

An adverse reaction, the nature or severity of which is not consistent with applicable product information (eg, Investigators Brochure for an unapproved investigational medicinal product).

**Suspected Unexpected Serious Adverse Reaction (SUSAR)**

A SUSAR is an SAE that is suspected to be related to the administered medicinal product and the nature or severity of which is not consistent with applicable product information.

### 11.4.1. Assessment of Causality

**Severity**

The severity (intensity) of each AE will be classified by the Investigator as:

- **Mild**: Awareness of sign of symptom, but easily tolerated
- **Moderate:** Sign or symptom causes discomfort, but does not interfere with normal activities
- **Severe:** Sign or symptom of sufficient intensity to interfere with normal activities

**Causality**

The likely relationship of each AE to the medicinal product will be assessed by the Investigator and reported according to the definitions below:

- **Unrelated**
  - Event occurred before dosing or
  - Event or intercurrent illness due wholly to factors other than drug treatment.
- **Possibly**
  - Reasonable temporal relationship with drug treatment.
  - Event could be explained by patient's clinical state or other factors.
- **Probably**
  - Reasonable temporal relationship with drug treatment.
  - Likely to be known reaction to agent or chemical group, or predicted by known pharmacology.
  - Event cannot easily be explained by patient's clinical state or other factors.
- **Definitely**
  - Distinct temporal relationship with drug treatment.
  - Known reaction to agent or chemical group, or predicted by known pharmacology.
  - Event cannot be explained by patient's clinical state or other factors.

### 11.4.2. Adverse Event Reporting

The Investigator shall immediately report any serious adverse event that occurs to the Sponsor. Immediate reporting allows the Sponsor to take the appropriate measures to address potential new risks in a clinical trial. Therefore, the immediate report should be made by the Investigator within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the serious adverse event

The Sponsor is required to expedite the reporting to all concerned Investigators / Institutions, to the Institutional Review Boards (IRBs), where required, and to the regulatory authorities of all ADRs that are serious unexpected and reasonably associated

with the investigational product as assessed by the Sponsor. Such expedited reports should comply with the applicable regulatory requirements and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A). The Sponsor should submit to the regulatory authorities all safety updates and periodic reports, as required by applicable regulatory requirements.

The Sponsor will submit to the regulatory authorities all safety updates and periodic reports, as required by applicable regulatory requirements.

### 11.5. Concomitant Medications

All concomitant medications will be recorded.

## 12. STATISTICAL CONSIDERATIONS

This section outlines the general statistical considerations for the study. Details regarding study statistics are described in the Statistical Analysis Plan.

### 12.1. Estimated Sample Size

The primary efficacy endpoints for this study are the time to complete target wound closure within 3 months and the proportion of patients experiencing complete closure of their target wound within 3 months. These variables will be compared between SD-101-6.0 and SD-101-0.0 (placebo) via step-down testing to control type 1 error at overall level of 0.025 1-sided. Time to complete target wound closure is the first endpoint to be tested. Complete target wound closure is defined as skin re-epithelialization without drainage. The two treatment groups will be compared with respect to the primary endpoints using Cox Proportional Hazards model and Logistic Regression, respectively. Both models will be adjusted for covariates. For time to complete target wound closure, which is the first primary endpoint to be tested, the data will be right censored at 3 months or at the time of withdrawal from the study. If the first primary endpoint is significant, then the successful evidence of efficacy of SD-101-6.0 will be concluded and testing will proceed further to the second primary endpoint and then to the key secondary endpoints.

For the second primary endpoint and for relevant secondary endpoints, missing data will be imputed using Multiple Imputation (MI) method with the Missing At Random (MAR) assumption. Details will be described in the Statistical Analysis Plan.

To assess the robustness of the missing data, imputation methodology sensitivity analyses will also be conducted including an approach that subjects with missing wound healing data within month 3 will be considered ‘failures’ for the wound healing rate. Details will be provided in the Statistical Analysis Plan.

Assumptions underlying the sample size estimation are that 35% of placebo patients will experience complete closure of their target wound at or before the 3-month follow-up

visit and at least 60% of patients treated with SD-101-6.0 will experience complete closure of their target wound by this time (hazard ratio approximately 2.127, assuming exponential hazards over time). Note that ALL wounds are open at baseline; hence, the survival endpoint is an open wound. It is expected that fewer wounds will stay open on test treatment than on placebo; hence, the expected proportions of open wounds at 3 months are 65% on placebo and 40% on test treatment, which corresponds to a HR=2.127. These yield the 35% expected wound closures for placebo (35% = 100% - 65% surviving open), and 60% for SD-101-6.0 (60% = 100% - 40% surviving open). Using these assumptions and a 1-sided overall alpha of 0.025, approximately 150 patients will be required (75 in each group) to provide at least 86% power for time to complete target wound closure. There is estimated 85% power for the proportion of patients with complete target wound closure.

Therefore, approximately 150 patients are to be enrolled.

## 12.2. Study Populations

**Analysis Populations**

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

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

**Intent-to-Treat (ITT) Population**

The intent-to-treat (ITT) population will be defined as all patients who have been randomized to study treatment. These patients will be analyzed according to the assigned treatment.

**Safety (SAF) Population**

The Safety (SAF) population is defined as all randomized patients who applied/were administered the study medication at least once. These patients will be analyzed according to the treatment actually received.

**Per Protocol (PP) Population**

The per protocol (PP) population will be defined as the ITT patients who have no major protocol deviations and have target wound data at baseline and from ≥1 post-baseline assessment.

Major protocol deviations include but are not limited to:

1. Entry criterion deviations that impact primary endpoint analyses

2. Non-compliance to study drug (as defined by compliance to study drug <70% as per patient diary)
3. Administrative dispensing errors

A final list of major protocol deviation criteria and patients who have any major protocol deviations will be documented before final database lock. A listing will also be created.

## 12.3. Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented for the ITT Population and Safety Populations by treatment group.

Continuous variables such as patient age, weight, height/length and temperature, will be summarized using number of observations, mean, standard deviation, median, minimum, and maximum values. Categorical variables such as patient sex and race will be summarized using number of observations and percentages for each category.

Medical history and concomitant medications will be summarized using the number of observations and percentages of patients reporting each category.

## 12.4. Statistical Methods for Efficacy Parameters

Primary Efficacy Parameters:

The primary efficacy endpoints for this study are the difference between SD-101-6.0 and SD-101-0.0 (placebo) in:

- The time to complete target wound closure within 3 months
- The proportion of patients experiencing complete closure of their target wound within 3 months

The two treatment groups will be compared with respect to the primary endpoint using Cox Proportional hazards model and Logistic Regression, respectively. Covariates in both models are: baseline target wound size, target wound age, and EB type. The proportional hazards assumption will be assessed and if important departure is observed, then the stratified log rank test will be used. For the time to target wound closure analysis, data will be right censored at 3 months or the time of withdrawal from the study.

For the proportion of patients with complete target wound closure, missing data will be imputed using the Multiple Imputation (MI) method with the Missing At Random (MAR) assumption.

To assess the robustness of the missing data, imputation methodology sensitivity analyses will also be conducted including an approach that subjects with missing wound healing data within month 3 will be considered ‘failures’ for the wound healing rate. Details will be provided in the Statistical Analysis Plan.

Key Efficacy Endpoints:

Key secondary efficacy parameters include the following:

- Proportion of patients experiencing complete closure of their target wound within 2 months
- Proportion of patients experiencing complete closure of their target wound within 1 month
- Change in lesional skin based on BSAI at Month 3, compared to Baseline
- Change in Total Body Wound Burden based on BSAI at Month 3, compared to Baseline
- Change in itching assessed at Day 7, compared to Baseline
- Change in pain assessed at Day 7, compared to Baseline

Other Secondary Efficacy Endpoints:

Other secondary efficacy endpoints include the following:

- Change in Total Body Wound Burden based on BSAI at Week 2 and Months 1 and 2, compared to Baseline
- Percent change from Baseline in Total Body Wound Burden based on BSAI at Week 2 and Months 1, 2, and 3
- Change in lesional skin based on BSAI at Week 2 and Months 1 and 2, compared to Baseline
- Percent change in lesional skin based on BSAI at Week 2 and Months 1, 2, and 3, compared to Baseline
- Presence of scarring of healed target wound at the visit where the complete closure is documented
- Change in target wound characteristics (ie, inflammation, blistering, granulation tissue, erythema, exudate) at Week 2 and Months 1, 2, and 3, compared to Baseline
- Change in itching and pain at Days 1 to 6, Week 2, and Months 1, 2, and 3, compared to Baseline
- Proportion of patients experiencing target wound closure within Week 2

A detailed Statistical Analysis Plan will be completed prior to database lock.

## 12.5. Statistical Methods for Safety Parameters

Adverse events will be coded using MedDRA. The number of events, incidence, and percentage of treatment-emergent AEs (TEAE) will be calculated overall, by system

organ class (SOC), and by preferred term. Treatment-emergent AEs will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be summarized.

Baseline and Month 3 physical examination results, together with changes during the study period, will be described using summary statistics.

# 13. END OF THE STUDY

The end of the study will be defined as the last patient's last visit.

The study will be terminated early if, in the opinion of the Sponsor, Investigators, or IRBs, an unacceptable risk to the safety and welfare of patients is posed by the continuation of the study in light of review of the key unexpected AEs occurring during the trial.

Within the provisions of informed consent / assent and good clinical judgment with respect to safety, every attempt will be made to have patients complete the study.

The following reasons are grounds to terminate a patient's participation in the study:

1. Patient develops intolerable adverse effects, including but not limited to:
    - Severe and widespread dermatological reactions beyond the area of application.
    - Severe local reactions requiring systemic steroid therapy.
2. Any patient who becomes significantly noncompliant with study drug administration, study procedures, or study requirements should be withdrawn from study treatment when the circumstances increase risk to the subject or substantially compromise the interpretation of study results.
3. The patient's health would be jeopardized by continued participation.
4. Investigator judgment deems it appropriate.
5. The patient wishes to withdraw for any reason.
6. The Sponsor elects to end the study, or any portion thereof, for any reason.

# 14. ETHICAL CONDUCT OF THE STUDY

This study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki and in compliance with the protocol, International Conference on Harmonisation [ICH] GCP, and applicable local legal and regulatory requirements (including ICH guidelines, the European Union Clinical Trials Directive 2001/20/EC, the GCP Directive 2005/28/EC, the requirements of local IEC/IRB, and the US Code of Federal Regulations, Title 21 CFR Part 50, 54, 56 and 312).

## 14.1. Independent Ethics Committee (IEC) and Relevant Authorities

This protocol and the subject informed consent form (ICF) must be reviewed and approved by an institutional review board (IRB)/independent ethics committee (IEC) complying with the requirements of 21 CFR Part 56 and local regulatory requirements before subject enrollment at each site. The letter (or certificate of approval) from the IRB/IEC must be received by the Sponsor or its designee prior to delivery of clinical supplies. The IRB/IEC will be notified of any SAE or suspected unexpected serious adverse reaction in accordance with local regulatory requirements.

Any changes to the study design will be formally documented in protocol amendments and approved by the IRB prior to implementation, except in the case of changes made to protect patient safety, which will be implemented immediately.

Clinical Trial Authorization will be obtained prior to initiation of the study from the US Food and Drug Administration.

## 14.2. Informed Consent

The principles of informed consent in the Declaration of Helsinki, in ICH Good Clinical Practice and in US 21 CFR Part 50 (Protection of Human Subjects) will be implemented before any protocol-specified procedures or interventions are carried out.

A signed informed consent / assent form (ICF) shall be obtained from each patient and/or legal guardian if under 18 years of age prior to entering the study. The Investigator is responsible for obtaining written informed consent / assent from the patient and or legal guardian after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or any study medications are administered. Information should be given in both oral and written form whenever possible and deemed appropriate by the IRB. Patients will also be asked to consent to allow the Sponsor, Sponsor representative or external regulatory auditor to review their medical records to confirm compliance with GCP.

The acquisition of informed consent / assent should be documented in the patient's medical record and the ICF should be signed and personally dated by the patient and or legal guardian and by the person who conducted the informed consent / assent discussion (not necessarily by the Investigator). The original signed ICF should be retained in the Investigator Site File and a copy of the signed consent should be provided to the patient prior to participation in the trial.

The patient will be informed that they may withdraw from the study at any time without prejudice to further treatment. They will receive all information that is required by local regulations and ICH guidelines.

# 15. STUDY AND DATA MANAGEMENT

## 15.1. Protocol Amendments

No amendments to the protocol will be implemented prior to agreement from the Sponsor, and prior to approval from appropriate authorities.

## 15.2. Monitoring

The study monitor will review the progress of the study on a regular basis to ensure adequate and accurate data collections. Monitoring site visits to review eCRFs, patient case notes, patient diaries, administrative documentation including the Investigator Site File and frequent telephone communications with site will be performed throughout the study.

At each study monitoring visit the Investigator will make available all records pertaining to the study. To allow sufficient time to assemble documentation for the study monitor, monitoring visits will be confirmed in advance of planned visits.

All relevant communications, between the Sponsor, designated study representative, and Investigator should be documented for the study file.

## 15.3. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the Investigator[s]/Institution[s] will permit study-related audits, IRB/IEC review, and regulatory inspection[s], providing direct access to source data/documents.

The Sponsor or Sponsor representative or external regulatory agency may at any time during or after completion of the study conduct a Good Clinical Practice (GCP) audit.

Prior notice will be given to each site selected for audit in advance of a planned GCP audit.

## 15.4. Data Recording

The Investigator has the responsibility for ensuring that all source documents (ie, study and/or medical records and patient's diary) are completed and maintained according to the study protocol, and are available at the site.

Patients/Caretaker will utilize the diaries to record the following:

- Date cream is applied
- Rate overall itching each day, at a similar time during the day outside of wound care/dressing changes or applying the cream, for the first 7 days of treatment at home

- Rate overall skin pain each day, at a similar time during the day outside of wound care/dressing changes or applying the cream, for the first 7 days of treatment at home

## 15.5. Data to be Considered as Source Data

The following are considered source data: Informed consents, laboratory reports, patient files, IMP accountability list, and patient´s diary.

The following information must be entered in the patient's file:

- Patient's name, address and date of birth
- Patient's weight, height/length, and temperature
- Medical history
- Bandage history including (type of bandage used and frequency of usage)
- Concomitant medication
- Unambiguous reference to the clinical study (clinical study number, screening number and patient number)
- Information on main selection criteria (diagnosis)
- Dates of study drug administration and amount of drug used/returned by the subject
- Date of informed consent / assent
- Physical examinations and results done at the appropriate visits
- Dates and time of urine pregnancy test
- Body Surface Area calculation sheets for lesional skin and wound burden
- Pain Scales
- Itching Scales
- Anatomical location of the target wound and corresponding ARANZ report with photograph
- Documentation of EB diagnosis
- Did AE(s) occur, improve or worsen?
- Date of discontinuation / completion of the clinical study.
- For patients that are lost to follow-up, the site is to document attempts made to contact the patient, ie, telephone, email, certified letter

Relevant general medical and medication history needs to be checked and documented in the eCRF.

All other data recorded directly in the eCRF (ie, no prior written or electronic record of data) will be considered as source data.

## 15.6. Confidentiality

The Investigator must assure that the patients' anonymity will be maintained. On all study documentation, with the exception of the consent form, patient ID logs or as

otherwise outlined and agreed within the Informed Consent/Assent, patients will only be identified by their unique identification code and initials and will not be referred to by name.

## 15.7. Retention of Study Data

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the test article for investigation. If it becomes necessary for the Sponsor or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records. During the study, the Investigator must make study data accessible to the Sponsor, IRB and the Food and Drug Administration. A file for each patient must be maintained that includes the signed ICF and copies of all source documentation related to that patient. The Investigator must ensure the availability of source documents from which the information on the eCRF was derived.

## 15.8. Communication and Publication of Results

The results of the study will be presented in an integrated Clinical Study Report according to GCP.

The results from the study will be presented to the Principal Investigators when the statistical analyses have been completed. On the basis of these data, the CRO in cooperation with the Sponsor, will write and report on the trial.

A summary of the Clinical Study Report will be sent to the regulatory authorities and to the IRB after termination of the study.

The Clinical Study Report shall form the basis for a manuscript intended for publication in an international, scientific journal at a suitable time agreed to by the Sponsor.

No data from the study will be published, presented, or communicated without the mutual agreement of the Sponsor.

This is a multi-site study, and results from an individual site will not be published before the first multi-site publication by the Sponsor. If there is no multi-site publication within 18 months after the study has been completed or terminated at all sites and all data have been received, an individual site will have the right to publish its results, subject to the following requirements:

- Prior to submitting or presenting a manuscript or other study-related material to a publisher, reviewer, or other external party, the Investigator or site will provide the Sponsor with a copy of the manuscript or other material, and the Sponsor will have 60 days from receipt of the material to review it and comment.

- At the Sponsor's request, the Investigator or site will remove any confidential information, other than study results, prior to submitting or presenting the material.
- The Investigator or site will, at the Sponsor's request, further delay publication or presentation for up to 120 days, to allow the Sponsor to protect its interests in any of its inventions described in the material (Netherlands CEC).

## 16. SIGNATURES AND AGREEMENT WITH THE PROTOCOL

**Sponsor Approval**

*I have reviewed and approved the protocol and confirm that the protocol follows GCP.*

Signature: PPD

Date: 14 March 2017

Amicus Therapeutics

Signature: PPD

Date: 13 MARCH 2017

Amicus Therapeutics

Signature: PPD

Date: 13 MAR 2017

Amicus Therapeutics

## Principal Investigator Approval

*I agree to conduct the study according to the terms and conditions of this protocol, current Good Clinical Practice and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.*

Signature: _____ Date: _____
Name of Principal Investigator

Printed: _____
Name of Principal Investigator

# 17. APPENDICES

## 17.1. Appendix 1: EB Subtypes

**Clinical Features of EB**

Epidermolysis Bullosa Simplex (EBS)

| EBS Subtypes | Features |
|---|---|
| Weber-Cockayne | • Most common and localized form of EBS.<br>• Blisters develop on hands and feet in response to friction.<br>• Usually presents in infancy as child is starting to crawl and walk.<br>• Lesions heal without scarring but there may be thickening of the skin on soles and palms. |
| Koebner | • Generalized EBS where blisters develop all over the body but commonly on hands, feet and extremities.<br>• Presents at birth or early in infancy.<br>• May be mild involvement of mucous membranes and nails.<br>• Thickening of skin and plaques develop on palms and soles. |
| Dowling-Meara | • Generalized and severe form of EBS.<br>• Presents at birth with blistering on the face, trunk and limbs.<br>• Thickened skin may cause calluses that limit or interfere with joint movement.<br>• Nails often affected.<br>• May involve other organs including inside the mouth, gastrointestinal and respiratory tract.<br>• Widespread involvement may cause death in infancy but usually there is significant improvement with age. |
| EB with muscular dystrophy | • Due to plectin mutation.<br>• Variable degree of blistering followed later in life by muscular dystrophy.<br>• Muscular dystrophy does not arise in all cases with plectin mutation. |

Recessive Dystrophic Epidermolysis Bullosa (RDEB)

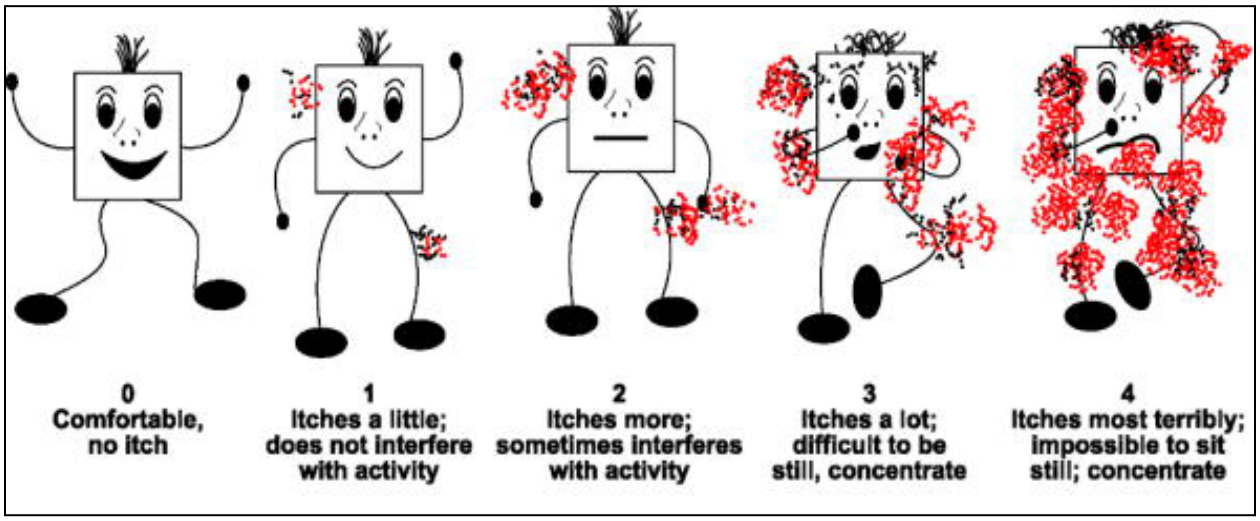
| DEB Subtypes | Features |
|---|---|
| Recessive DEB | • May present with severe blistering (Hallopeau-Siemens) or mild disease (non-Hallopeau-Siemens).<br>• Generalized severe blistering is more common and involves large areas of skin and mucous membranes.<br>• Blisters heal but with scarring and deformity causing limited movement as fingers and toes may be fused together (mitten hands).<br>• Complications such as infection, malnutrition and dehydration may cause death in infancy and those that survive are at great risk of developing squamous cell carcinoma.<br>• Milia (small white cysts) are often present at healed but scarred sites. |

Junctional Epidermolysis Bullosa (JEB)

| JEB Subtypes | Features |
|---|---|
| Non-Herlitz JEB | • Generalized blistering and mucosal involvement present at birth or soon after.<br>• Scalp, nails and teeth involved.<br>• Often sparse hair.<br>• Complications such as infection, malnutrition and dehydration may cause death in infancy but many survive. |

## 17.2. Appendix 2: Itch Man Pruritus Assessment Tool

Itch Man Pruritus Assessment Tool




Reference: Morris V, Murphy L, Rosenberg M, Rosenberg L, Holzer C, Meyer W. Itch Assessment Scale for the Pediatric Burn Survivor. Journal of Burn Care & Research. 2012; 33(3): 419-424.

## 17.3. Appendix 3: FLACC Behavioral Scale

### FLACC Behavioral Scale

| **Categories** | **Scoring** | | |
|---|---|---|---|
| | **0** | **1** | **2** |
| Face | No particular expression or smile | Occasional grimace or frown, withdrawn, disinterested | Frequent to constant frown, clenched jaw, quivering chin |
| Legs | Normal position or relaxed | Uneasy, restless, tense | Kicking, or legs drawn up |
| Activity | Lying quietly, normal position, moves easily | Squirming, shifting back and forth, tense | Arched, rigid, or jerking |
| Cry | No cry (awake or asleep) | Moans or whimpers, occasional complaint | Crying steadily, screams or sobs, frequent complaints |
| Consolability | Content, relaxed | Reassured by occasional touching, hugging, or being talked to, distractable | Difficult to console or comfort |
| Each of the five categories (F) Face; (L) Legs; (A) Activity; (C) Cry; (C) Consolability is scored from 0-2, which results in a total score between zero and ten. | | | |

## FLACC Behavioral Pain Scale

**Patients who are awake:** Observe for at least 1-2 minutes. Observe legs and body uncovered. Reposition patient or observe activity, assess body for tenseness and tone. Initiate consoling interventions if needed

**Patients who are asleep:** Observe for at least 2 minutes or longer. Observe body and legs uncovered. If possible reposition the patient. Touch the body and assess for tenseness and tone.

**F**ace

Score 0 point if patient has a relaxed face, eye contact and interest in surroundings

Score 1 point if patient has a worried look to face, with eyebrows lowered, eyes partially closed, cheeks raised, mouth pursed

Score 2 points if patient has deep furrows in the forehead, with closed eyes, open mouth and deep lines around nose/lips

**L**egs

Score 0 points if patient has usual tone and motion to limbs (legs and arms)

Score 1 point if patient has increase tone, rigidity, tense, intermittent flexion/extension of limbs

Score 2 points if patient has hyper tonicity, legs pulled tight, exaggerated flexion/extension of limbs, tremors

**A**ctivity

Score 0 points if patient moves easily and freely, normal activity/restrictions

Score 1 point if patient shifts positions, hesitant to move, guarding, tense torso, pressure on body part

Score 2 points if patient is in fixed position, rocking, side-to-side head movement, rubbing body part

**C**ry

Score 0 points if patient has no cry/moan awake or asleep

Score 1 point if patient has occasional moans, cries, whimpers, sighs

Score 2 points if patient has frequent/continuous moans, cries, grunts

**C**onsolability

Score 0 points if patient is calm and does not require consoling

Score 1 point if patient responds to comfort by touch or talk in $\frac{1}{2}$- 1 minute

Score 2 points if patient require constant consoling or is unconsoled after an extended time

Whenever feasible, behavioral measurement of pain should be used in conjunction with self-report. When self-report is not possible, interpretation of pain behaviors and decision making regarding treatment of pain requires careful consideration of the context in which the pain behaviors were observed.

Each category is scored on the 0-2 scale which results in a total score of 0-10

**Assessment of Behavioral Score:**

0 = Relaxed and comfortable

1-3 = Mild discomfort

4-6 = Moderate pain

7-10 = Severe discomfort/pain

## 17.4. Appendix 4: Wong-Baker FACES Pain Rating Scale

**Subject #_____Wong-Baker FACES® Pain Rating Scale Date_____**

| 0 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|
| No Hurt | Hurts Little Bit | Hurts Little More | Hurts Even More | Hurts Whole Lot | Hurts Worst |

www.wongbakerFACES.org