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

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Sponsor: Scioderm, INC.
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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

PROTOCOL TITLE	An Open Label Extension, Multi-Center, Study to Evaluate the Safety of SD-101 Cream in Subjects with Epidermolysis Bullosa
PROTOCOL No.	SD-004
VERSION No.	4
SPONSOR	Scioderm, INC An Amicus Therapeutics Company 4601 Creekstone Drive Suite 160 Durham, NC 27703
INVESTIGATIONAL PRODUCT	SD-101 cream administration containing 6% allantoin
PHASE OF DEVELOPMENT	Open Label Extension
INDICATION AND RATIONALE	The aim is to assess the continued safety of topical use of SD-101 cream containing 6% allantoin in subjects with Epidermolysis Bullosa.
STUDY DESIGN	This is an open label extension, multi-center, study to assess the continued safety of topically applied SD-101 cream containing 6% allantoin in subjects with Simplex, Recessive Dystrophic, and Junctional non-Herlitz Epidermolysis Bullosa. SD-101 cream containing 6% allantoin will be applied topically, once a day to the entire body for the duration of the study. Subjects who successfully complete the entire SD-003 study will have the option to roll over into the SD-004 study. The baseline visit 1 will occur at the final visit date for SD-003. The Body Surface Area (BSA) coverage of blisters and lesions assessment made at the final SD-003 study visit will be used as the baseline information at visit 1 for the SD-004 study. The subject will return to the study site once every 3 months for visit 2 (14 days ±7 days from baseline) through visit 14 (1080 days ±7 days from baseline) to have Body Surface Area (BSA) assessed. Body Surface Area will be assessed at all subsequent scheduled study center visits. Scheduled study center visits occur every 6 months after visit 14 (visits 16, 18, 20, etc.). After completion of visit 14, the next subject visit (visit 15) will be a phone call from the site to the patient. Telephone visits will occur every

	6 months thereafter (visits 17, 19, 21, etc.) and include assessment of adverse events and concomitant medications only. At the Investigator's discretion, the subject may be asked to complete a study center visit in place of a phone call visit. If a study center visit is requested, no additional assessments for that visit (other than collection of information on adverse events and concomitant medications) will be required. Urine pregnancy tests will be performed at visit 4 and every 6 months up to and including the final study visit.
STUDY OBJECTIVES	**Primary Objective** The primary objective is to demonstrate in subjects with Simplex, Recessive Dystrophic, and Junctional non-Herlitz Epidermolysis Bullosa, the continued safety of SD-101 cream containing 6% allantoin. **Secondary Objective** The secondary objective is to continue to assess the change in Body Surface Area (BSA) of blisters or lesions.
PLANNED SAMPLE SIZE	Approximately 48 subjects are expected to roll over from Study SD-003 into this open-label extension.
PATIENT POPULATION Inclusion Criteria	1. Informed Consent form signed by the subject or subject's legal representative; if the subject is under the age of 18 but capable of providing assent, signed assent from the subject. 2. Subject (or caretaker) must be willing to comply with all protocol requirements. 3. Subjects must successfully complete the SD-003 study.
PATIENT POPULATION Exclusion Criteria	1. Subjects who do not meet the entry criteria outlined above. 2. Pregnancy or breastfeeding during the study. (A urine pregnancy test will be performed at the final visit for SD-003 for female subjects of childbearing potential). 3. 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 the duration of the study. Application will consist of SD-101 containing 6% allantoin.
ROUTE OF ADMINISTRATION	Topical administration of SD-101 dermal cream containing 6% allantoin
DURATION/FREQUENCY OF TREATMENT	Topical application of SD-101 containing 6% allantoin once daily for the duration of the study. The planned duration of the treatment will vary among subjects and will continue until commercialization or availability of an alternate access approach or study termination by the Sponsor (see Section 8.4 and Section 13 for details).
SAFETY ASSESSMENTS	The safety of SD-101 containing 6% allantoin will be assessed by monitoring tolerability at the application sites, adverse events, and periodic physical examinations.
STATISTICAL CONSIDERATIONS	This study is an open label extension of SD-003 and will include those patients completing that study and wishing to receive SD-101 (allantoin 6%). In general, results will be summarized using descriptive statistics.

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3. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
BSA	Body Surface Area
BSAI	Body Surface Area Index
CRF	Case Report Form
EB	Epidermolysis Bullosa
EBS	Epidermolysis Bullosa Simplex
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
JEB-nH	Junctional non-Herlitz EB
MOA	Mechanism of Action
mITT	Modified-intent-to-treat
PP	Per Protocol
RDEB	Recessive Dystrophic Epidermolysis Bullosa
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
WMA	World Medical Association

4. ADMINISTRATIVE STRUCTURE

Medical Expert (Sponsor)	Amicus 1 Cedar Brook Drive Cranbury, NJ 08512 Amicus 1 Cedar Brook Drive Cranbury, NJ 08512
Contract Research Organization Monitors	Novella Clinical 1700 Perimeter Park Drive Morrisville, NC USA 27560

5. BACKGROUND INFORMATION

There is a dearth of effective agents for skin disorders involving blistering and lesion formation. Current approved therapies are minimally effective and have safety issues. Yet an active ingredient currently approved for use in topical OTC products, allantoin, is considered safe and effective at low concentrations of 0.5% to 2.0% but only as a "skin protectant". The OTC monograph only allows claims that relate to minor cuts, scrapes, burns or chapped skin. Because historical data suggest that allantoin may have significant lesion healing properties, we believe there may be an unrealized medical opportunity for allantoin at higher concentrations beyond the traditional uses as a cosmetic moisturizer or an OTC skin protectant. Allantoin has been cited in the literature as being effective in the treatment of various types of ulcers and lesions. However, there is a near absence of well-designed clinical studies to investigate the efficacy of allantoin as a single active ingredient in humans. One reason that few studies exist exploring the effectiveness of allantoin is that it is very insoluble in any aqueous media above a concentration of 0.5%, and degrades quickly in ointments or creams. Higher solubility of allantoin in aqueous solutions is pH dependent (at pH levels above 12), but at higher pH levels allantoin is unstable and readily degrades. Hence, formulation development has been problematic. Scioderm has patented technology that overcomes the chemical stability and solubility challenges present when formulating allantoin at higher concentrations.

5.1. Overview of Drug Product

Pharmacology of Allantoin

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 capacity to deliver the active moiety to the target in skin is key in topical products, since the skin is an effective barrier to penetration. Some skin products contain ingredients thought to be active but do not provide the desired effect because of failure to cross the skin barrier, e.g., topical application of Cyclosporine A for psoriasis.

Allantoin is a well characterized substance, which is known to be the active component in the Comfrey plant, and the active ingredient in the secretions of maggots used for tissue debridement and repair. Comfrey and maggots can produce high amounts of allantoin, as high as 10%, depending on the portion of plant and time of harvesting. The mechanism of action (MOA) of allantoin is complex, including demonstrated healing properties, antibacterial effects, keratolytic activity in humans, in addition to anti-inflammatory / soothing properties.

Pharmacokinetics of Allantoin

Allantoin is a compound that is found endogenously in rats, rabbits, pigs, dogs, monkeys, in addition to a lesser 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 have been shown to be produced in great apes and humans via non-enzymatic conversion of uric acid.

5.2. Summary of Animal and Human Studies with Allantoin

Toxicology studies assessing topical administration of SD-101 (containing concentrations of allantoin up to 9%) 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 containing 9% allantoin 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 (containing 3, 6, or 9% allantoin), and in EB patients with topical usage of SD-101 (containing 1.5% or 3% allantoin) 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 (containing 1.5% allantoin) was found to be non-sensitizing in healthy subjects. Studies in human subjects or EB patients (including children) with SD-101 containing allantoin concentrations above 3% have not been conducted to date. However, the lack of local or systemic safety effects demonstrated in animals to date with topical SD-101 administration (containing up to 9% allantoin) or systemic administration of allantoin (achieving high systemic exposure), suggest that topical administration of SD-101 in healthy subjects (containing allantoin at concentrations greater than 3%) should be well tolerated.

An open-label study using SD-101 (containing a 3.0% concentration of allantoin) was previously conducted. Eight EB subjects with a diagnosis of EB (Simplex, Recessive Dystrophic, or Junctional) based on diagnostic immunomapping or electron microscopy, were treated with 3% SD-101 cream applied once 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 3% SD-101 for three months showed significant improvements in the complete healing of lesions (typified by the results with the target lesions), statistically significant and clinically meaningful reductions in the extent of total skin surface involvement with active disease (BSA), and reduced pain and itching. Daily use of 3% SD-101 cream in treatment up to 3 months was well tolerated by all patients in the study, with no related adverse events noted. There were no serious adverse events that occurred in any patient during the 3 month treatment period.

6. RATIONALE FOR STUDY

The aim is to assess the continued safety of SD-101 cream (6% allantoin) in the treatment of subjects with Epidermolysis Bullosa.

7. STUDY OBJECTIVES AND PURPOSE

7.1. Primary Objective

The primary objective is to demonstrate in subjects with Simplex, Recessive Dystrophic, and Junctional non-Herlitz Epidermolysis Bullosa, the continued safety of SD-101 cream containing 6% allantoin.

7.2. Secondary Objective

The secondary objective is to continue to assess the change in Body Surface Area (BSA) of blisters or lesions.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Numbers

Up to forty-eight EB patients are expected to be enrolled at seven study centers, following completion of their participation in Study SD-003.

8.2. Inclusion Criteria

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

1. Informed Consent form signed by the subject or subject's legal representative; if the subject is under the age of 18 but capable of providing assent, signed assent from the subject.
2. Subject (or caretaker) must be willing to comply with all protocol requirements.
3. Subjects must successfully complete the entire SD-003 study.

8.3. Exclusion Criteria

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

1. Subjects who do not meet the entry criteria outlined above.
2. Pregnancy or breastfeeding during the study. (A urine pregnancy test will be performed at the final visit for SD-003 for female subjects of childbearing potential).
3. Females of childbearing potential who are not abstinent and not practicing a medically acceptable method of contraception.

8.4. Withdrawal Criteria/Study Discontinuation

Subjects may withdraw from the study at any time without stating a reason and without prejudice to further treatment. The Investigator may withdraw a subject from the study and discontinue study treatment and assessments at any time due to safety concerns. Full skin examination will be performed at each scheduled study center visit. If SD-101 causes any significant rash that has not occurred previously in the subject, the Investigator should consider discontinuing the subject. 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 subject.

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

1. Adverse Event (Adverse Reaction): Clinical events occurred that are reported that in the medical judgment of the Investigator are grounds for discontinuation in the best interests of the subject.
2. Withdrawal of Consent: The subject desired to withdraw from further participation in the study. The subject 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 subject failed to adhere to the protocol requirements, at the Investigator's discretion.

4. Lost to Follow-Up: The subject stopped coming for visits and study personnel were unable to contact the subject.
5. Other: The subject was terminated for a reason other than those listed above, such as, termination of study by Sponsor.

8.5. Handling of Withdrawals

Although a subject 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 subject's rights. If there is a medical reason for withdrawal, the subject will remain under the supervision of the study physician until in satisfactory health. In the case of withdrawal due to an adverse event, the subject will be followed per Section 11.3. Reasonable efforts will be made to contact a subject 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 Objective

The primary objective is to demonstrate in subjects, with Simplex, Recessive Dystrophic, and Junctional non-Herlitz Epidermolysis Bullosa, the continued safety of SD-101 cream containing 6% allantoin.

9.2. Secondary Objective

- Body coverage in blisters or lesions based on body surface area (BSA) measurements at Baseline (end of Study visit measurement from Study SD-003) week 2, month 3, month 6, month 9, month 12, month 15, month 18, month 21, month 24, month 27, month 30, month 33, and month 36, and each subsequent scheduled study center visit 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 scheduled study center visit to assess the total affected area before and after using the product.

BSAI of Lesional Skin Calculation Charts

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

1 ☐ Ages 0 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 blisters and/or lesions. 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.**

9.3. Study Design

This is an open label extension, multi-center study to assess the continued safety of SD-101 cream (containing 6% allantoin) in treating subjects with Simplex, Recessive Dystrophic, and Junctional non-Herlitz Epidermolysis Bullosa.

SD-101 cream (containing 6% allantoin) will be applied topically, once a day to the entire body for the duration of the study. Subjects who successfully complete the SD-003 study will be eligible to roll over into the SD-004 study. The baseline visit 1 will occur at the final visit date for SD-003. The BSA assessment from the final SD-003 study will be used as the baseline information at visit 1 for the SD-004 study. The subject will return to the study site once every 3 months for visit 2 (14 days ±7 days from baseline) through visit 14 (1080 days ±7 days from baseline) to have BSA assessed. Body Surface Area will be assessed at all subsequent scheduled study center visits. Scheduled study center visits occur every 6 months after visit 14 (visits 16, 18, 20, etc.). After completion of visit 14, the next subject visit (visit 15) will be a phone call from the site to the patient. Telephone visits will occur every 6 months thereafter (visits 17, 19, 21, etc.) and include assessment of adverse events and concomitant medications only. At the Investigator's discretion, the subject may be asked to complete a study center visit in place of a phone call visit. If a study center visit is requested, no additional assessments (other than collection of information on adverse events and concomitant medications) will be required (see Section 11 – Study Schedule for details).

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. Since a pregnancy test will be performed at the final visit for SD-003, the results from that test can be utilized for entry into the SD-004 study. In addition, a urine pregnancy test will be performed every 6 months and at the final visit.

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

10. STUDY MEDICATION AND ADMINISTRATION

10.1. Study Medication and Administration

The SD-101 cream (containing 6% allantoin) concentrations will be supplied in 8 ounce tubes, to be reclosed after use and stored at room temperature.

SD-101 dermal cream (containing 6% allantoin) will be applied once a day to the entire body for the duration of the study.

The study cream will be returned during each study center visit to evaluate compliance. Any unused study medication will be re-dispensed to the patient at each visit.

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 dermal cream (containing 6% allantoin) will be applied topically once a day to the entire body.

10.3. Allocation to Treatment

Up to forty-eight subjects may be eligible to roll over to this study and receive SD-101 (containing 6% allantoin).

10.4. Duration of Patient Participation

The planned duration of the treatment will vary among subjects and will continue until commercialization or availability of an alternate access approach or study termination by the Sponsor (see Section 8.4 and Section 13 for additional details).

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 will be destroyed in accordance with CRO processes

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 and re-dispensing. This record is in addition to any drug accountability information recorded on the 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. Concurrent Therapy

Medications considered necessary for the subject'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.

11. STUDY SCHEDULE

Procedure Visit	**1 Screening/ Baseline**	**2 Week 2**	**3 Month 3**	**4 Month 6**	**5 Month 9**	**6 Month 12**	**7, 9, 11, and 13 Months 15, 21, 27, and 33**	**8, 10, 12, and 14 Months 18, 24, 30, and 36**	**15 (odd visits) Month 39 Phone Call**	**16 (even visits) Month 42 Site Visit**	**Alternate Phone Call and Site Visit until Final Study Visit/Early Termination[a]**	**Final Study Visit/Early Termination**
Study Day (± 7 Days)	**0**	**14**	**90**	**180**	**270**	**360**	**450, 630, 810, and 990**	**540, 720, 900, and 1080**	**1170**	**1260**	**-**	**-**
Informed consent / assent signed	X											
Inclusion/Exclusion assessment	X											
Demographic, medical and medication history	X								X	X		X
Physical examination[b]	X											X
Height, weight, and temperature	X											X
Assess BSA[c]	X	X	X	X	X	X	X	X		X		X
Urine pregnancy test (females only)[d]	X			X		X		X		X		X
Dispense/re-dispense SD-101 cream[e]	X	X	X	X	X	X	X	X		X		X
Collect SD-101 cream for the purpose of drug accountability		X	X	X	X	X	X	X		X		X
Collect all SD-101 cream												X

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

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

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

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

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

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

11.1. Efficacy Assessments

The body surface coverage (BSA) of lesional skin will be measured during the study to monitor the extent of coverage with extended use of SD-101 (containing 6% allantoin).

11.2. Safety Assessments

The safety of SD-101 dermal cream (containing 6% allantoin) applied to the skin, will be assessed by monitoring tolerability at the application sites, adverse events, and physical examinations.

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

Physical Examination including height, weight, and temperature

Physical examinations will be done by a physician at the final study visit. The physical examination performed at the final visit for SD-003 will be utilized as the baseline assessment for SD-004. 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, and temperature will be recorded.

Urinalysis

Urine pregnancy test for female subjects of child bearing potential (sensitivity at least 25 mIU/mL) will be performed at visits 4, 6, 8, 10, 12, 14, and at all subsequent study center visits. The urine pregnancy test performed at the final visit for SD-003 will be utilized for entry into SD-004.

11.3. Adverse Events

Adverse events may be volunteered spontaneously by the patient or discovered as a result of general, non-leading questioning. All adverse events should be recorded in the Case Report Form. Adverse events will be collected after signing the informed consent / assent at all visits through the final study visit. Information on AEs will be followed to 30 days after the last dose of study drug has been administered.

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 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.

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, with the exception of skin site changes determined by the Investigator to be related to SD-101 dermal cream. These changes will be captured during the skin site evaluations (refer to Section 9.3). The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, *i.e.*, the relationship cannot be ruled out.

Serious Adverse Event (SAE)

An adverse event that at any dose:

- Results in death
- Is life-threatening (i.e. 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 a serious adverse event.

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 adverse event 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 AE or SAE.

Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with applicable product information (*e.g.*, Investigator's Brochure for an unapproved investigational medicinal product).

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a serious adverse event 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 adverse event 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 adverse event 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 IRBs, where required, and to the regulatory authorities of all adverse drug reactions (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 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 and non-drug therapies will be recorded. In addition, concomitant medications and non-drug therapies will be coded for those subjects that experience adverse events.

12. STATISTICAL CONSIDERATIONS

12.1. Sample Size

All patients who complete the basic protocol SD-003 and who wish to receive SD-101 (containing 6% allantoin) will be eligible to enter this open label extension.

12.2. Study Populations

Study populations are the same as defined for SD-003.

12.3. Analysis Considerations

This study is an open label extension of SD-003 and will include those patients completing that protocol and wishing to receive SD-101 (containing 6% allantoin**)**. In general, results will be summarized using descriptive statistics. Additional evaluations may be made to compare responses of patients in this extension study with their responses in SD-003.

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/ECs, an unacceptable risk to the safety and welfare of subjects is posed by the continuation of the study in light of review of the key unexpected adverse events 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 subjects complete the study.

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

1. Subject 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 subject 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 subject's health would be jeopardized by continued participation.

4. Investigator judgment deems it appropriate.
5. The subject wishes to withdraw for any reason.
6. The Sponsor elects to end the study, or any portion thereof, for any reason.
7. If SD-101 becomes commercially available, the Sponsor may transition subjects to commercial drug supply.

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 U.S. 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, and 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 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 (i.e., study and/or medical records) are completed and maintained according to the study protocol, and are available at the site.

15.5. Data to be Considered as Source Data

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

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

- Patient's name, address and date of birth
- Subject's weight, height, and temperature
- Medical history
- 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 tube count of study drug obtained at each visit indicated
- Date of informed consent / assent
- Physical examinations and results done at the appropriate visits
- Dates and time of urine pregnancy test
- Did AE(s) occur, improve or worsen?
- Date of discontinuation / completion of the clinical study
- For subjects that are lost to follow-up, the site is to document attempts made to contact the subject *i.e., telephone, email, certified letter*

All other data recorded directly in the eCRF [*i.e.*, 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 and patient ID logs, 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 Investigator is required to maintain all study documentation, including regulatory documents, copies of eCRFs, signed informed consent forms, and records for the receipt and disposition of study medications, for a period of two years following approval date of a New Drug Application for the drug, or until 15 years after completion of the study, whichever is later.

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 informed consent / assent form 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.

16. SIGNATURES AND AGREEMENT WITH THE PROTOCOL

Sponsor Approval

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

Signature: Amicus Date: 25/JAN/2017

Amicus Therapeutics

Signature: Amicus Date: 30 Jan 2017

Amicus Therapeutics

Signature: Amicus Date: 25 JAN 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
Title

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. • Blisters develop on hands and feet in response to friction. • Usually presents in infancy as child is starting to crawl and walk. • 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. • Presents at birth or early in infancy. • May be mild involvement of mucous membranes and nails. • Thickening of skin and plaques develop on palms and soles.
Dowling-Meara	• Generalized and severe form of EBS. • Presents at birth with blistering on the face, trunk and limbs. • Thickened skin may cause calluses that limit or interfere with joint movement. • Nails often affected. • May involve other organs including inside the mouth, gastrointestinal and respiratory tract. • Widespread involvement may cause death in infancy but usually there is significant improvement with age.
EB with muscular dystrophy	• Due to plectin mutation. • Variable degree of blistering followed later in life by muscular dystrophy. • 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). • Generalized severe blistering is more common and involves large areas of skin and mucous membranes. • Blisters heal but with scarring and deformity causing limited movement as fingers and toes may be fused together (mitten hands). • 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. • 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. • Scalp, nails and teeth involved. • Often sparse hair. • Complications such as infection, malnutrition and dehydration may cause death in infancy but many survive.