An Open Label Multi-Center Extension Study to Evaluate the Long-term Safety of Zorblisa™ (SD-101-6.0) in Patients 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 Multi-Center Extension Study to Evaluate the Long-term Safety of Zorblisa™ (SD-101-6.0) in Patients with Epidermolysis Bullosa**
PROTOCOL No.	SD-006
VERSION No.	3
SPONSOR	Scioderm, Inc. An Amicus Therapeutics Company 4601 Creekstone Drive Suite 160 Durham, NC 27703
INVESTIGATIONAL PRODUCT	ZORBLISA (SD-101-6.0)
PHASE OF DEVELOPMENT	Open Label Extension
INDICATION AND RATIONALE	The aim is to assess the long-term safety of topical use of ZORBLISA in patients with Epidermolysis Bullosa (EB).
STUDY DESIGN	This is an open label, multi-center extension study to assess the long-term safety of topically applied ZORBLISA in Patients with Simplex, Recessive Dystrophic, and Junctional non-Herlitz Epidermolysis Bullosa. ZORBLISA will be applied topically, once a day, to the entire body for a period of 1440 days. This study may be further extended by amendment until either SD-101 becomes commercially available or the clinical development of SD-101 in EB is discontinued. Patients who have successfully completed Study SD-005 (on study drug at Visit 5) will have the option to roll over into the SD-006 study. The baseline visit (Visit 1) will occur at Visit 5 for SD-005. The Body Surface Area (BSA) assessments of lesional skin and wound burden performed at the Visit 5 for SD-005 will be utilized as the baseline assessment for SD-006. Patients will return for follow-up visits at Months 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42,

	45, and48 after Visit 1. At each visit, assessments will include BSAI of lesional skin and wound burden. For target wounds that are not closed by the end of Study SD-005, the ARANZ picture and calculation of target wound area at the final visit for Study SD-005 will used as the baseline area size of the target wound for SD-006. These unhealed target wounds from SD-005 will be assessed via ARANZ at each subsequent scheduled visit until the target wound is documented as closed. Closed wounds will be assessed for scarring.
STUDY OBJECTIVES	**Primary Objective** The primary objective is to demonstrate the long-term safety of ZORBLISA in patients, with Simplex, Recessive Dystrophic, and Junctional non-Herlitz Epidermolysis Bullosa. **Secondary Objectives** The secondary objectives are to assess the efficacy of ZORBLISA in terms of the change in Body Surface Area (BSA) of lesional skin and wound burden; as well as closure of unhealed target wounds from the SD-005 study.
PLANNED SAMPLE SIZE	Up to approximately 150 patients are expected to roll over from Study SD-005 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. Patients who completed the SD-005 study (on study drug at Visit 5).

PATIENT POPULATION Exclusion Criteria	1. Patients 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-005 for female patients of childbearing potential and repeated at Visit 1 if these visits do not occur on the same day) 3. Females of childbearing potential who are not abstinent or not practicing a medically acceptable method of contraception.
FORMULATION/DOSE	ZORBLISA (containing 6% allantoin)
ROUTE OF ADMINISTRATION	Topical
DURATION/FREQUENCY OF TREATMENT	Once daily for 1440 days (48 months).
SAFETY ASSESSMENTS	The safety of ZORBLISA will be assessed by monitoring tolerability at the application sites, adverse events, and periodic physical examinations.
STATISTICAL CONSIDERATIONS	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-005.

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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
PP	Per Protocol
RDEB	Recessive Dystrophic Epidermolysis Bullosa
SAE	Serious Adverse Event
SD-101	Drug Product Formulation
SD-101-0.0	Contains 0% allantoin (placebo)
SD-101-1.5	Contains 1.5% allantoin
SD-101-3.0	Contains 3% allantoin
SD-101-6.0	Contains 6% allantoin – referred to as ZORBLISA
SD-101-9.0	Contains 9% allantoin
SUSAR	Suspected Unexpected Serious Adverse Reaction
WMA	World Medical Association

4. ADMINISTRATIVE STRUCTURE

Medical Expert (Sponsor)	Amicus 1 Cedar Brook Drive Cranbury, NJ 08512
Contract Research Organization Monitors	Amicus 1 Cedar Brook Drive Cranbury, NJ 08512 Chiltern, Inc. 1016 West Ninth Ave. King of Prussia, PA 19406-1221 Quintiles Suite 2, Level 10, 606 St Kilda Road Melbourne, VIC 3004 Australia HungaroTrial CRO Fehérvári út 89 95 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 (see Appendix 1 Epidermolysis Bullosa Subtypes). 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 Formulation (SD-101)

5.1.1. 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.

5.1.2. 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.

5.1.3. SD-101 Topical Cream

Allantoin is the active ingredient contained within the SD-101 topical product, 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.

The SD-101 proprietary formulation 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%.

The SD-101 topical product 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 (containing various concentrations of allantoin) 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, SD-101-3.0, and SD-101-6.0) demonstrated 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 placebo 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. The results of Study SD-003 support that SD-101-6.0 is the most efficacious and safe concentration. It is the concentration used in the 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 are the population for this study.

6. RATIONALE FOR STUDY

The aim is to assess the long-term safety of ZORBLISA in the treatment of patients with Epidermolysis Bullosa.

7. STUDY OBJECTIVES AND PURPOSE

7.1. Primary Objective

The primary objective is to demonstrate the long-term safety of ZORBLISA in patients with Simplex, Recessive Dystrophic, and Junctional non-Herlitz Epidermolysis Bullosa.

7.2. Secondary Objective

The secondary objectives are to assess the efficacy of ZORBLISA in terms of the change in Body Surface Area (BSA) of lesional skin and wound burden; as well as assessment of closure of unhealed target wounds in patients rolling over from the SD-005 study.

8. SELECTION AND WITHDRAWAL OF PATIENTS

8.1. Subject Numbers

Approximately 150 EB patients will be enrolled at study sites worldwide, following completion of their participation in Study SD-005.

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 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. Patients who completed the SD-005 study (on study drug at Visit 5).

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. Pregnancy or breastfeeding during the study. (A urine pregnancy test will be performed at the final visit for SD-005 for female patients of childbearing potential and repeated at Visit 1 if these visits do not occur on the same day)
3. Females of childbearing potential who are not abstinent or 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 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 visit. If ZORBLISA 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 ZORBLISA, 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 and Adverse Reactions: 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. In the case of withdrawal due to an adverse event the subject will be followed per Section 13.3. Reasonable efforts will be made to contact a subject who fails to attend any follow-up appointments, to ensure that he/she is in satisfactory health.

9. STUDY DESIGN AND ENDPOINTS

9.1. Study Design

This is an open label, multi-center extension study to assess the long-term safety of ZORBLISA in treating patients with Simplex, Recessive Dystrophic, and Junctional non-Herlitz Epidermolysis Bullosa. All patients must have completed SD-005 to be eligible to participate in this open label extension.

ZORBLISA will be applied topically, once a day, to the entire body for a period of 1440 days. Patients will return to the study site at Month 1, then once every 3 months until Month 48 (Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, and 48).

9.2. Primary Endpoint

The primary endpoint is the long-term safety of ZORBLISA in patients with Simplex, Recessive Dystrophic, and Junctional non-Herlitz Epidermolysis Bullosa. Safety is assessed via monitoring of local tolerability at the application sites, occurrence of adverse events and physical examinations.

9.3. Secondary Endpoints

The secondary endpoints include the change from baseline in BSA coverage of lesional skin and wound burden; as well as closure of unhealed target wounds from the SD-005 study.

9.3.1. Change from Baseline of Body Surface Area of Lesional Skin

Change in lesional skin based on BSA estimates at Months 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, and 48 compared to Baseline will be measured using the Body Surface Area Index (BSAI). The BSAI is a global measure of disease extent with weighting factors. The BSA affected with lesional skin will be calculated at baseline and at each visit to assess the total affected area before and after using the product. The BSA will be assessed as in Figure 9-1 per the definition below by a study physician. Preferably the same study physician will perform this assessment at each patient visit.

9.3.1.1. Definition of Lesional Skin for Assessment and Calculation of BSA Coverage

- Consists of area(s) that could 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 do 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.

Figure 9-1: BSAI of Lesional Skin Calculation Charts

(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.**

9.3.2. Change in Total Body Wound Burden Compared to Baseline

Change in total body wound coverage based on BSA estimates at Months 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, and 48 compared to Baseline will be measured using the BSAI. 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 to assess the total wound area before and after using the product. The BSA of wounds will be assessed by a study physician as per Figure 9-2. Preferably the same study physician will perform this assessment for each patient visit.

9.3.2.1. Definition of Wound for Assessment and Calculation of BSA Coverage

A wound is defined as an open area on the skin (epidermal covering is disrupted).

Figure 9-2: BSAI of Total Wound Burden Calculation Charts

(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.**

9.3.3. Assessment of Closure of Target Wounds Non-Healed from Study SD-005

For target wounds that are not closed by the end of Study SD-005, the ARANZ picture and calculation of target wound area at the final visit for Study SD-005 will be used as the baseline area size of the target wound for SD-006. The unhealed target wound from SD-005 will be

assessed via the ARANZ SilhouetteStar™ at each subsequent scheduled visit until the target wound is documented as closed. The closed target wound will be assessed for scarring.

9.3.3.1. 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 9-3 ARANZ SilhouetteStar™

10. STUDY MEDICATION AND ADMINISTRATION

10.1. Study Medication and Administration

ZORBLISA will be supplied in 8-ounce tubes, to be reclosed after use and stored at room temperature.

ZORBLISA will be applied once a day to the entire body for a period of 1440 days (48 months).

The study cream will be returned at Visit 3, and all visits up to and including Visit 18 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

All patients will receive ZORBLISA (containing 6% allantoin) daily.

10.3. Allocation to Treatment

All patients will receive open-label ZORBLISA.

10.4. Duration of Patient Participation

It is anticipated that each eligible subject will participate in the trial for approximately 1440 days. This study may be further extended by amendment until either SD-101 becomes commercially available or the clinical development of SD-101 in EB is discontinued.

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. 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 may be given at the discretion of the investigator. The administration of all such medication / therapy must be recorded in the appropriate section of the eCRF.

11. STUDY SCHEDULE

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

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

12. EFFICACY ASSESSMENTS

The body surface coverage (BSA) of lesional skin and wound burden will be measured at each visit via the BSAI as described in Sections 9.3.1 and 9.3.2 to monitor the extent of coverage with extended use of ZORBLISA.

Any target wound not completely healed during the SD-005 study will continue to be monitored for closure at each study visit, as described in Section 9.3.3.

13. SAFETY ASSESSMENTS

The safety of ZORBLISA 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.

13.1. Physical Examination including Height, Weight, and Temperature

The physical examination performed at the final visit for SD-005 will be utilized as the baseline assessment for SD-006 unless Visit 1 is ≥ 14 days after the final SD-005 visit, in which case a physical examination will be repeated An additional physical examination will be done by a physician at Visit 18. The following sites will be examined: head, eyes, ears, nose, throat, neck, chest, lungs, heart, abdomen, skin, and lymph nodes; and the following systems will be assessed: musculoskeletal and neurological. Weight, height, and temperature will be recorded.

13.2. Urinalysis

The urine pregnancy test performed at the final visit for SD-005 will be utilized for entry (Visit 1) into SD-006 only if the visits occur on the same day, otherwise, urine pregnancy test will be performed at Visit 1. Urine pregnancy tests for female patients of child bearing potential (sensitivity at least 25 mIU/ml) will also be performed at Visit 3 through 18.

13.3. 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 through Visit 18. 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.

Note: All AEs experienced in SD-005 and medical events occurring between the end of SD-005 and the enrollment into SD-006 after completion of SD-005 should be noted in the medical history for SD-006 at Visit 1 only.

13.3.1 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 captured during the skin site evaluations (refer to Section 9.3). A lack of efficacy (i.e. worsening EB) should not be considered an ADR. Changes outside of the intended effect (e.g. rash) should be considered ADRs. 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:

- 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.*, Investigators Brochure).

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.

13.3.2 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.

13.3.3 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.

13.4. Concomitant Medications

All concomitant medications will be recorded. In addition, concomitant medications will be coded for those patients that experience adverse events.

14. STATISTICAL CONSIDERATIONS

14.1. Sample Size

All patients who complete the basic protocol SD-005 (on study drug at Visit 5) and who wish to receive ZORBLISA will be eligible to enter this open label extension.

14.2. Study Populations

Study populations are the same as defined for SD-005.

14.3. Analysis Considerations

In general, results will be summarized using descriptive statistics. Summary statistics to be used include proportion of patients with complete closure of their target lesion at each visit, mean and standard deviation of BSAI compared with baseline at each visit, and incidence rates of specific adverse events.

Additional evaluations may be made to compare responses of patients in this extension study with their responses in SD-005. For those patients randomized to ZORBLISA in SD-005, the use of summary statistics as described in the previous paragraph will provide an understanding of the long term effect of ZORBLISA in these patients. For those patients randomized to the control arm in SD-005, summary statistics will be used to compare their response to ZORBLISA in SD-006 with their response to control in SD-005.

In addition to the evaluations described above for the primary efficacy and safety variables, secondary and exploratory variables will also be evaluated using summary statistics.

15. 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 patients 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 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.
7. If SD-101 becomes commercially available,
   the Sponsor may transition subjects to commercial drug supply.

16. 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).

16.1. 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.

16.2. 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.

17. STUDY AND DATA MANAGEMENT

17.1. Protocol Amendments

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

17.2. 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, 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.

17.3. 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.

17.4. 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.

17.5. 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
- Patient's weight, height, 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 patient
- Date of informed consent / assent
- Physical examinations and results done at the appropriate visits
- Dates and time of urine pregnancy test
- Anatomical location of the target wound and corresponding ARANZ report with photograph
- 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 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.

17.6. 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.

17.7. 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.

17.8. 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).

18. SIGNATURES AND AGREEMENT WITH THE PROTOCOL

Sponsor Approval

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

Signature: Amicus

Amicus Therapeutics

Date: 10 Nov 2016

Signature: Amicus

Amicus Therapeutics

Date: 10 Nov 2016

Signature: Amicus

Amicus Therapeutics

Date: 10 NOV. 2016

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: _____
Principal Investigator

Printed: _____
Name of Principal Investigator

19. APPENDICES

19.1. Appendix 1 Epidermolysis Bullosa 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.