Design of a Confirmatory, Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study of SD-101 6% Topical Cream in Patients With Epidermolysis Bullosa

Amy S. Paller[1], Eric Cantor[2], Allen L. Reha[2], Willistine Lenon[3], Ronald V. Nardi[3], Jamie Gault[3], Jay Barth[2]

[1]Northwestern University, Chicago, IL, USA; [2]Amicus Therapeutics, Cranbury, NJ, USA; [3]Scioderm – An Amicus Therapeutics Company, Durham, NC, USA

BACKGROUND

Epidermolysis Bullosa (EB)

- 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[1]
- In consequence, the skin is extremely fragile, which can result in shearing of the skin, causing a high risk of infection[1]
- EB types differ by physical manifestations, genetic makeup, and prognosis (**Figure 1**)[2,3]
- All forms of EB are both debilitating and life-threatening (**Table 1**)[2,3]
- In some EB subtypes, high mortality occurs before the age of 1 year (junctional Herlitz), and in others mortality occurs from adolescence to early adulthood, typically due to infection or failure to thrive[2]
- In addition, those who survive into their 20s and 30s are at risk for development of a virulent and sometimes fatal form of squamous cell carcinoma[2]
- There are no pharmaceutical products with proven efficacy that improve upon current practices for the treatment of dermal manifestations of EB, and there is no approved drug for EB in either Europe or the United States[4]

Figure 1. Sites of Primary Blister Formation in EB[3]

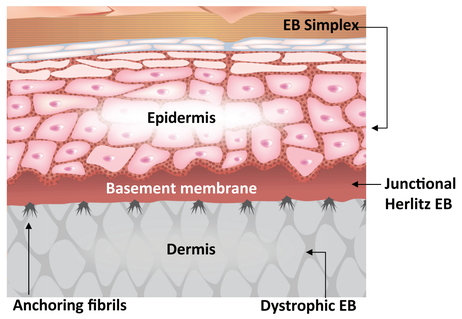


Table 1. EB Types (representing ≈99% of the patient population)[3]

Subtypes	Symptoms	Frequency	Mortality Risk
Junctional	▪ Blistering of skin/mucosa ▪ Severe complications, especially infection ▪ Usually fatal early in life	**≈5%**	
Dystrophic	▪ Skin and mucosal blistering ▪ Scarring leads to narrowing of esophagus and orificial constriction ▪ Growth retardation, anemia ▪ Higher risk of aggressive skin cancer, especially after first decade	**≈25%**	
Simplex	▪ Superficial blistering with variable extent and mucosal involvement	**≈70%**	

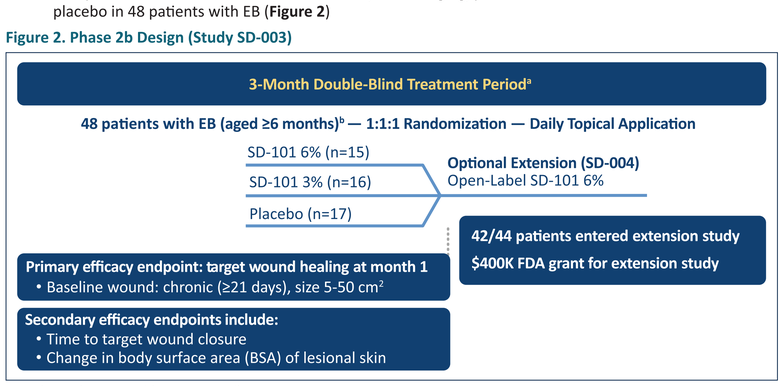
SD-101

- SD-101 is a topical investigational therapy for the treatment of EB-associated wounds
  - Is a proprietary formulation of allantoin designed to deliver a high concentration (up to 6%) in a highly stable, soluble form
  - Allantoin appears to have multiple wound-healing effects, including anti-inflammatory and antimicrobial activity and tissue formation and differentiation, specifically in stimulating development of granulations and a tendency towards epithelialization[5,6]
  - SD-101 has been studied in all major EB types (simplex, dystrophic, and junctional) in a previous phase 2b study[7]

Phase 2b Findings[7]

- Study SD-003 was a randomized, double-blind, dose-ranging, phase 2b trial of SD-101 6% or 3% or placebo in 48 patients with EB (**Figure 2**)

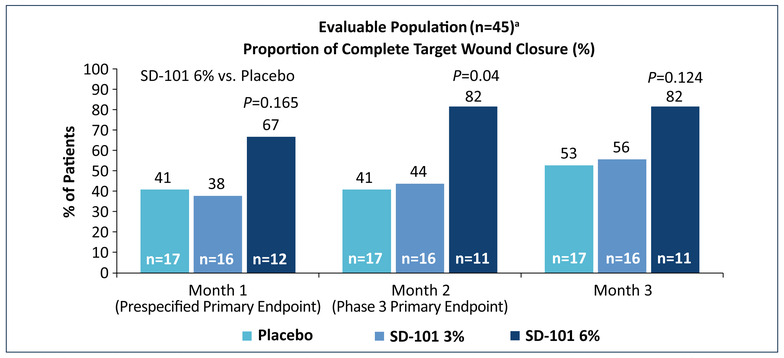
Figure 2. Phase 2b Design (Study SD-003)



Mean lesional BSA: 19.4% (range: 0.4-48%).
Mean wound age: 182 days (range: 21-1639).
FDA, US Food and Drug Administration.
[a]Assessments: 0, 14, 30, 60, and 90 days.
[b]Initial disease severity: mean target lesion size 14.0 cm² (range 5-39).

- Phase 2b results
  - Study SD-003 enrolled 48 patients with EB (intention-to-treat population: aged 0.5-43.6 years; target wound ≥21 days old measuring 5-50 cm²)
  - Efficacy
    - Complete wound healing at month 1 (primary endpoint) was found for 53%, 38%, and 41% of SD-101 6%, SD-101 3%, and placebo patients, respectively (*P*=NS)
    - In post hoc analyses (month 2; evaluable population), complete wound healing was shown in 82%, 44%, and 41% of SD-101 6%, SD-101 3%, and placebo patients, respectively (nominal *P*=0.04 for SD 101 6% vs. placebo) (**Figure 3**)
    - The treatment effect for SD-101 6% was first observed at day 14, with complete wound closure observed in 27% of patients compared with 11% of patients given placebo
    - The treatment effect for SD-101 6% was maintained throughout month 3
    - Median time-to-wound closure (evaluable population) was 30, 86, and 91 days for SD-101 6%, SD-101 3%, and placebo, respectively

Figure 3. Evaluable Population (n=45): Proportion of Complete Target Wound Closure (%)



[a]Excluded from evaluable population: 1 patient lost to follow-up and 2 patients who did not have a single identified and qualified target lesion. One additional patient was lost to follow-up after month 1 visit and was excluded from target wound assessment at later timepoints.

- Safety
  - Treatment-emergent adverse events (TEAEs) were similar across treatment groups (**Table 2**)
  - No deaths or severe TEAEs were reported
  - No serious adverse events (AEs) were reported with SD-101 6%

Table 2. TEAEs of ≥10% Frequency

	Placebo	SD-101 3%	SD-101 6%
Number of patients	**17**	**16**	**15**
Number of patients with TEAEs (%)	**12 (70.6)**	**13 (81.3)**	**9 (60.0)**
Nasopharyngitis	12	25	7
Pyrexia	12	19	33
Application-site pain	6	19	13
Pain	-	-	13
Pruritus	6	13	13
Rash	12	-	7
Rash, erythematous	12	-	-
Cough	6	-	13
Oropharyngeal pain	12	-	-
Rhinorrhea	-	-	13
Vomiting	6	6	13
Headache	12	-	7

- Key learning points from the results of the phase 2b study for the phase 3 study design
  - The SD-101 6% concentration was selected for the phase 3 study based on the phase 2b dose response
    - Treatment with SD-101 6% demonstrated a higher rate of wound closure relative to both placebo treatment and treatment with SD-101 3%
    - The rates and types of TEAEs for all treatment groups were similar
  - A subgroup analysis indicated reduction of the placebo effect in patients with wounds ≥10 cm²
    - By 2 months, 50% of patients given SD-101 6% (n=4) had complete target wound closure, vs. 12.5% of patients given placebo (n=8)
  - Wound closure at month 2 (vs. month 1) is the optimal time to measure primary endpoint
    - Greatest difference between SD-101 6% and placebo is at month 2

OBJECTIVE

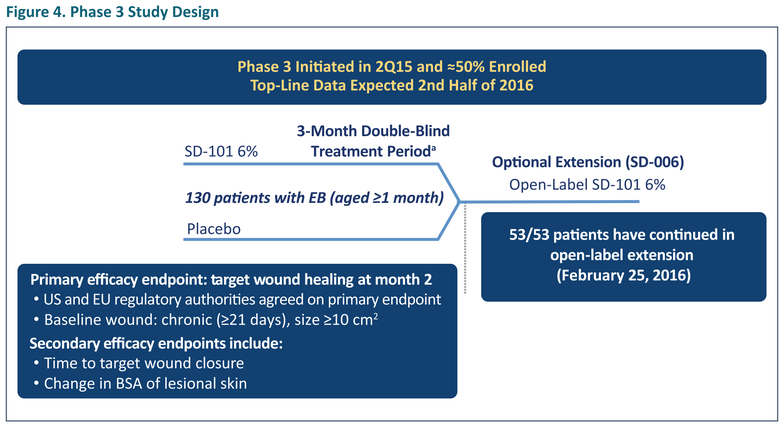
- To describe the rationale and design for a currently ongoing, pivotal, phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of SD-101 6% in patients with all major subtypes of EB

METHODS

Study Design

- Phase 3, multicenter, randomized, double-blind, placebo-controlled study (**Figure 4**)
- 130 patients will be randomized 1:1 to either placebo or SD-101 6%

Figure 4. Phase 3 Study Design



[a]Assessments: 0, 14, 30, 60, and 90 days; 1:1 randomization and daily topical application.

- All major EB types will be evaluated (simplex, dystrophic, and junctional)
- The study was 3 months long, with an option for continuation in the open-label extension Study SD-006

Patient Eligibility

Key Inclusion Criteria

- Diagnosis of simplex, recessive dystrophic, or junctional non-Herlitz EB
- Aged ≥1 month
- EB-related target wound is ≥21 days old and between 10 and 50 cm² in size
  - The criteria for wound size were based on results of a post hoc analysis of patients in the SD-101 phase 2b trial with target wounds ≥10 cm² at baseline, in which 50% of patients receiving SD-101 6% achieved complete target wound closure at month 2 (n=4) vs. 12.5% in patients receiving placebo (n=8)

Key Exclusion Criteria

- No clinical evidence of local infection in the selected target wound
- Use of any investigational drug ≤30 days before enrollment
- Use of immunotherapy or cytotoxic chemotherapy ≤60 days before enrollment
- Use of systemic or topical steroidal therapy ≤30 days before enrollment (inhaled steroids and ophthalmic drops containing steroids are allowed)
- Use of systemic antibiotics ≤7 days before enrollment
- Arterial or venous disorder resulting in ulcerated lesions

Study Drug Dosing

- SD-101 6% cream or placebo will be applied topically once daily to the entire body as a thin layer for a period of 90 days

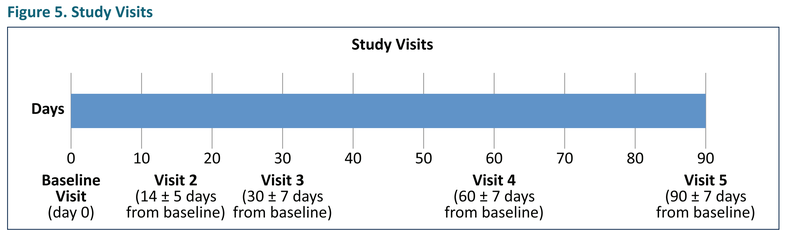
Clinical Assessments

- The primary endpoint is target wound closure at month 2
  - In the phase 2b study, the difference of SD-101 6% vs. placebo at month 2 in target wound closure was ≈20% in the intention-to-treat population (n=48) and ≈40% in the evaluable population (n=45)
- Secondary measures include:
  - Median time to target wound healing
  - BSA coverage of lesional skin
  - Patient/caregiver-reported itching/pain
  - Total body wound burden
- Safety will be assessed throughout the study duration by monitoring tolerability, AEs, and results from physical examinations
  - AEs and serious AEs, coded using the Medical Dictionary for Regulatory Activities, will be monitored at week 2 (visit 2) and then at months 1, 2, and 3 (visits 3-5, respectively)
    - The severity of each AE is classified as mild (easily tolerated), moderate (causes discomfort but does not interfere with normal activities), or severe (discomfort sufficient to interfere with normal activities)
  - Physical examinations performed at baseline (visit 1) and month 3 (visit 5, end of treatment)

Study Visits

- Patients will have 1 target wound selected at baseline by the investigator
- Photographic confirmation of the target wound location will be collected at baseline, and the picture saved from the first visit will be used to confirm location of the target wound at subsequent visits
- The patient will return to the study site for visit 2 (14 days ± 5 days from baseline), visit 3 (30 days ± 7 days from baseline), visit 4 (60 days ± 7 days from baseline), and visit 5 (90 days ± 7 days from baseline) to have the target wound, previously identified at baseline, re-assessed for the level of healing (**Figure 5**)
  - The ARANZ SilhouetteStar™, a portable device that easily photographs and analyzes a patient's target wound, will be used to measure the target wound at all visits
- In addition, itching, pain, BSA, target wound closure, and scarring of healed target wound will also be assessed at each visit

Figure 5. Study Visits



Statistical Analyses

- Primary endpoint: difference between SD-101 6% and placebo regarding the proportion of patients with complete target wound closure within 2 months
- Safety: baseline and month 3 physical examination results and changes during the study period will be described using summary statistics

CONCLUSIONS

- The phase 3 study design for SD-101 in EB reflects lessons learned from prior clinical studies and targets a study population and timepoint(s) for evaluation to best demonstrate treatment effects
- This study is the largest clinical trial of an investigational drug in EB and is designed to test the efficacy and safety of SD-101 6% cream

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