Efficacy and Safety of SD-101 Cream in Patients with Epidermolysis Bullosa: Results From a Phase 2b Study

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

Amy S. Paller, MD
F097 – Late-breaking Research

DISCLOSURE
Investigator and consultant for Scioderm/ Amicus
Epidermolysis Bullosa (EB)

- Mutations in several genes cause EB, leading to fragility of skin and mucosal surfaces
- Usually diagnosed in neonates
- Severe blistering, open wounds in response to minor friction to the skin
- Residual scarring in forms with deeper blisters
- Disfiguring, excruciatingly painful, and can be fatal
- Given few treatment options, any reduction in disease signs and symptoms would be considered meaningful
- 30,000 – 40,000 diagnosed patients in major global regions

Hereditary Blistering Disorders without Approved Treatments
Three Major EB Types

Skin structure

Sites of primary blister formation

EB Types

Represent ~99% of EB Population

<table>
<thead>
<tr>
<th>Subtypes</th>
<th>Symptoms</th>
<th>Frequency</th>
<th>Mortality risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Junctional</td>
<td>- Blistering of skin/ mucosae</td>
<td>~5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Severe complications, esp. infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Usually fatal early in life</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystrophic</td>
<td>- Skin and mucosal blistering</td>
<td>~20%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Scarring leads to narrowing of esophagus and orificial constriction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Growth retardation, anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Higher risk of aggressive skin cancer, esp after 1st decade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simplex</td>
<td>- Superficial blistering with variable extent and mucosal involvement</td>
<td>~75%</td>
<td></td>
</tr>
</tbody>
</table>

Source: Adapted from DebRA America
SD-101 Overview

*Patented High Concentration Allantoin with Breakthrough Therapy Designation*

<table>
<thead>
<tr>
<th>Active Ingredient &amp; ROA</th>
<th>Proprietary topical cream containing 6% allantoin, applied to entire body once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposed Indication</td>
<td>All major EB types (Simplex, Dystrophic, Junctional)</td>
</tr>
<tr>
<td>Development Phase</td>
<td>Phase 3 registration study (SD-005) ongoing</td>
</tr>
<tr>
<td>Proposed MOA*</td>
<td>Aids inflammatory response, bactericidal effects, loosens protein bridges, promotes collagen</td>
</tr>
<tr>
<td>Formulation</td>
<td>Patented formulation to deliver high concentration in highly stable, soluble form</td>
</tr>
</tbody>
</table>

*Margraf and Covey 1977; Meixell and Mecca 1966; Settle 1969; Flesch 1958; Fisher 1981; Cajkovac et al., 1992; Medda 1976*
**Phase 2b Design (Study 003)**

**3-Month Double-Blind Treatment Period\(^1\)**

48 EB patients (age ≥ 6 months)\(^1\) - 1:1:1 Randomization - Daily Topical Application

- SD-101 6% (n=15)
- SD-101 3% (n=16)
- Placebo (n=17)

**Optional Extension (SD-004)**
Open-Label SD-101 6%

42/44 Patients entered extension study
$400K FDA Grant for Extension Study

**Primary Efficacy Endpoint:** Target Wound Healing at Month 1
- Baseline wound: Chronic (≥ 21 days), size 5-50 cm\(^2\)

**Secondary Efficacy Endpoints Include:**
- Time to target wound closure
- Change in Body Surface Area (BSA) of lesional skin

**48 EB patients (age ≥ 6 months)\(^1\)**

\(^1\)Assessments: 0, 14, 30, 60, 90 Days
\(^2\)Initial Disease Severity: Mean target lesion size (cm\(^2\))
14.0 (range 5-39)
Mean lesional BSA: 19.4% (range 0.4-48%)
Mean wound age (days): 182 (range 21-1,639)
Study 003

• Demographics
  – Study population age: 6 months to 43.6 years with a mean age of 12.2 years
  – Majority of the ITT population was White/Caucasian (87.5%)
  – Balance of male and female patients

• Median (range) baseline target wound size
  – 9.5 cm² (5.2, 39.4) in the SD-101-0.0 group
  – 9.2 cm² (5.0, 34.7) in the SD-101.3.0 group
  – 7.6 cm² (5.0, 32.7) in the SD-101-6.0 group

• Disease subtype of patient population
  – 11 patients with EB Simplex (3 or 4 in each group)
  – 29 patients with Recessive Dystrophic EB (9 or 10 in each group)
  – 8 patients diagnosed with Junctional EB (2 or 3 in each group)
  – Subtypes evenly balanced across treatment arms
SD-101 6% Trended towards Higher Proportion of Complete Target Wound Closure

**ITT Population (n=48)**

**Proportion of Complete Target Wound Closure (%)**

<table>
<thead>
<tr>
<th></th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SD-101 0%</td>
<td>N=17</td>
<td>N=17</td>
<td>N=17</td>
</tr>
<tr>
<td>SD-101 3%</td>
<td>N=16</td>
<td>N=16</td>
<td>N=16</td>
</tr>
<tr>
<td>SD-101 6%</td>
<td>N=15</td>
<td>N=15</td>
<td>N=15</td>
</tr>
</tbody>
</table>

SD-101 6% vs Placebo

- **Month 1 (Pre-specified Primary Endpoint)**
  - SD-101 6%: 53%
  - Placebo: 38%
  - Trended towards Higher Proportion of Complete Target Wound Closure (p=0.37)

- **Month 2 (Phase 3 Primary Endpoint)**
  - SD-101 6%: 60%
  - Placebo: 44%
  - Trended towards Higher Proportion of Complete Target Wound Closure (p=0.24)

- **Month 3**
  - SD-101 6%: 60%
  - Placebo: 56%
  - Trended towards Higher Proportion of Complete Target Wound Closure (p=0.48)
SD-101 6% Demonstrated Higher Proportion of Complete Target Wound Closure

**Evaluable Population¹ (n=45)**

**Proportion of Complete Target Wound Closure (%)**

<table>
<thead>
<tr>
<th></th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SD-101 6%</strong></td>
<td>67% (N=12)</td>
<td>82% (N=11)</td>
<td>82% (N=11)</td>
</tr>
<tr>
<td><strong>SD-101 3%</strong></td>
<td>41% (N=17)</td>
<td>44% (N=16)</td>
<td></td>
</tr>
<tr>
<td><strong>SD-101 0%</strong></td>
<td>38% (N=16)</td>
<td>53% (N=17)</td>
<td>56% (N=16)</td>
</tr>
</tbody>
</table>

¹ Excluded from Evaluable population: 1 patient (due to lost to follow-up), 2 patients (did not have single identified and qualified target lesion). 1 additional patient lost to follow up after Month 1 visit and is excluded from target wound assessment at later time points.

**SD-101 6% vs Placebo**

- (p=0.165)
- (p=0.04)
- (p=0.124)

**SD-101 6%** vs Placebo

**Phase 3 Primary Endpoint**

**Pre-specified Primary Endpoint**
Phase 2b Results – Secondary Endpoint

SD-101 6% Showed Fastest Time to Target Wound Closure

**ITT Population (n=48)**
- Median Time to Target Wound Closure (Days): 91 Days, 86 Days, 40 Days
- N=17, N=16, N=15

**Evaluable Population (n=45)**
- Median Time to Target Wound Closure (Days): 91 Days, 86 Days, 30 Days
- N=17, N=16, N=12
Phase 2b (Study 003) Safety Summary

Adverse Events Similar Across Placebo, SD-101 3%, and SD-101 6%

- Treatment-emergent adverse events (TEAE) generally similar across treatment groups
- No deaths and no severe TEAEs
- No serious adverse events reported in SD-101 6% group

### Treatment Emergent Adverse Events ≥10% Frequency

<table>
<thead>
<tr>
<th>N subjects</th>
<th>SD-101 0% (Placebo)</th>
<th>SD-101 3%</th>
<th>SD-101 6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>N subjects with TEAEs (%)</td>
<td>17</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12%</td>
<td>25%</td>
<td>7%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>12%</td>
<td>19%</td>
<td>33%</td>
</tr>
<tr>
<td>Application Site Pain</td>
<td>6%</td>
<td>19%</td>
<td>13%</td>
</tr>
<tr>
<td>Pain</td>
<td>-</td>
<td>-</td>
<td>13%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6%</td>
<td>13%</td>
<td>13%</td>
</tr>
<tr>
<td>Rash</td>
<td>12%</td>
<td>-</td>
<td>7%</td>
</tr>
<tr>
<td>Rash Erythematous</td>
<td>12%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cough</td>
<td>6%</td>
<td>-</td>
<td>13%</td>
</tr>
<tr>
<td>Oropharyngeal Pain</td>
<td>12%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>-</td>
<td>-</td>
<td>13%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6%</td>
<td>6%</td>
<td>13%</td>
</tr>
<tr>
<td>Headache</td>
<td>12%</td>
<td>-</td>
<td>7%</td>
</tr>
</tbody>
</table>
Efficacy

• Treatment with the SD-101 formulation containing 6% allantoin (SD-101-6.0) demonstrated a higher rate of wound closure relative to both placebo treatment and treatment with the SD-101 formulation containing 3% allantoin (SD-101-3.0)

Safety

• The profiles of TEAEs for all treatment groups were similar
• The 6% formulation is associated with an acceptable safety profile for the Phase 3 program
SD-101 6% concentration selected for Phase 3 study based on Phase 2b dose response

Subgroup analysis indicates reduction of placebo response in patients with wounds ≥ 10 cm²

- Complete target wound closure by 2 months
  - SD-101 6%: 50% (n= 4) vs. Placebo (SD-101 0%): 12.5% (n=8)

Wound closure at Month 2 (vs. Month 1) is optimal time to measure primary endpoint

- Greatest difference between SD-101 6% and Placebo is at Month 2
EXTENSION STUDY: Phase 2b Extension (Study 004) Results

**Total Body Surface Area (BSA) Affected by Wounds/ Lesions Decreased with Time**

Mean Absolute Change to Month 12 (95% CI): -3.41% (-7.0, 0.2)

<table>
<thead>
<tr>
<th>Time, Months</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>42</td>
</tr>
<tr>
<td>M3</td>
<td>37</td>
</tr>
<tr>
<td>M6</td>
<td>33</td>
</tr>
<tr>
<td>M9</td>
<td>30</td>
</tr>
<tr>
<td>M12</td>
<td>28</td>
</tr>
</tbody>
</table>

Note: Baseline BSA for entire group = 11.3; Baseline BSA for group at 12 mos. = 10.9
Phase 3 Initiated in 2Q15 and ~50% Enrolled  
Top-Line Data Expected 2H16

~150 EB patients (age ≥ 1 month)

Primary Endpoint: Target Wound Healing at Month 2
- US and EU regulatory authorities agreed on primary endpoint
- Baseline wound: Chronic (≥ 21 days), size ≥10 cm²

Secondary Endpoints Include
- Time to target wound closure
- Change in Body Surface Area (BSA) of lesions and blisters

SD-101 6%  
3-Month Double-Blind Treatment Period

Optional Extension (SD-006)  
Open-Label SD-101 6%

53/53 Patients Have Continued in Open-Label Extension  
(Feb. 25, 2016)

1Assessments: 0, 14, 30, 60, 90 Days. 1:1 randomization, daily topical application
Phase 3 Design (SD-005)

Study Design Incorporates Key Learning Points from Phase 2b Study

3-Month Double-Blind Treatment Period

SD-101 6%

Optimal concentration

~150 EB patients (age ≥ 1 month)

Sample Size (p ≤ 0.05 if treatment difference ~17% or greater)

Placebo

Primary Endpoint: Target Wound Healing at Month 2

- US and EU regulatory authorities agreed on primary endpoint
- Baseline wound: Chronic (≥ 21 days), size ≥10 cm²

Secondary Endpoints Include

- Time to target wound closure
- Change in Body Surface Area (BSA) of lesions and blisters

Optional Extension (SD-006)

Open-Label SD-101 6%

53/53 Patients Have Continued in Open-Label Extension (Feb. 25, 2016)

Increases Ability to Distinguish SD-101 vs. Placebo¹

¹Complete target wound closure in patients with target wounds ≥ 10 cm² at Month 2 in Phase 2b: SD-101 6% - 50% (n= 4) vs. Placebo - 12.5% (n=8)
Study 003 Acknowledgments

• Special thanks to all those who have helped bring SD-101 to Phase 3:

Patients and their families

Investigators:
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• Amy Paller, MD
• Susan Bayliss, MD
• Aida Lugo-Somolinos, MD
• John Browning, MD
• Robert Sidbury, MD
• Rummana Aslam, MD

Study Site Staff

EB patient organizations