INTRODUCTION

- Allantoin is a heterocyclic organic compound that has been investigated in wound healing, using formulations with minimal or unknown dermal penetration properties.

- SD-101 is a novel, proprietary, topical, allantoin-containing cream in development for the daily treatment of wounds caused by all major types of epidermolysis bullosa (EBS). SD-101 has received Breakthrough Therapy designation from the US Food and Drug Administration.

- Epidermolysis bullosa is a rare genetic disorder typically manifesting at birth as skin blistering/erosion and, in some cases, the epithelial lining of other organs, in response to minimal friction/traction.

- In a phase 2b study, patients with epidermolysis bullosa treated with SD-101 6% (SD-101 with 6% allantoin) demonstrated a higher rate of wound closure over a 1-month period than placebo-treated patients.

- In vitro human cadaver and porcine models are recognized as valuable tools to assess the skin absorption and to determine the pharmacokinetics of topically applied drugs.

- Separate preclinical studies of SD-101 with allantoin concentrations of up to 9% indicated that allantoin is a heterocyclic organic compound that has been investigated in wound healing, using formulations with minimal or unknown dermal penetration properties.

OBJECTIVE

- To investigate the skin absorption of 0.5%, 1.5%, 3%, 6%, and 9% concentrations of allantoin, the active ingredient in the SD-101 formulation, in skin models that mimic intact, broken, or blistered human skin.

METHODS

Models

- The skin absorption of 0.5%, 1.5%, 3%, 6%, and 9% concentrations of allantoin, the active ingredient in the SD-101 formulation, was investigated in 5 in vitro models:
  - Barrier-free to simulate delivery directly to the capillary bed
  - Unbraded porcine skin
  - Abraded porcine skin to simulate compromised skin
  - Intact (full thickness) human skin
  - Dermis-only human to mimic loss of skin barrier function due to broken skin

Skin Cadaver Preparation

- All human and porcine cadaver trunk skin without obvious signs of skin disease was stored at less than −70°C within 24 hours of death. On experiment day, the bagged tissue was thawed and rinsed to remove any adherent blood or material from the surface.

- Approximately 75% of the dermis was removed by dermatome or scalpel visually.

- Donor skin was cut into smaller sections and fitted on 0.8-cm diffusion cells.

- Blood vessels were ligated, and the dorsal chamber, which was filled with magnetically stirred phosphate-buffered saline, was sampled at selected time points (Figure 1).

- The permeability to tritiated water was determined prior to experimentation to assure skin integrity.

RESULTS

- In the SD-101 formulation:
  - There was evidence of skin absorption of allantoin in all models (Figures 2 and Table 1).
  - Skin absorption increased with higher concentrations of allantoin in the dermis-only human model, uptake between the barrier-free and dermis-only human models was similar.
  - Allantoin skin absorption in the human skin models was slow (~8 hours for dermis-only), suggesting a long skin-exposure time (Figures 2C and 2D).

Figure 1. Schematic of the Skin Franz Cell Diffusion System

Figure 2. Skin Absorption of Allantoin (0.5% to 9%), a Component of SD-101, Within 40 Hours in Various Skin Models

CONCLUSIONS

- Allantoin, the active ingredient of the SD-101 formulation, is absorbed by the intact stratum corneum, or skin, which may reduce wound formation.

- In the SD-101 formulation, allantoin skin absorption in the intact (full thickness) human model was slow, suggesting a long skin-exposure time.

- In damaged skin models that provide insight into the absorption of wounded skin, absorption of allantoin increased significantly.

- Substantial skin absorption of 6% allantoin occurred over several hours in the intact full-thickness human skin model, suggesting that SD-101 formulation, with higher concentrations of allantoin than are currently used, is capable of penetrating human skin.

- In summary, these findings further support the therapeutic investigation of SD-101 6% to treat wounds in a clinical setting and the ongoing phase 3 ESSENCE trial in epidermolysis bullosa (NCT02384460).

DISCLOSURES

- AP is an investigator and a consultant for Amicus Therapeutics. RN and JG are employees of Scioderm – An Amicus Therapeutics Company and own stock in Amicus Therapeutics.

REFERENCES

3. Xi H et al. Presented at: 43rd Annual Meeting of the Society for Investigative Dermatology; July 14-17, 2010; Minneapolis, MN.

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DISCLOSES

Conflicts of Interest

AP is an investigator and a consultant for Amicus Therapeutics. RN and JG are employees of Scioderm – An Amicus Therapeutics Company and own stock in Amicus Therapeutics. HD, AR, CV, HL, IPC, and JAB are employees of and own stock in Amicus Therapeutics.

Table 1. Total Skin Absorption of Allantoin (µg) Over 48 Hours from a Single Application

<table>
<thead>
<tr>
<th>Skin Model</th>
<th>Allantoin Concentration (%)</th>
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<tbody>
<tr>
<td></td>
<td>0.5%</td>
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<tr>
<td>Intact (full thickness) human</td>
<td>12.05 ± 1.88</td>
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<tr>
<td>Abraded porcine</td>
<td>38.80 ± 13.84</td>
</tr>
<tr>
<td>Barrier-free</td>
<td>196.48 ± 45.30</td>
</tr>
<tr>
<td>Dermis-only human</td>
<td>412.60 ± 96.30</td>
</tr>
</tbody>
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Data are represented as mean ± standard error from ≥3 replicates per formulation as total mass (µg).