Use of an Investigator's Global Assessment Scale to Evaluate Disease Severity in Patients With Epidermolysis Bullosa Simplex

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Introduction
- A Phase 2 study of diacerein 1% topical ointment in patients with epidermolysis bullosa simplex (EBS) has demonstrated efficacy as compared with placebo with regard to blister count reduction.
- Static scales that measure a clinician's global impression of disease severity at a single time point are widely used in clinical trials for dermatological conditions and, although EBS scales exist in clinical practice, a standardized static scale for assessing EBS severity has yet to be developed.
- This report presents an analysis of data from the first treatment course and corresponding follow-up in the phase 2 crossover trial, conducted to validate a novel, EBS-specific 5-point Investigator's Global Assessment (IGA) scale based on efficacy data generated from the phase-2 study to measure the effects of diacerein 1% ointment vs vehicle control in the treatment of EBS.

Analysis Objectives
- End points for the analysis of the Phase 2 data were as follows:
  - Primary end point was the proportion of patients with moderate to severe lesions who achieved "treatment success" at year 1
  - Treatment success was defined as an IGA disease severity grade of 0 or 1 at Visit 3 (Week 16) with at least a 2-point reduction in the IGA score, as compared with Visit 2 (Week 0) at year 1
  - The z test was used to determine the statistically significant difference between the diacerein 1% ointment and the control ointment treatment groups
  - Additional end points included the proportion of patients from baseline to week 16 with a 2-point reduction and the mean decrease in IGA

Phase 2, Randomized, Controlled Original Study Design
- Treatment in a 4-week intervention period, with a 3-month follow-up, was conducted in 2 successive years, with a cross-over of patients after the first year (Figure 1)
- Secondary end points included the recurrence of blisters after a 12-week follow-up, a reduction in pain and pruritus, and quality of life measurements.

Methods for Analysis
- Each photograph taken during the Phase 2 blister-counting analysis study was labelled by patient ID (1001-2011), visit number (0-7), and location to ensure a complete list of available areas for analysis.
- For patients with several affected locations in a sequence of visits, these locations were split into separate images to allow for independent analysis.
- Photographs of the same location were displayed together on the same page, resulting in some pages with several photographs but one rating area.
- Patients without images for all visits were not included in the IGA analysis.
- Following the organization of the photographs using this method, a 16-page IGA Rating Document was developed.
- Each page contained a photograph (or photographs) of an affected location of a patient on the left side of the page and the IGA rating scale on the right of the page, with a checklist for the dermatologist to check, indicating the IGA score that he or she assigned to the affected area (Figure 3).
- 10 leading dermatologists and EB experts from the US, Europe, and Australia selected to blindly review and rate the photographs using the IGA scale.
- Each investigator was mailed a packet that contained instructions for the IGA assessment project, an IGA Training Manual, an IGA Rating Document, and a prepaid return label and envelope.
- The photographs mailed to each dermatologist were randomly sorted during printing. Thus, each dermatologist reviewed the same photographs.
- 10 investigators rated all photographs independently using the IGA scale and reported the one integer that best described the average overall severity of all the EBS lesions considered together.

Results
- At 16 weeks during the first treatment cycle, a higher proportion of moderate and severe lesions at baseline treated with diacerein 1% ointment achieved treatment success, as compared with vehicle-treated lesions (58% vs 40%; P=.036) (Figure 4).
- Similarly, at 16 weeks, the proportion of lesions treated with diacerein 1% ointment showing a 2-point reduction in IGA score trended higher, as compared with vehicle-treated lesions (70% vs 47%; P=.067) (Figure 5).
- The mean absolute change in the IGA score from baseline to the end of the follow-up period at 16 weeks was significantly greater for diacerein-treated lesions vs vehicle-treated lesions (2.4 vs 1.7; P=.001).
- The mean IGA for diacerein-treated lesions was significantly lower than that of vehicle-treated lesions at 16 weeks (1.08 vs 1.74; P=.004) (Figure 6).
- A reduction in blister counts positively correlated to improvements in overall disease severity (Figure 7).

IGA Scale for Analysis
- The IGA is the investigator's clinical assessment of the average overall severity of all EBS lesions, considered together, at a particular time point (Table 1).

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Clear</td>
</tr>
<tr>
<td>1</td>
<td>Near Clear</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Table 1. Investigator's Global Assessment (IGA) scale for EBS

Figure 3. Example of IGA Rating Document layout.

- 10 leading dermatologists and EB experts from the US, Europe, and Australia selected to blindly review and rate the photographs using the IGA scale.
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Figure 6. Mean IGA at each study visit (baseline, 4 weeks, 16 weeks)

Figure 7. Linear relationship between mean IGA score and total blister count

Original Phase 2 Efficacy at 4 and 16 Weeks of Year 1
- Significantly more patients in the diacerein group achieved the primary end point of >40% reduction in blister numbers at both 4 weeks and at the end of the follow-up period at 16 weeks of year 1 (Figure 2).

Figure 2. (A) Proportion of patients with >40% reduction in blister numbers at 4 weeks (T4) and 3 months (T7) (B) Representative images of improvements in lesions.

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- 10 investigators rated all photographs independently using the IGA scale and reported the one integer that best described the average overall severity of all the EBS lesions considered together.

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Conclusion
- Analysis of the Phase 2 diacerein 1% ointment study demonstrated that more moderate or severe lesions achieved treatment success with diacerein than with placebo.
- Treatment success was defined as the proportion of lesions resolving to IGA 0 or 1 with a minimum 2-point reduction in the IGA score.
- A reduction in blister counts positively correlated to improvements in overall disease severity.
- In addition, a significantly greater mean reduction in the IGA score from baseline was achieved with diacerein as compared with placebo.

Reference