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, was 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

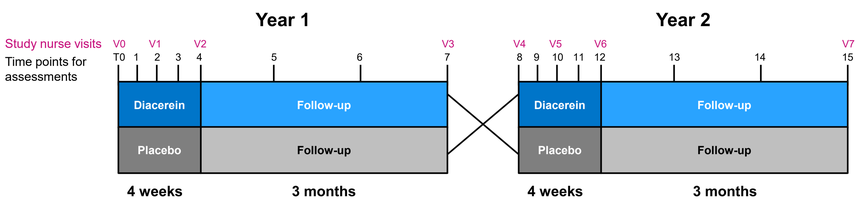
- End points for the analysis of the Phase 2 data were as follows:
  - Primary end point was the proportion of patients with moderate to severe lesions who achieved "treatment success" at year 1
    - Treatment success was defined as an IGA disease severity grade of 0 or 1 at Visit 3 (Week 16) with at least a 2-point reduction in the IGA score, as compared with Visit 2 (Week 0) at year 1
    - The χ^2 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-pointreduction 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 of pain and pruritus, and quality of life measurements

Figure 1. Diacerein 1% topical ointment for the treatment of EBS

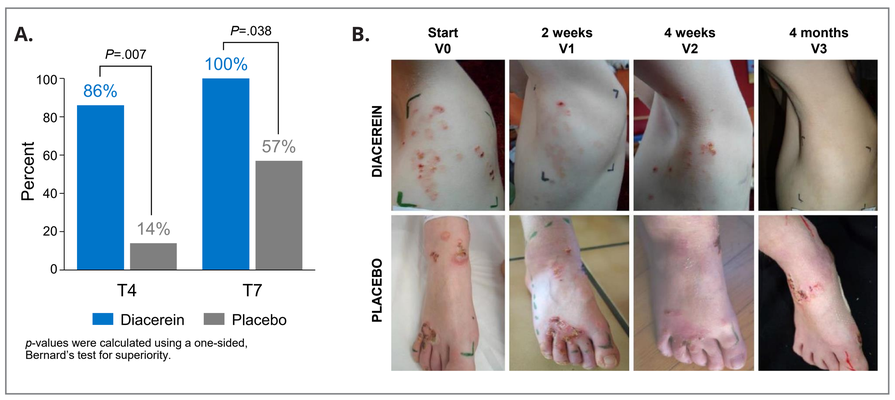
Indication	Generalized, severe EBS
Primary objective	Reduction of blister numbers (by 40%) in the treated skin area (3% of body surface) vs placebo after 4 weeks
Study design	Cross-over design, randomized, double-blind, vehicle-controlled Part 1: Intervention phase for 4 weeks; Part 2: 3-month follow-up
Study population	Generalized, severe EBS with K14 or K5 gene mutations, age 4-19 yr
Number of patients	17
Therapy	Once-daily, self-application for 4 weeks



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.



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**)

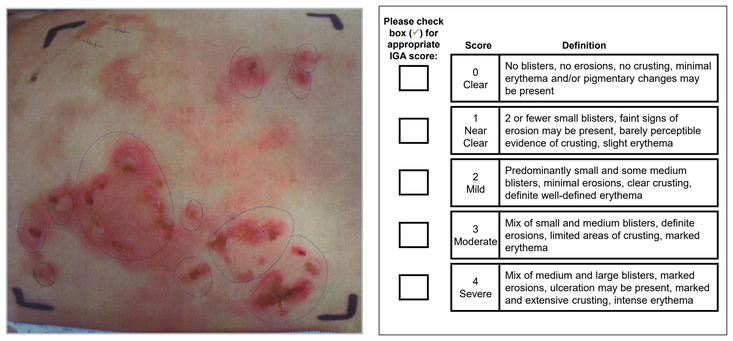
Table 1. Investigator's Global Assessment (IGA) scale for EBS

Score	Definition
0 = Clear	No blisters, no erosions, minimal erythema and/or pigmentary changes may be present
1 = Near Clear	2 or fewer small blisters, faint signs of erosion may be present, barely perceptible evidence of crusting, slight erythema
2 = Mild	Predominantly small and some medium blisters, minimal erosions, clear crusting, definite well-defined erythema
3 = Moderate	Mix of small and medium blisters, definite erosions, limited areas of crusting, marked erythema
4 = Severe	Mix of medium and large blisters, marked erosions, ulceration may be present, marked and extensive crusting, intense erythema

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 164-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 checkbox for the dermatologist to check, indicating the IGA score that he or she assigned to the affected area (**Figure 3**)

Figure 3. Example of IGA Rating Document layout



- 10 leading dermatologists and EB experts from the US, Europe, and Australia were 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

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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)**

Figure 4. Percentage of moderate and severe lesions achieving treatment success (IGA 0/1 and a 2-point reduction)

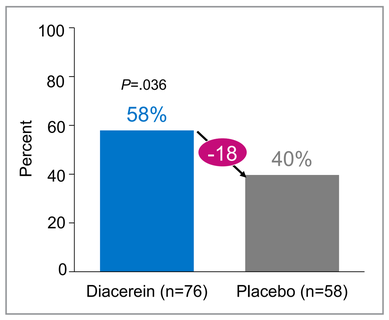
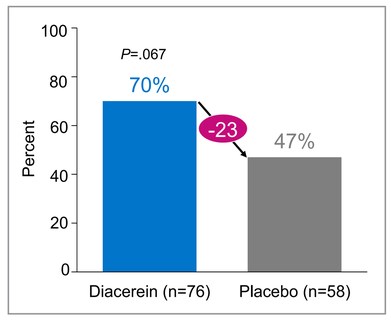
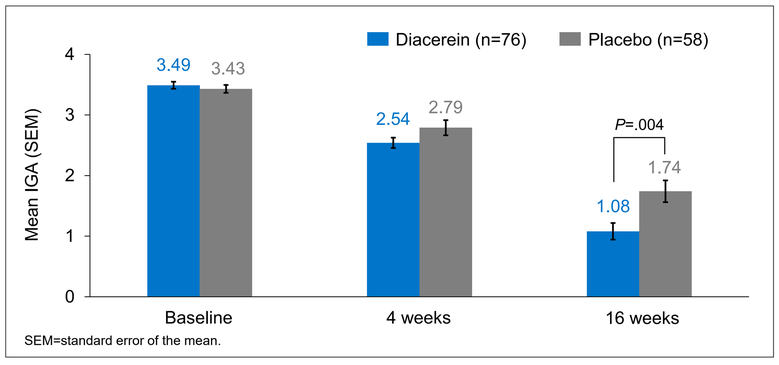


Figure 5. Percentage of lesions with a 2-point reduction in IGA score



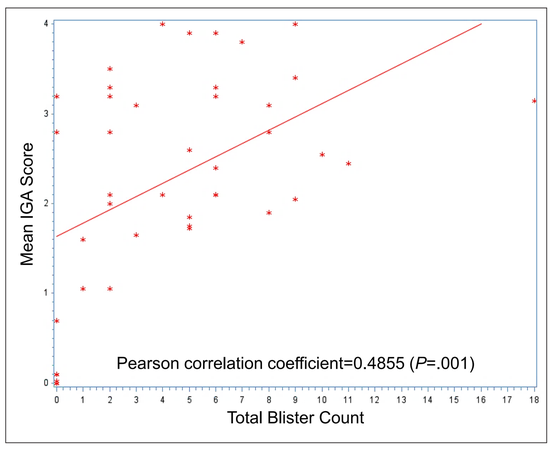
- The mean absolute change in the IGA score from baseline to the end of the follow-up period at 16 weeks was significantly greater for diacerein-treated lesions vs vehicle-treated lesions **(2.4 vs 1.7; *P*=.001)**
- The mean IGA for diacerein-treated lesions was significantly lower than that of vehicle-treated lesions at 16 weeks **(1.08 vs 1.74; *P*=.004)** **(Figure 6)**

Figure 6. Mean IGA at each study visit (baseline, 4 weeks, 16 weeks)



- A reduction in blister counts positively correlated to improvements in overall disease severity (**Figure 7**)

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



[a]The correlation was between the total blister count and the mean (over lesions) IGA score for the 14 patients who have the IGA scores available. Blister count data are available for each of the 3 timepoints (baseline, 4 weeks, and 16 weeks) for each of the 14 patients (N=42 timepoints)

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

Bauer J. Diacerein for the treatment of epidermolysis bullosa – a phase II randomized, placebo controlled, double-blind multi-center clinical trial. Presented at AAD, 2017.