**Supplemental material**

This appendix forms part of the manuscript submission for review.

Supplement to: Kern JS, Sprecher E, Fernandez MF, et al. Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa – results from the phase 3, randomised, double-blind phase of the ‘EASE’ study. BJD 2022.

The clinical study protocol and statistical analysis plan can be made available on request via the corresponding author.

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# List of investigators

**Argentina:** M. F. Fernandez, I. Massimo, M. Larralde

**Australia:** D. Murrell, J. Kern, O. Wargon, S. Robertson

**Austria:** M. Laimer

**Belgium:** I. Spanoudi

**Brazil:** J. Magno Frantz, M. Carrera, S. Barbosa

**Chile:** F. Palisson

**Colombia:** M. Torres Pradilla

**Croatia:** B. Marinovic

**Czech Republic:** H. Buckova

**Denmark:** M. Sommerlund

**France:** C. Bodemer, J. Mazereeuw-Hautier, C. Chiaverini

**Georgia :** G. Galdava

**Germany:** F. Schauer, H. Ott, R. Folster-Holst

**Greece:** A. Katsarou-Katsari

**Hong Kong:** E. Kam Lun Hon

**Hungary:** M. Sardy

**Ireland:** F. Browne

**Israel:** E. Sprecher

**Italy:** A. Diociaiuti, B. Didona, S. Guez

**Romania:** C. Salavastru

**Russia Federation:** A. Kubanov, N. Murashkin

**Serbia:** M. Nikolic

**Singapore:** M. Koh

**Spain:** E. Arana, J. Bernabeu Wittel, M. Vicente Villa, R. De Lucas

**Switzerland:** C. Gouveia

**Ukraine :** I. Gedeon

**United Kingdom:** A. Martinez, M. Ogboli

**United States:** A. Bruckner, B. Dasgeb, H. Price, I. Amjad, J. Browning, J. Slutsky, K. Hook, L. Wine Lee, A. Lucky, L. Castelo-Soccio, J. Raoof, J. Woodson

# Inclusion and exclusion criteria

EASE enrolled female and male patients (≥21 days old) with DEB, JEB, or KEB. After a protocol amendment, EBS patients were excluded from this study as this subtype is often considered mild, with shorter wound healing cycle times than other forms of EB. Chronic wounds lasting more than 3 weeks are unusual in EBS, and are therefore likely to heal spontaneously, thereby favouring the control arm. Moreover, very few EBS lesions met the minimum size requirements for the study.

|  |  |
| --- | --- |
| **Inclusion criteria** | **Exclusion criteria** |
| * Male and female subjects aged ≥4 years with the following subtypes of inherited epidermolysis bullosa (EB): dystrophic EB, junctional EB, and Kindler EB (KEB; the EB simplex [EBS] subtype was removed from the eligibility criteria in a protocol amendment). * Note: Children ≥21 days old and <4 years could be included, but only after confirmation by the Independent Data Monitoring Committee (IDMC) upon review of the safety and bioanalytical (betulin) data at the interim safety review. * Subjects with an EB target wound (i.e., EB partial-thickness wound of 10 cm2 to 50 cm2 in size, aged ≥21 days and <9 months) outside of the anogenital region. * Subject and/or his/her legal representative was informed, read, and understood the subject information/informed consent form (ICF), and gave written informed consent. * Subject and/or his/her legal representative had to be able and willing to follow study procedures and instructions. | * Subject had EB subtype EBS (added in protocol amendment). * Epidermolysis bullosa target wound that was ≥9 months old (added in protocol amendment) or had clinical signs of local infection. * Use of systemic antibiotics for wound-related infections within 7 days prior to enrolment. * Administration of systemic or topical steroids (except for inhaled, ophthalmic, or topical applications, such as budesonide suspension for oesophageal strictures [e.g., Pulmicort Respules® 0.25 mg/2 ml or 0.5 mg/2 ml]) within 30 days before enrolment. * Immunosuppressive therapy or cytotoxic chemotherapy within 60 days prior to enrolment. * Subject had undergone stem cell transplant or gene therapy for the treatment of inherited EB. * Current and/or former malignancy including basal cell carcinomas and squamous cell carcinomas. * Enrolment in any interventional study or treated with any investigational drug for any disease within 4 weeks prior to study entry. * Factors present in the subject and/or his/her legal representative that could have interfered with study compliance such as inability to attend scheduled study visits or compliance with home dressing changes. * Pregnant or nursing women. * Women of childbearing potential, including post-menarchal female adolescents, and men (reference to men added in Protocol Version 4.0) who were not willing to use an effective form of birth control with failure rates <1% per year (e.g., implant, injectable, combined oral contraceptive, intra-uterine contraceptive device, sexual abstinence, vasectomy or vasectomised partner) during participation in the study (and at least 3 months thereafter). * Subject was a member of the investigational team or his/her immediate family. * Subject lived in the same household as a study participant. |

# Permitted and non-permitted concomitant medications

## Permitted concomitant medications and therapies

The following medications and other therapies were permitted during both phases of the study (double-blind phase [DBP] and open-label phase [OLP]):

* Liquid antiseptics such as polyhexanide, iodine products, or octenidine dihydrochloride at each wound dressing change to clean the epidermolysis bullosa (EB) target wound (and additional wounds matching target wound criteria) and/or to reduce microbial colonization of the EB target wound (and additional wounds matching target wound criteria) prior to study treatment
* Bathing (e.g., with chlorhexidine, diluted bleach, or salt) prior to study treatment at each wound dressing change
* Systemic antibiotics, except for treatment of infections of the EB target wound or additional wounds matching target wound criteria
* Inhaled, ophthalmic, or topical steroids, such as budesonide suspension for oesophageal strictures (e.g., Pulmicort Respules 0.25 mg/2 ml or 0.5 mg/2 ml)
* Supportive therapy upon the investigator’s discretion.

During both phases of the study, the following medications were permitted for treatment of any EB wound, except for the EB target wound or additional wounds matching target wound criteria:

* silver dressings
* silver sulfadiazine
* topical antibiotics
* topical steroids.

## Non-permitted concomitant medication

On areas on the subject’s body that were affected by EB wounds, the following medications were not permitted during the DBP of the study:

* Skin products such as creams (including barrier creams), ointments (and dressings containing topical emollients, e.g., vaselinised gauze), gels, or emollients.

During both the DBP and OLP of the study, the following medications were not permitted on the EB target wound or additional wounds matching target wound criteria unless there was complete closure and confirmed epithelialization of the wound before use:

* silver dressings
* silver sulfadiazine
* topical antibiotics
* topical steroids.

The following medications were not permitted until Month 3 of the OLP (i.e., only assessment of target wound in the OLP):

* Systemic steroids (except for inhaled, ophthalmic, or topical applications, such as budesonide suspension for oesophageal strictures [e.g., Pulmicort Respules 0.25 mg/2 ml or 0.5 mg/2 ml])
* Immunosuppressive therapy or cytotoxic chemotherapy
* Systemic antibiotics for treatment of infections of the EB target wound or additional wounds matching target wound criteria.

# Clinical assessment and photography of EB target wound and additional wounds that met target criteria

On Day 0, the investigator selected the epidermolysis bullosa (EB) target wound and up to four other wounds that met target criteria (i.e., additional wounds). In the event that several EB partial-thickness wounds matched the target wound criteria, the wound of the largest size, maximum depth and longest duration was selected as the target wound, based on the investigator’s clinical judgement.

Both EB target wounds and additional wounds that met target wound criteria were evaluated for closure based on clinical assessment and photography.

The primary efficacy assessment of the EB target wound for closure was made by the investigator at site visits, or in case of a home visit, by the investigator, site study member, or home health professional.

In addition, the investigator or delegated site study team member photo-documented the EB target wound and all additional wounds that matched target wound criteria with the ARANZ Silhouette® system for blinded efficacy assessment by an independent panel made up of three independent assessors with experience in EB wounds.

The investigator and authorized site study team members received both the ARANZ Silhouette system and a standardized training before start of the study. The investigator selected the EB target wound and two appropriate anatomical landmarks on either side of the EB target wound. The investigator or delegated site study team member took a baseline reference image with these landmarks. He/she created a separate image of the EB target wound with tracings. At all post-baseline visits, the investigator or delegated site study team member referred to the baseline reference image to ensure that the correct wound was assessed. All additional wounds that matched target wound criteria were photo-documented similarly.

The baseline reference image(s) of the target wound and of additional wounds that matched target wound criteria were uploaded to the wound documentation report and the results (wound area size) were recorded in the electronic case report form (eCRF). The target wound and all additional wounds that matched target wound criteria were mapped for size, location, and duration in a body chart and appropriately photo-documented until complete closure or until Month 3 of the open-label phase. Photo compilations by visit were prepared for the blinded expert landmark analysis (i.e., presence of complete wound closure and EB target wound size).

To determine the required study sample size, the true control rate for the primary endpoint of first complete closure of the EB target wound was assumed to be 27% based on estimation of the expected wound-healing rate in the control arm of EASE. There was a single prespecified primary efficacy analysis and a fixed sequence testing procedure was used for assessing the results of several key secondary analyses. This procedure controlled the overall level of significance for the primary and key secondary analyses. The results of all other analyses are exploratory and hypothesis generating.

# Randomisation and blinding

Subjects were stratified according to their epidermolysis bullosa (EB) subtype and size of target wound (cm2) to the following groups: dystrophic EB (DEB) 10 to <20 cm2; DEB 20 to <30 cm2; DEB 30 to 50 cm2; junctional EB (JEB)/Kindler EB (KEB) 10 to <20 cm2; JEB/KEB 20 to <30 cm2; and JEB/KEB 30 to 50 cm2. Patient numbers were assigned by the electronic data capture system (Medidata Rave) and blinded treatment was assigned through the interactive response technology (Medidata Balance). Randomisation date, time, number, kit number, and date of allocation were captured at randomization.

An independent unblinded biostatistics team maintained the randomization scheme key in a separate location and was only to distribute this to approved personnel. All randomisation materials, including the key, were placed in an unblinded folder with restricted access, which remained restricted until after completion of the DBP and subsequent locking of the study database for the DBP.

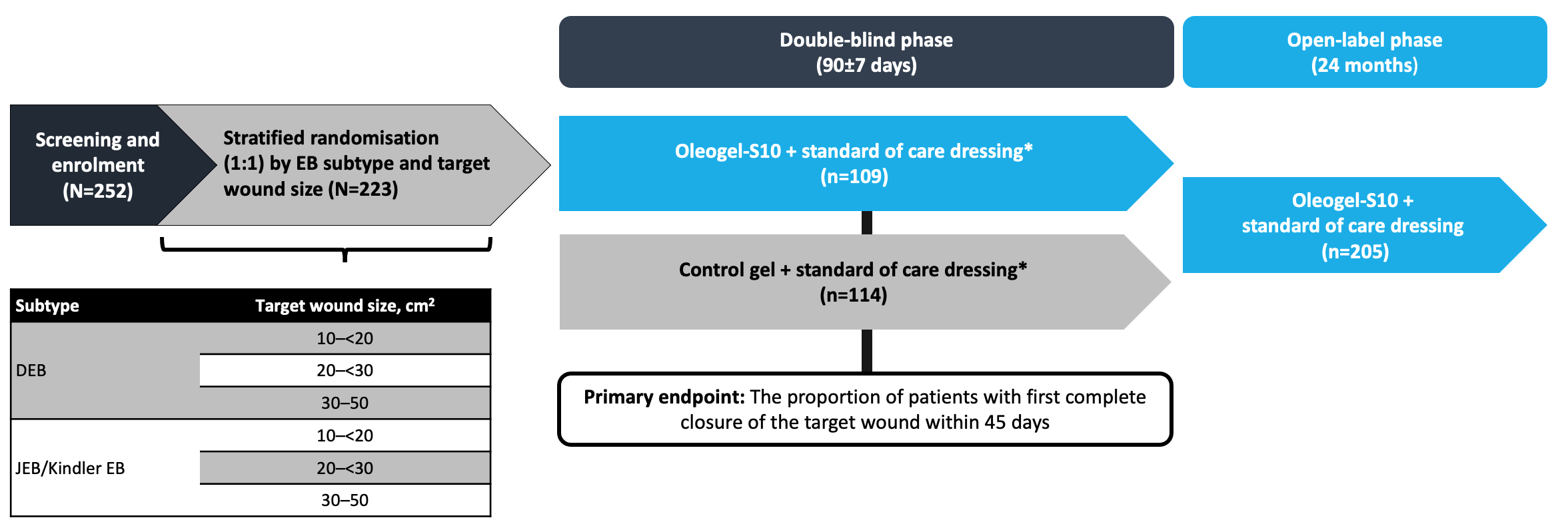
Subjects or investigators were not unblinded except in an emergency when it was necessary to know the treatment assignment. Unblinding was to be performed in the electronic system Medidata Balance. This system records the date and time and reason for unblinding, as well as the person requesting the code break. The system also notifies the Sponsor in a blinded fashion of a code break.

# Formulation of the investigational product

Oleogel-S10 consisted of 10% active pharmaceutical ingredient (birch triterpenes) and 90% sunflower oil. The control gel consisted of 85% sunflower oil, 5% cera flava/yellow wax, and 10% carnauba wax. Inert wax excipients were added to sunflower oil to create a gel with identical colour and physical properties to Oleogel-S10, thereby providing a matched control to enable maintained blinding to treatment allocation – both waxes are safe and non-detrimental ingredients in other wound healing products. Standard-of-care non-adhesive dressings were applied to all wounds.

# Supplementary figures and tables

## **Figure S1.** Trial design



\*Oleogel-S10/control gel applied at least every 4 days

EASE: NCT03068780, EudraCT 2016-002066-32

DEB, dystrophic EB; EB, epidermolysis bullosa; JEB, junctional EB

## **Figure S2.** Methodology for the assessment of target wounds

The eligibility criteria for target wounds included partial thickness wound of 10 cm2 to 50 cm2 in size and aged ≥21 days and <9 months.

The wounds had to be correctly traced. The wound images had to be taken from similar angles and/or it was required that closure could be assessed properly. For each wound size stratum, i.e., wounds of 10 to <20 cm2, 20 to <30 cm2, and 30 to 50 cm2 in size, examples meeting the above-mentioned criteria were selected. Patient could not be identifiable.

A picture containing graphical user interface

Description automatically generated

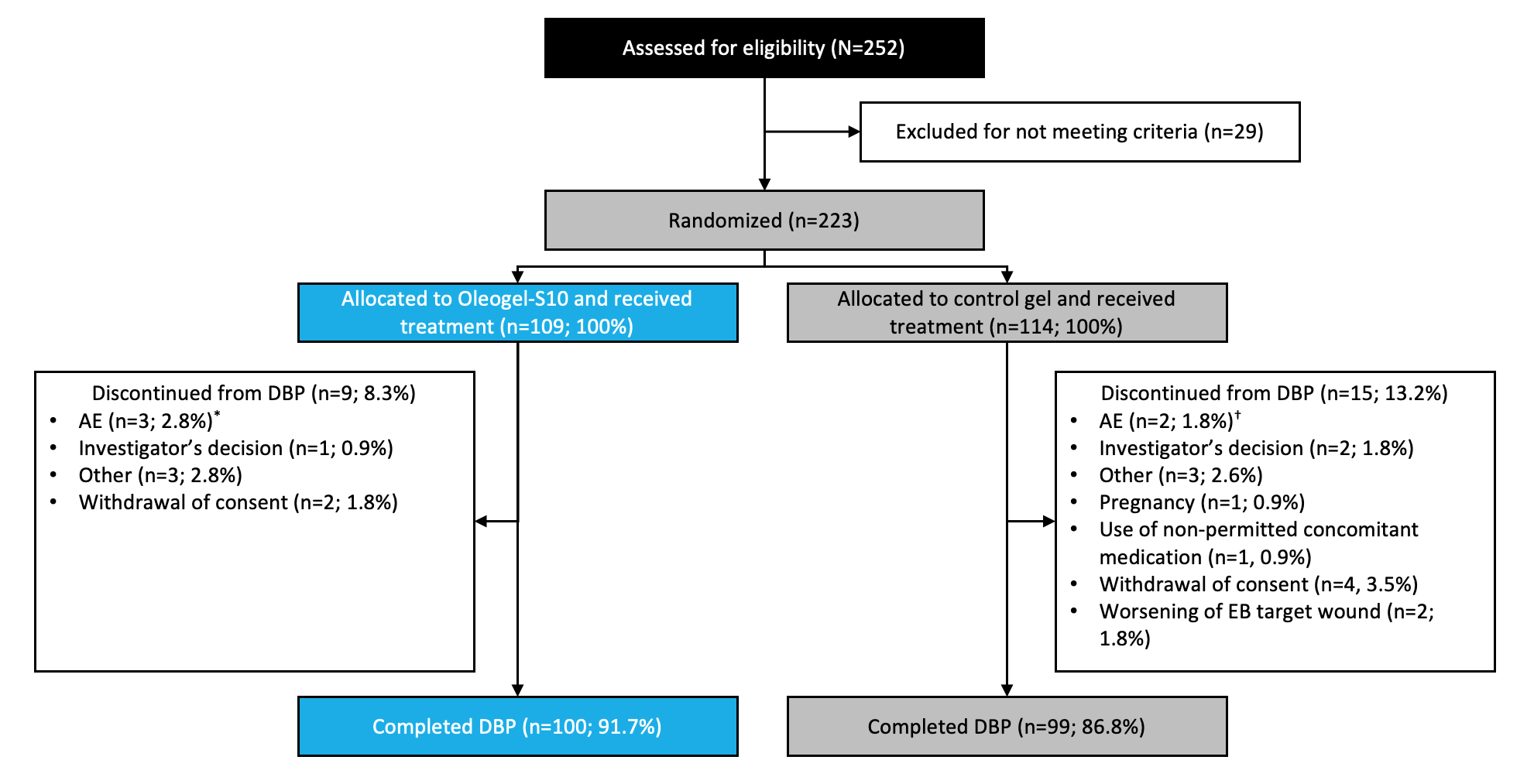
\*Target wound size 10.0 cm2, wound age 25 days, neck, right lateral (RDEB generalised severe, 14-year-old)

†Target wound size 20.5 cm2, wound age 180 days, left back, lumbar region (RDEB generalised intermediate, 23-year-old)

‡Target wound size 30.3 cm2, wound age 40 days, lower left leg, lateral (RDEB generalised severe, 18-year-old)

RDEB, recessive dystrophic epidermolysis bullosa

## **Figure S3.** CONSORT flow diagram

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\*1 patient with procedural pain, 1 patient with squamous cell carcinoma, 1 patient with wound haemorrhage

†1 patient with allergic rash, 1 patient with increase in wound size compared to baseline

AE, adverse event; DBP, double-blind phase; EB, epidermolysis bullosa

## **Figure S4.** Change in target wound size

***Chart, line chart

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RDEB, recessive dystrophic epidermolysis bullosa

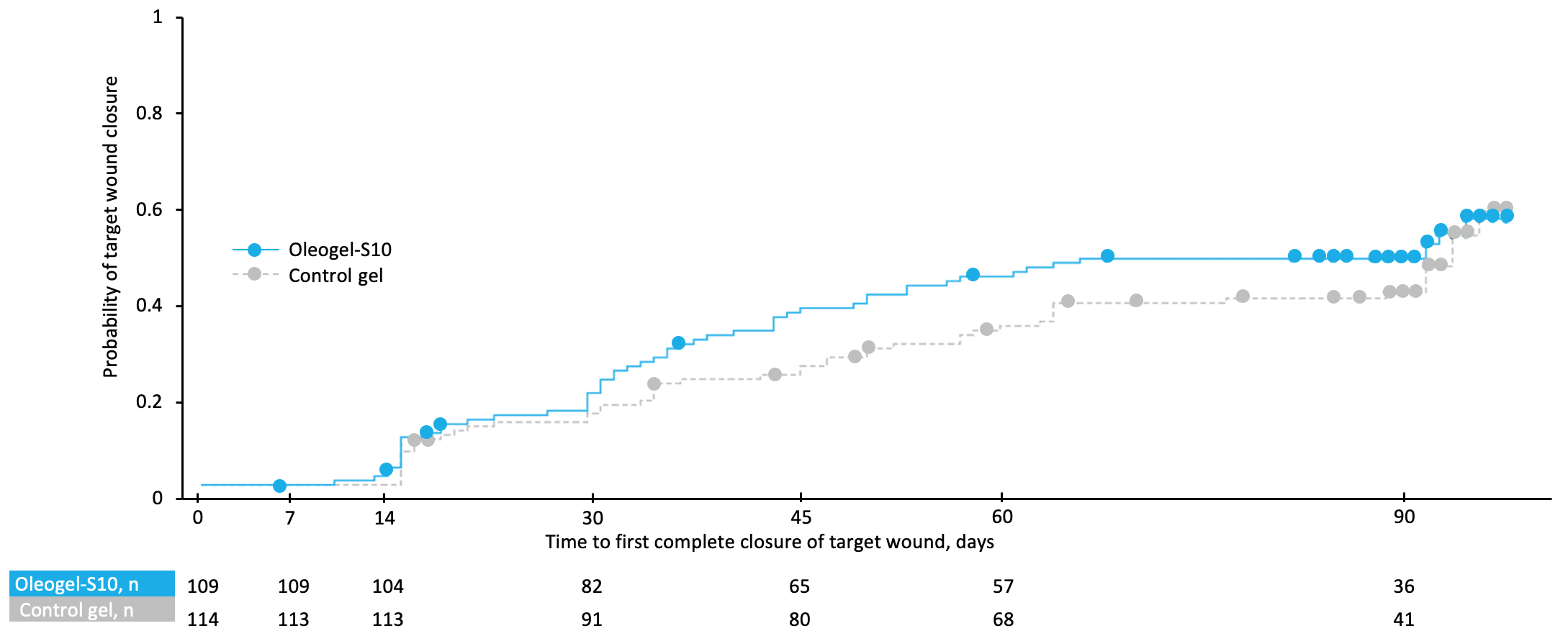
## **Figure S5.** Subgroup analyses of the primary efficacy endpoint

Graphical user interface

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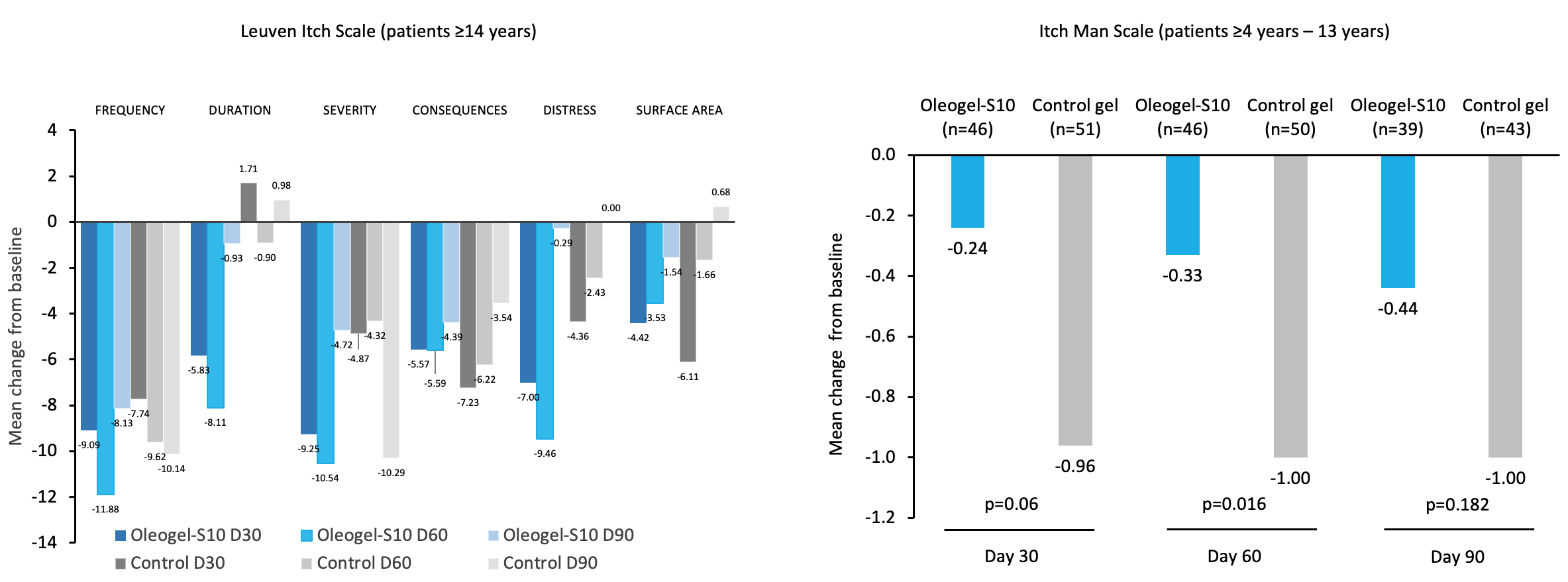
CI, confidence interval; CMH, Cochran-Mantel-Haenszel; DDEB, dominant dystrophic epidermolysis bullosa; EB, epidermolysis bullosa; EBS, epidermolysis bullosa simplex; eCRF, electronic case report form; JEB, junctional epidermolysis bullosa; NE, not estimable (due to small number of patients available); RDEB, recessive dystrophic epidermolysis bullosa.

## **Figure S6.** Cumulative incidence of first target wound closure computed using the Kaplan-Meier method by treatment group.

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Cumulative incidence of first target wound closure was computed using the Kaplan-Meier method. Each line is a probability function that is calculated based on the proportion of wounds healing relative to the number of wounds available to heal. When a target wound closure occurs, it was visualised as a step up on the KM curve and was associated with respective reduction in the number of target wounds available to experience target wound closure.

## **Figure S7.** Evaluation of itch over 90 daysin patients ≥14 years of age and ≥4–13 years of age

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P-value for Itch Man Scale derived from Wilcoxon Rank Sum Test.

D, day

## **Figure S8.** Change from baseline in weekly frequency of dressing changes

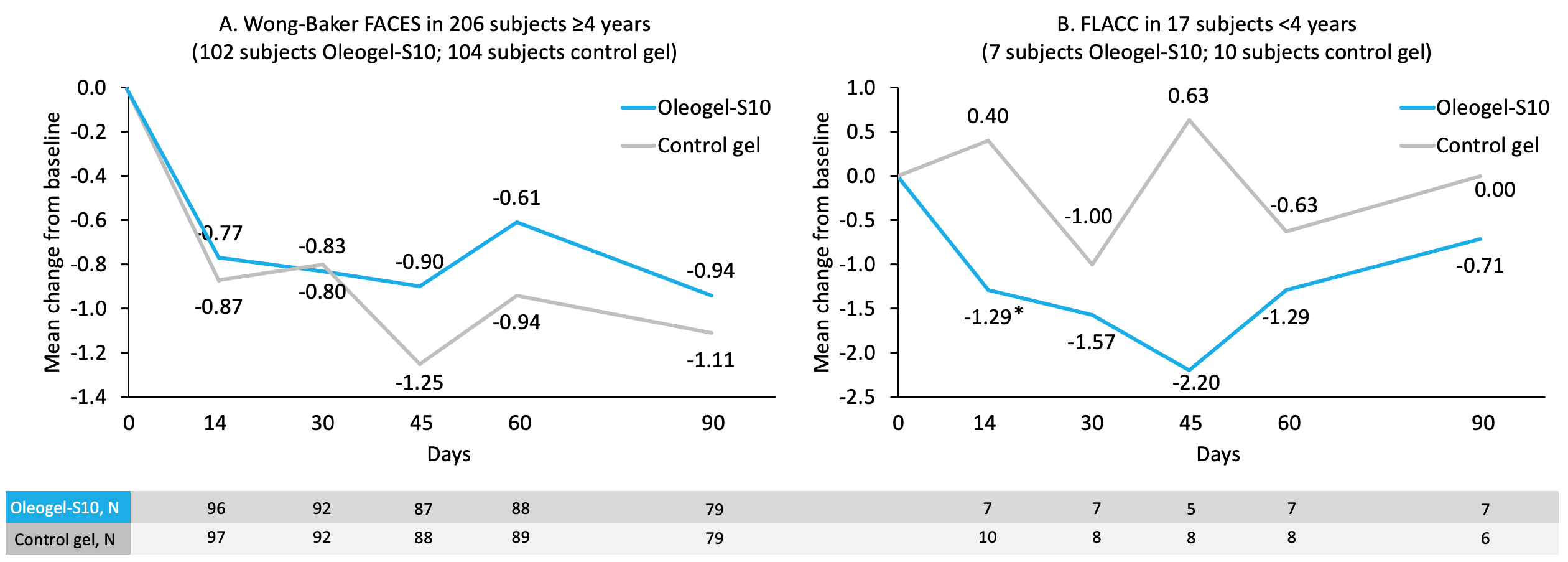
Chart, line chart

Description automatically generated

Frequencies are calculated based on the response at each visit. Daily dressing changes are assigned a frequency of 1.000, dressing changes every 2 days are assigned a value of 0.5000 etc. Where a combination of frequencies is reported the frequency is calculated for each and then the mean value is taken e.g., dressings every 1–2 days; (1.000 + 0.500)/2 = 0.750. Frequencies per day are multiplied by 7 to obtain the weekly frequency.

\*Analysis of covariance (ANCOVA) was conducted and a statistically significant difference between Oleogel-S10 and control gel was observed at Day 7 (p=0.037), Day 45 (p=0.003), Day 60 (p=0.005), and Day 90 (p=0.001).

## **Figure S9.** Background pain prior to wound dressing



\*nominal p=0.027 vs control gel

Nominal p values for FLACC as these endpoints have not been powered

FLACC, Face, Legs, Activity, Cry, Consolability scale

## **Figure S10.** Patient satisfaction/dissatisfaction of treatments as assessed using Treatment Satisfaction Questionnaire for Medication (TSQM) in patients ≥14 years of age (full analysis set)

Chart, bar chart

Description automatically generated

\*Satisfied patients include those who were: somewhat satisfied, satisfied, very satisfied and extremely satisfied. Dissatisfied patients include those patients who were: Dissatisfied, very dissatisfied and extremely dissatisfied.

ANCOVA favours Oleogel-S10 at D30, D60 and D90 (all p<0.001), although the analysis is limited as it uses D7 as a covariate with the numbers that completed D7 are small (Oleogel-S10 n=28)

ANCOVA, Analysis of covariance; D, days; FAS, full analysis set; TSQM, Treatment Satisfaction Questionnaire for Medication

## **Figure S11.** Least-square mean score of patients ≥14 years of age satisfaction/dissatisfaction of treatments as assessed using Treatment Satisfaction Questionnaire for Medication (TSQM) (full analysis set)

Chart, box and whisker chart

Description automatically generated

Higher score indicates a higher satisfaction with treatment

ANCOVA favours Oleogel at D30, D60 and D90 (all P<0.001), although the analysis is limited as it uses D7 as a covariate and the numbers that completed D7 are small (Oleogel-S10 n=28).

ANCOVA, analysis of covariance; D, day; FAS, full analysis set; LS, least square mean; SE, standard error; TSQM, Treatment Satisfaction Questionnaire for Medication

## **Figure S12.** Number of days missed from school or from work (full analysis set)

Chart, bar chart, waterfall chart

Description automatically generated

Days missed were recorded for the last 14 days or since the last visit if it was performed within less than 14 days.

Summary statistics presented on the sum of the number of days missed during DBP excluding Day 0 cumulatively per visit, and only including patients where the question “Currently Attending School or Employed” is ‘Yes’.

Data reported by patients ≥14 years or a parent of patients <14 years.

D, day

## **Table S1.** Location of epidermolysis bullosa target wounds

|  |  |  |  |
| --- | --- | --- | --- |
| Wound location | Patients, n (%) | | |
| Oleogel-S10 (n=109) | Control gel (n=114) | All patients (N=223) |
| Head and neck | 4 (3.7) | 2 (1.8) | 6 (2.7) |
| Shoulder | 3 (2.8) | 4 (3.5) | 7 (3.1) |
| Upper arm | 4 (3.7) | 4 (3.5) | 8 (3.6) |
| Elbow | 4 (3.7) | 2 (1.8) | 6 (2.7) |
| Forearm | 3 (2.8) | 2 (1.8) | 5 (2.2) |
| Hand | 1 (0.9) | 0 | 1 (0.4) |
| Thorax | 6 (5.5) | 6 (5.3) | 12 (5.4) |
| Sternum | 1 (0.9) | 0 | 1 (0.4) |
| Breast | 0 | 2 (1.8) | 2 (0.9) |
| Abdomen | 4 (3.7) | 6 (5.3) | 10 (4.5) |
| Spine | 0 | 3 (2.6) | 3 (1.3) |
| Back | 12 (11.0) | 8 (7.0) | 20 (9.0) |
| Pelvis | 7 (6.4) | 5 (4.4) | 12 (5.4) |
| Thigh | 17 (15.6) | 13 (11.4) | 30 (13.5) |
| Knee | 12 (11.0) | 18 (15.8) | 30 (13.5) |
| Lower leg | 20 (18.3) | 25 (21.9) | 45 (20.2) |
| Ankle | 5 (4.6) | 6 (5.3) | 11 (4.9) |
| Foot | 6 (5.5) | 8 (7.0) | 14 (6.3) |

## **Table S2.** Method of epidermolysis bullosa diagnosis and medical and surgical histories reported for ≥5% of all patients by preferred term (safety analysis set)

|  |  |  |  |
| --- | --- | --- | --- |
| **Method of diagnosis** | **Oleogel-S10 (n=109) n (%)** | **Control gel (n=114) n (%)** | **All patients (N=223) n (%)** |
| Clinical diagnosis only | 25 (22.9) | 24 (21.1) | 49 (22.0) |
| Immunofluorescence mapping or electron microscopy | 16 (14.7) | 25 (21.9) | 41 (18.4) |
| Genetic mutation identified | 67 (61.5) | 62 (54.4) | 129 (57.8) |
| Other | 1 (0.9) | 3 (2.6) | 4 (1.8) |
| **Medical and surgical histories** | | | |
| Constipation | 36 (33.0) | 43 (37.7) | 79 (35.4) |
| Anaemia | 35 (32.1) | 40 (35.1) | 75 (33.6) |
| Oesophageal stenosis | 28 (25.7) | 28 (24.6) | 56 (25.1) |
| Pruritus | 23 (21.1) | 32 (28.1) | 55 (24.7) |
| Oesophageal dilation procedure | 21 (19.3) | 25 (21.9) | 46 (20.6) |
| Gastrostomy | 18 (16.5) | 18 (15.8) | 36 (16.1) |
| Iron deficiency anaemia | 15 (13.8) | 18 (15.8) | 33 (14.8) |
| Pain | 9 (8.3) | 23 (20.2) | 32 (14.3) |
| Malnutrition | 16 (14.7) | 12 (10.5) | 28 (12.6) |
| Pseudosyndactyly | 11 (10.1) | 10 (8.8) | 21 (9.4) |
| Vitamin D deficiency | 11 (10.1) | 10 (8.8) | 21 (9.4) |
| Gastroesophageal reflux disease | 8 (7.3) | 11 (9.6) | 19 (8.5) |
| Dental caries | 10 (9.2) | 8 (7.0) | 18 (8.1) |
| Dry eye | 6 (5.5) | 12 (10.5) | 18 (8.1) |
| Hand repair operation | 6 (5.5) | 12 (10.5) | 18 (8.1) |
| Dysphagia | 10 (9.2) | 5 (4.4) | 15 (6.7) |
| Iron deficiency | 8 (7.3) | 7 (6.1) | 15 (6.7) |
| Syndactyly | 9 (8.3) | 6 (5.3) | 15 (6.7) |
| Wound infection | 5 (4.6) | 8 (7.0) | 13 (5.8) |
| Limb operation | 7 (6.4) | 5 (4.4) | 12 (5.4) |
| Tooth extraction | 3 (2.8) | 9 (7.9) | 12 (5.4) |

## **Table S3.** Summary of study drug administration and dressing change by visit

|  |  |  |  |
| --- | --- | --- | --- |
| Study day | Frequency of dressing change | Oleogel-S10 (n=109), n (%) | Control gel (n=114), n (%) |
| 0 | Daily | 47 (43.1) | 52 (45.6) |
| Every 2 days | 45 (41.3) | 39 (34.2) |
| Every 3 days | 7 (6.4) | 7 (6.1) |
| Every 4 days | 4 (3.7) | 4 (3.5) |
| 2 times per week | 0 | 1 (0.9) |
| 3 times per week | 0 | 1 (0.9) |
| Other | 6 (5.5) | 10 (8.8) |
| 30 | Daily | 36 (35.3) | 49 (47.1) |
| Every 2 days | 41 (40.2) | 30 (28.8) |
| Every 3 days | 12 (11.8) | 11 (10.6) |
| Every 4 days | 3 (2.9) | 3 (2.9) |
| 2 times per week | 0 | 0 |
| 3 times per week | 0 | 2 (1.9) |
| Other | 10 (9.8) | 9 (8.7) |
| 45 | Daily | 34 (33.3) | 50 (49.5) |
| Every 2 days | 47 (46.1) | 31 (30.7) |
| Every 3 days | 11 (10.8) | 6 (5.9) |
| Every 4 days | 4 (3.9) | 4 (4.0) |
| 2 times per week | 0 | 0 |
| 3 times per week | 0 | 2 (2.0) |
| Other | 6 (5.9) | 8 (7.9) |
| 60 | Daily | 33 (33.0) | 48 (47.5) |
| Every 2 days | 47 (47.0) | 30 (29.7) |
| Every 3 days | 10 (10.0) | 7 (6.9) |
| Every 4 days | 3 (3.0) | 4 (4.0) |
| 2 times per week | 0 | 0 |
| 3 times per week | 0 | 2 (2.0) |
| Other | 7 (7.0) | 8 (7.9) |
| 90 | Daily | 33 (32.0) | 55 (50.9) |
| Every 2 days | 45 (43.7) | 29 (26.9) |
| Every 3 days | 14 (13.6) | 9 (8.3) |
| Every 4 days | 4 (3.9) | 6 (5.6) |
| 2 times per week | 0 | 0 |
| 3 times per week | 1 (1.0) | 2 (1.9) |
| Other | 6 (5.8) | 7 (6.5) |

## **Table S4.** Time to first complete closure of EB target wound up to Day 90

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Oleogel-S10 (n=109)** | | **Control gel (n=114)** |
| Mean time to first complete closure, days ±SD | 37.7±21.7 | | 44.5±26.2 |
| Median time to first closure, days | 33.0 | | 39.0 |
| Median time to first complete closure, days /  95% CI of median time to first complete closure, days | 92.0 / (50.0, NE) | | 94.0 / (89.0, NE) |
| P value | 0.302 | | |
| **EB subtypes** | | | |
| RDEB | Oleogel-S10 (n=91) | Control gel (n=84) | |
| Mean time to first complete closure, days ±SD | 37.9±20.8 | 46.9±27.3 | |
| DDEB | Oleogel-S10 (n=6) | Control gel (n=14) | |
| Mean time to first complete closure, days ±SD | 28.8±19.8 | 31.0±14.7 | |
| JEB | Oleogel-S10 (n=11) | Control gel (n=15) | |
| Mean time to first complete closure, days ±SD | 24.0±15.6 | 48.0±29.2 | |

Parameter and model estimates based on a Log-rank test performed without consideration of any stratification. Time to first complete closure of the EB target wound in days was calculated as date of complete closure –date of first study treatment +1. If wound closure did not occur prior to EDBP, time to first complete closure is censored at the EDBP visit date or at last assessment date of the EDBP in case of early discontinuation from DBP.

Any reference to 'Mean time to first complete wound closure' refers to analyses conducted only on target wounds that achieved complete closure by Day 90.

CI, confidence Interval; DDEB, dominant dystrophic EB; EB, epidermolysis bullosa; JEB, junctional EB; NE, not estimable; RDEB; recessive dystrophic EB; SD, standard deviation

## **Table S5.** Proportion of patients with first complete closure of EB target wound by EB subtype and wound size up to Day 90

|  |  |  |
| --- | --- | --- |
|  | **Oleogel-S10 (n=109) n (closure, non-closure)** | **Control gel  (n=114) n (closure, non-closure)** |
| All patients | 109 (55, 54) | 114 (50, 64) |
| EB subtypes | | |
| DEB 10 to <20 cm² | 62 (38, 24) | 66 (36, 30) |
| DEB 20 to <30 cm² | 22 (10, 12) | 21 (8, 13) |
| DEB 30 to 50 cm² | 14 (5, 9) | 12 (1 ,11) |
| JEB 10 to <20 cm² | 7 (1, 6) | 9 (4, 5) |
| JEB 20 to <30 cm² | 1 (0, 1) | 3 (1, 2) |
| JEB 30 to 50 cm² | 3 (1, 2) | 3 (0, 3) |

DEB, dystrophic EB; EB, epidermolysis bullosa; JEB, junctional EB

## **Table S6.** Mean days missed from school/work (full analysis set)

|  |  |  |  |
| --- | --- | --- | --- |
| **Cumulative school/work days missed, mean [95%CI]** | **Oleogel-S10 (n=109)** | **Control gel (n=114)** | **All patients (N=223)** |
| Baseline (Day 0) | 1.6 [0.9, 2.4]  (n=68) | 1.8 [1.1, 2.5]  (n=73) | 1.7 [1.3, 2.2]  (n=141) |
| Day 14 | 1.4 [0.7, 2.1]  n=63 | 1.0 [0.5, 1.5] (n=71) | 1.2 [0.8, 1.6] (n=134) |
| Day 30 | 2.5 [1.2, 3.7]  (n=61) | 1.9 [1.0, 2.7]  (n=72) | 2.1 [1.4, 2.9]  (n=133) |
| Day 45 | 3.1 [1.6, 4.7] (n=56) | 2.7 [1.5, 3.9] (n=69) | 2.9 [2.0, 3.8] (n=125) |
| Day 60 | 4.7 [2.7, 6.7] (n=61) | 3.8 [2.3, 5.3] (n=70) | 4.2 [3.0, 5.5] (n=131) |
| Day 90 | 4.7 [2.6, 6.7] (n=54) | 5.0 [3.0, 7.0] (n=57) | 4.8 [3.4, 6.3] (n=111) |

Days missed were recorded for the last 14 days or since the last visit if it was performed within less than 14 days.  
Summary statistics presented on the sum of the number of days missed during DBP excluding Day 0 cumulatively per visit, and only including patients where the question “Currently Attending School or Employed” is ‘Yes’.

Data reported by patients ≥14 years or a parent of patients <14 years.

CI, confidence interval

## **Table S7.** Impact of wounds on sleep using W-QoL Scale by visit in patients ≥14 years of age (full analysis set)

|  |  |  |  |
| --- | --- | --- | --- |
| **Change from baseline in mean W-QoL Score [95%CI]** | **Oleogel-S10 (n=52)** | **Control gel (n=48)** | **All patients (N=100)** |
| Baseline (Day 0)\* | 4.6 [3.6, 5.5] (n=52) | 4.4 [3.5, 5.3] (n=48) | 4.5 [3.9, 5.2] (n=100) |
| Day 30 | -1.0 [-1.7, -0.2] (n=45) | -1.1 [-2.0, -0.2]  (n=42) | -1.0 [-1.6, -0.4]  (n=87) |
| Day 60 | -0.9 [-1.7, 0.0]  (n=40) | -0.3 [-1.3, 0.3]  (n=39) | -0.7 [-1.2, -0.1]  (n=79) |
| Day 90 | -1.5 [-1.5, -0.1]  (n=40) | -1.0 [-2.1, 0.0]  (n=37) | -0.9 [-1.5, -0.3]  (n=77) |

\*Absolute values at baseline (last non-missing value prior to or on the date of first study medication of that study phase); W-QoL (quality of life): 11-point Likert scale: 0 = Not at all, 10 = Very much; High values indicate a negative outcome.

CI, confidence interval; W-QoL, wound quality of life

## **Table S8.** Summary of treatment-emergent adverse events with preferred term or lower-level term 'wound complication'

|  |  |  |  |
| --- | --- | --- | --- |
| **Category** | **Oleogel-S10  (n=109)**  **n (%) E** | **Control gel  (n=114)**  **n (%) E** | **All patients  (N=223)**  **n (%) E** |
| Any treatment emergent adverse event with PT/LLT 'wound complication'\* | 67 (61.5) 100 | 61 (53.5) 88 | 128 (57.4) 188 |
| Increase in wound size compared to baseline | 32 (29.4) 40 | 37 (32.5) 47 | 69 (30.9) 87 |
| Wound re-opening† | 31 (28.4) 38 | 20 (17.5) 23 | 51 (22.9) 61 |
| Increase in wound size compared to the previous visit | 12 (11.0) 16 | 7 (6.1) 8 | 19 (8.5) 24 |
| Other | 4 (3.7) 5 | 3 (2.6) 4 | 7 (3.1) 9 |
| Injury to the wound | 1 (0.9) 1 | 4 (3.5) 5 | 5 (2.2) 6 |
| Wound worsening compared to baseline | 0 | 1 (0.9) 1 | 1 (0.4) 1 |

Calculation of percentages based on n

AEs are assigned to study phases by AE start date

\*Refers to any treatment-emergent AEs with PT or LLT 'wound complication'; there are other treatment-emergent AEs involving wounds (e.g. wound haemorrhage) but with a different PT/LLT.

†Wound re-opening captured under AEs were not based on clinical assessments of the Investigators but derived from patient reports about new lesions in the former target wound area, irrespective of reason (e.g., local trauma), aetiology (real re-opening of previous wound versus new blister and corresponding EB partial thickness wound in the location of the previous target wound) or precise reports of time. Treatment-emergent AEs were defined as AEs that occurred from the first study treatment to 4 weeks after the last study treatment and did not necessarily have a causal relationship to the use of the study medication.

AE, adverse event; PT, preferred term; LLT, lower-level term; n, number of patients in specific group; n = number of patients; E, number of events

## **Table S9.** Serious adverse events

|  |  |  |  |
| --- | --- | --- | --- |
| **AE category/system organ class preferred term** | **Oleogel-S10 (n=109) n (%)** | **Control gel (n=114) n (%)** | **All patients (N=223) n (%)** |
| Any serious AE | 7 (6.4) | 6 (5.3) | 13 (5.8) |
| Infections and infestations | 4 (3.7) | 5 (4.4) | 9 (4.0) |
| Sepsis | 1 (0.9) | 2 (1.8) | 3 (1.3) |
| Wound infection bacterial | 1 (0.9) | 1 (0.9) | 2 (0.9) |
| Device related infection | 1 (0.9) | 0 | 1 (0.4) |
| Pneumonia | 1 (0.9) | 0 | 1 (0.4) |
| Erysipelas | 0 | 1 (0.9) | 1 (0.4) |
| Upper respiratory tract infection | 0 | 1 (0.9) | 1 (0.4) |
| Wound infection | 0 | 1 (0.9) | 1 (0.4) |
| Blood and lymphatic system disorders: anaemia | 3 (2.8) | 0 | 3 (1.3) |
| Injury, poisoning and procedural complications: | 1 (0.9) | 1 (0.9) | 2 (0.9) |
| Wound haemorrhage | 1 (0.9) | 0 | 1 (0.4) |
| Femur fracture | 0 | 1 (0.9) | 1 (0.4) |
| Neoplasms benign, malignant, and unspecified: squamous cell carcinoma of skin | 1 (0.9) | 0 | 1 (0.4) |
| Renal and urinary disorders: haematuria | 1 (0.9) | 0 | 1 (0.4) |
| Investigations: gamma-glutamyltransferase increased | 0 | 1 (0.9) | 1 (0.4) |

AE, adverse event

## **Table S10.** Betulin systemic exposure in venous blood samples (safety analysis set)

|  |  |  |  |
| --- | --- | --- | --- |
| **Visit** | **Statistic** | **Oleogel-S10 concentration (ng/ml)** | **Control gel concentration (ng/ml)** |
| Day 0 | n  Mean (SD)  Median  Min, max | 55  1.46 (6.145)  0.0  0, 27.4 | 57  0.76 (4.138)  0.0  0, 26.7 |
| Day 7 | n  Mean (SD)  Median  Min, max | 2  0 (0)  0.0  0, 0 | 10  0 (0)  0.0  0, 0 |
| Day 14 | n Mean (SD)  Median  Min, max | 4  0 (0)  0.0  0, 0 | 12  1.22 (4.215)  0.0  0, 14.6 |
| Day 30 | n Mean (SD)  Median  Min, max | 5  2.92 (6.529)  0.0  0, 14.6 | 11  0 (0)  0.0  0, 0 |
| Day 45 | n Mean (SD)  Median  Min, max | 3  0 (0)  0.0  0, 0 | 12  0 (0)  0.0  0, 0 |
| Day 60 | n Mean (SD)  Median  Min, max | 2  0 (0)  0.0  0, 0 | 11  0 (0)  0.0  0, 0 |
| Day 90 | n  Mean (SD)  Median  Min, max | 54  8.73 (31.257)  0.0  0, 207.0 | 54  1.74 (7.950)  0.0  0, 54.5 |
| CCC visit | n Mean (SD)  Median  Min, max | 0 0 (0)  0.0  0, 0 | 2  0 (0)  0.0  0, 0 |

CCC, confirmation of complete closure (of target wound); Max, maximum; Min, minimum; SD, standard deviation