Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: results from the phase III randomized double-blind phase of the EASE study

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> Linked Article: Mellerio *Br J Dermatol* 2023; **188**:10–11.

Abstract

Background   Epidermolysis bullosa (EB) is a heterogeneous group of rare, difficult-to-treat, inherited multisystem diseases affecting epithelial integrity. Patients with EB are affected by mechanical fragility of epithelial surfaces including the skin and, as a result, extensive recurrent blistering is a characteristic of the condition. Chronic wounds predispose patients with EB to the development of squamous cell carcinoma, which is a major cause of premature death.

Objectives   EASE was a double-blind, randomized, vehicle-controlled, phase III study to determine the efficacy and safety of the topical gel Oleogel-S10 (birch triterpenes) in EB. EASE was funded by Amryt Research Limited.

Methods   Patients with dystrophic EB, junctional EB or Kindler EB and a target partial-thickness wound lasting ≥21 days and < 9 months that was 10–50 cm^2, were enrolled and randomized via computer-generated allocation tables 1 : 1 to Oleogel-S10 or control gel – both with standard-of-care dressings. Study gel was applied to all wounds at least every 4 days. The primary endpoint was the proportion of patients with first complete closure of target wound within 45 days.

Results   A total of 223 patients were enrolled and treated (109 treated with Oleogel-S10, 114 with control gel). The primary endpoint was met; Oleogel-S10 resulted in 41·3% of patients with first complete target wound closure within 45 days, compared with 28·9% in the control gel arm (relative risk 1·44, 95% confidence interval (CI) 1·01–2·05; *P* = 0.013). Adverse events (AEs) occurred with similar frequency for Oleogel-S10 (81·7%) compared with control gel (80·7%). AEs were predominantly of mild-to-moderate intensity (4·6% were severe).

Conclusions   Oleogel-S10 is the first therapy to demonstrate accelerated wound healing in EB. Oleogel-S10 was well tolerated.

What is already known about this topic?

- Epidermolysis bullosa (EB) is group of rare, inherited, devastating skin disorders with skin fragility that affect patients from birth.
- Common causes of early mortality in patients with EB include squamous cell carcinoma, infections and other complications.
- EB is notoriously difficult to treat, and, until recently, there were no approved treatments, with wound management being a fundamental priority for patients living with the disease.

What does this study add?

- EASE is the largest phase III randomized controlled study in EB, which examined the efficacy and safety of Oleogel-S10 (birch triterpenes) vs. vehicle control gel.
- The primary endpoint was met; Oleogel-S10 resulted in a higher proportion of patients with target wound closure within 45 days compared with control gel ($P = 0.013$).
- Oleogel-S10 was well tolerated.
- The EASE study was central to the recent European Commission approval of Oleogel-S10 for the treatment of EB.

Epidermolysis bullosa (EB) is a rare multisystem genetic disease characterized by mechanical fragility of epithelial surfaces including the skin, gastrointestinal mucosa and bronchial and renal tracts. Effective treatment of wounds is a central concern in EB.[1] Chronic wounds predispose patients with EB to the development of squamous cell carcinoma (SCC), which is a major cause of premature death in this population, in particular for those with recessive dystrophic EB (RDEB). Premature death also results from septicaemia, renal or cardiac failure, or amyloidosis.[2–5]

Despite a number of early-phase clinical trials for targeted therapy in small groups of patients, there is presently no curative treatment available for EB.[6,7] Management is focused on wound care and protection of the fragile skin, irrespective of the complex genetics implicated in the pathogenesis of EB.[8–10] Oleogel-S10 (birch triterpenes, also known as birch bark extract) is a topical sterile gel containing 10% birch triterpenes (betulin, lupeol, erythrodiol, betulinic acid and oleanolic acid) formulated with sunflower oil.[11] Triterpenes have demonstrated antibacterial, antimycotic, antiviral, anti-inflammatory, antitumoral and wound-healing properties.[11–14]

Three phase III studies of Oleogel-S10 demonstrated accelerated wound-healing effects in split-thickness skin graft donor sites and grade 2a burn wounds.[15,16] A small, open-label, blindly evaluated, controlled, phase II study was conducted in 10 patients with dystrophic EB (DEB), which showed potential for faster epithelialization when EB wounds were treated with Oleogel-S10.[17]

The EASE trial objective was to compare the efficacy of Oleogel-S10 with a vehicle control gel in patients aged ≥ 21 days with DEB, junctional EB (JEB) or Kindler EB (KEB) to accelerate healing of EB wounds.[18] EASE consisted of a 90-day, double-blind phase (DBP), followed by a 24-month open-label extension study (EASE is registered as NCT03068780, EudraCT 2016-002066-32).[18] This report provides the efficacy and safety results of the DBP.

Patients and methods

Study design

EASE (BEB-13) was a phase III study with a double-blind, randomized, controlled, parallel-group design to compare the efficacy, safety and tolerability of Oleogel-S10 vs. a vehicle control gel in patients with DEB, JEB or KEB. The date of first observation was April 2017 and the last participant completed the DBP on 3 June 2020. The vehicle control gel (hereafter referred to as control gel) was developed to retain blinding. The control gel was a sterile formulation

of the following excipients utilized in the other dermatological topical treatments: sunflower oil, cera flava/yellow wax and carnauba wax. At the end of the DBP (day 90 ± 7 days), patients in both treatment arms were eligible to enter a single-arm, open-label, follow-up phase with Oleogel-S10 for 24 months (Figure S1; see Supporting Information).

The design of the EASE trial has been previously described.[18] In brief, patients were randomized 1 : 1 to Oleogel-S10 or control gel using a blind-maintained numerical assignation system, with stratification for EB subtypes and according to the size of the selected target partial-thickness wound (PTW) lasting ≥21 days to < 9 months (by definition) (DEB 10 cm² to < 20 cm²; DEB 20 cm² to < 30 cm²; or DEB 30–50 cm²; JEB/KEB 10 cm² to < 20 cm²; JEB/KEB 20 cm² to < 30 cm²; JEB/KEB 30–50 cm²). The clinical research organization responsible for EASE generated the allocation sequence, and patients were assigned to the allocations by the treating physician. Assessments for efficacy, safety and local tolerability were conducted at subsequent visits up to day 90 ± 7 days.

Patients

Patient inclusion and exclusion criteria and nonpermitted concomitant medications have been published previously[18] and are provided in File S1 (see Supporting Information). Written informed consent was received for all patients. EASE was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by relevant institutional review boards and ethics committees for each study site.

Procedures

At all visits up to day 90 ± 7 days, the PTW identified as the EB target wound and all other EB PTWs on the patient's body were treated with the study drug applied either directly to the wound or to the wound dressing at least every 4 days. Assessment visits and data collection were conducted in the participating centres. Dressing changes were conducted at home or in clinic according to patient and carer preference. Safety and local tolerability were documented.

Outcomes

The primary efficacy endpoint of the study was the proportion of patients with first complete closure of the EB target wound, determined by clinical assessment, within 45 days (± 7 days) of treatment.[18] The assessment for the primary endpoint was in accordance with the US Food and Drug Administration (FDA) *Guidance for Industry Chronic*
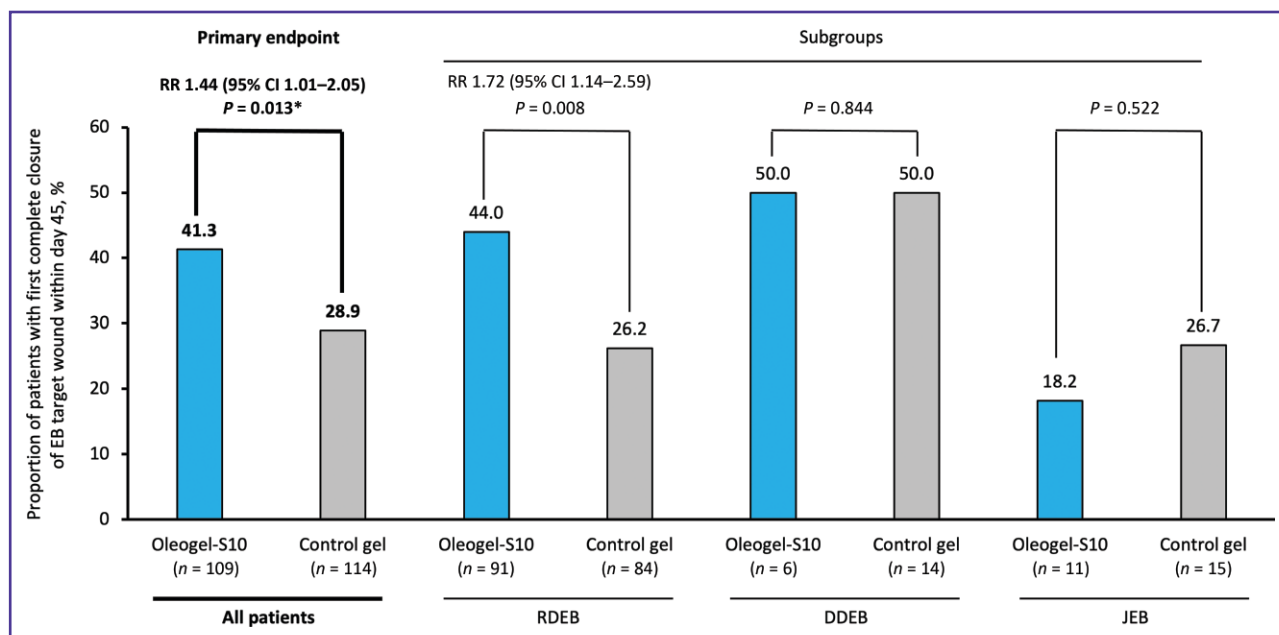
Figure 1 Proportion of patients with first complete closure of epidermolysis bullosa (EB) target wound within day 45 (all patients and by EB subgroup). CI, confidence interval; DDEB, dominant dystrophic EB; IDMC, Independent Data Monitoring Committee; JEB, junctional EB; RDEB; recessive dystrophic EB. *Prespecified adjustment to account for IDMC interim sample size re-estimation. The 'All patients' group includes two patients with EB simplex (one in each treatment arm). For all patients, the absolute difference in the probabilities of wound closure is 12·4%, providing a number needed to treat (NNT) of 8·06; for the RDEB subgroup, the absolute difference in probabilities is 17·8% (NNT 5·62).

Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment. The guidance states 'Complete wound closure of a chronic, nonhealing wound is one of the most objective and clinically meaningful wound healing endpoints.'[18,19] Complete wound closure was defined as skin re-epithelialization without drainage. The target closure time of 45 days is in accordance with the iscorEB definition of chronic EB wounds as being present for >6 weeks.[20] Oleogel-S10 acts by modulating inflammation in addition to enhancing keratinocyte migration and differentiation[14] and has the potential to target these wounds, which are

considered to be of high clinical relevance and a major source of complications in patients with EB. The first complete wound closure based on the clinical assessment by the investigator was confirmed by a second observation after 7 days (+2 days) at the confirmation of complete closure (CCC) visit. Assessments of target wounds and locations can be found in File S1, Figure S2 and Table S1 (see Supporting Information).

Key secondary efficacy endpoints have been previously described,[18] and included time to first complete closure of the EB target wound and proportion of patients with first
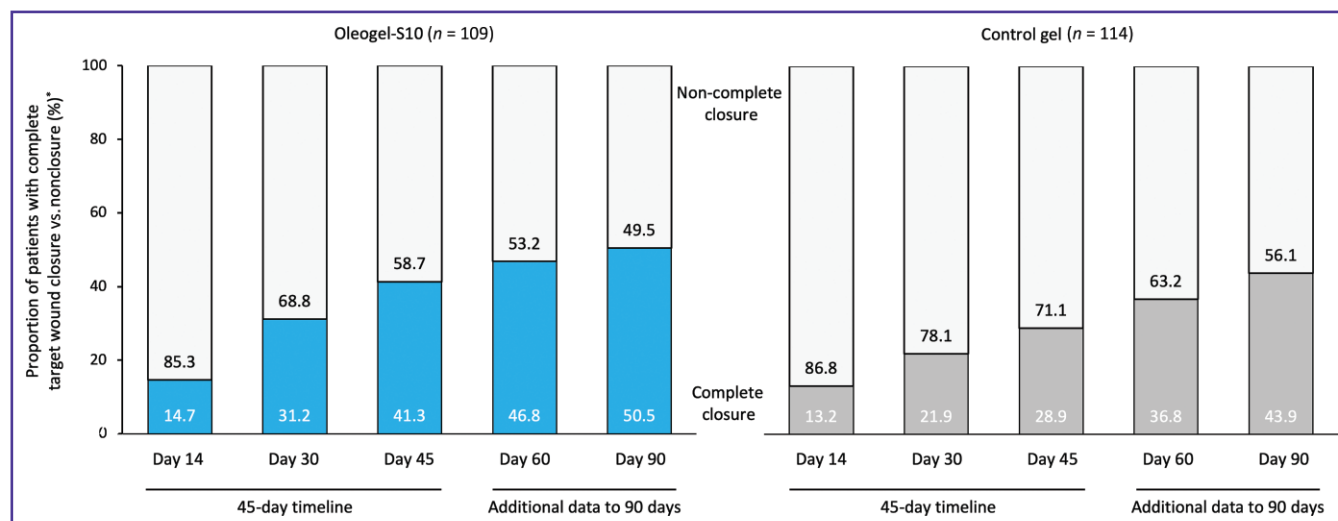

Figure 2 Percentage of patients with first complete closure of epidermolysis bullosa (EB) target wound by visit. Data represent the proportion of patients with first complete closure of target wound and noncomplete closure by assessment day based on clinical assessment (full analysis set). *Complete closure of the target wound refers to appearance of complete (100%) re-epithelialization without drainage.

Table 1 Baseline characteristics

Category	Oleogel-S10 (*n*=109)	Control gel (*n*=114)	All patients (*N*=223)
Age groups, *n* (%)			
0 to <4 years	7 (6·4)	10 (8·8)	17 (7·6)
4 to <12 years	42 (38·5)	43 (37·7)	85 (38·1)
12 to <18 years	25 (22·9)	29 (25·4)	54 (24·2)
≥18 years	35 (32·1)	32 (28·1)	67 (30·0)
Median age (95% CI), years	13·0 (14·2–19·5)	12·0 (13·8–19·2)	12·0 (14·8–18·5)
Sex, *n* (%)			
Male	68 (62·4)	66 (57·9)	134 (60·1)
Female	41 (37·6)	48 (42·1)	89 (39·9)
EB subtype, *n* (%)[a]			
Recessive DEB	91 (83·5)	84 (73·7)	175 (78·5)
Generalized severe	62 (56·9)	62 (54·4)	124 (55·6)
Generalized intermediate	23 (21·1)	16 (14·0)	39 (17·5)
Localized/other	6 (5·5)	6 (5·3)	12 (5·4)
Dominant DEB	6 (5·5)	14 (12·3)	20 (9·0)
JEB	11 (10·1)	15 (13·2)	26 (11·7)
Generalized severe	0 (0·0)	2 (1·8)	2 (0·9)
Generalized intermediate	8 (7·3)	9 (7·9)	17 (7·6)
Localized/other	3 (2·8)	4 (3·5)	7 (3·1)
Wound size group, *n* (%)[b]			
10 to <20 cm²	69 (63·3)	75 (65·8)	144 (64·6)
20 to <30 cm²	23 (21·1)	24 (21·1)	47 (21·1)
30–50 cm²	17 (15·6)	15 (13·2)	32 (14·3)
Median wound size (95% CI), cm²	16·0 (17·4–20·6)	15·5 (17·5–21·3)	15·6 (18·0–20·4)
Median age of target wound, days			
All	39·0 (62·1–186·5)	32·0 (40·6–212·1)	35·5 (72·5–178·2)
Mean EBDASI skin activity score ± SD	19·6 (11·3)	19·6 (12·6)	19·6 (11·9)
BMI group, *n* (%)			
Underweight	56 (51·4)	59 (51·8)	115 (51·6)
Normal	45 (41·3)	41 (36·0)	86 (38·6)
Overweight	5 (4·6)	6 (5·3)	11 (4·9)
Obese	3 (2·8)	8 (7·0)	11 (4·9)

BMI, body mass index; CI, confidence interval; EB, epidermolysis bullosa; DEB, dystrophic EB; EBDASI, Epidermolysis Bullosa Disease Activity and Scarring Index; JEB, junctional EB. [a]Patients with EB simplex (EBS; *n*=2) were enrolled and were included in the analysis; a subsequent protocol amendment excluded EBS. [b]Details of location of target wounds can be found in Table S2 (see Supporting Information).

target wound closure within day 90±7 days; incidence and maximum severity of target wound infection between baseline and day 90±7 days; total body wound burden using the skin activity component of the EB Disease Activity and Scarring Index (EBDASI);[21,22] pain and itch (with scales chosen according to patient age);[23,24] and body surface area percentage (BSAP) affected by EB PTWs. Additional patient-reported outcomes included background pain, Wound-QoL, sleep, work days/school days missed and Treatment Satisfaction Questionnaire for Medication. Safety was assessed as incidence, severity and relatedness of systemic and local adverse events (AEs).

Statistical analysis

Based on the use of a two-sided test of equality of binomial proportions at the α=0·05 level of significance, a total sample size of 182 participants (91 participants per arm) was determined to provide 80% power to detect an improvement of 20 percentage points. A total of 192 patients were planned for enrolment, accounting for an estimated dropout rate of 5%. A planned unblinded interim analysis was conducted to determine whether the sample size was sufficient, whether the sample needed to be increased, or whether the study should be stopped on the basis of futility. At 50% completion to day 45±7 days, the Independent Data Monitoring Committee (IDMC) recommended an increase in sample size by 48 patients (24 per arm), resulting in a

total of 230 patients. The significance level of the primary analysis was adjusted to account for IDMC interim sample size re-estimation.[25]

Statistical analysis of the primary efficacy endpoint was conducted on the full analysis set using a Cochran–Mantel–Haenszel (CMH) test, stratified by EB subtype and target wound size class.

Once superiority of the primary efficacy endpoint was shown at the 5% significance level, key secondary efficacy endpoints were tested hierarchically to ensure an overall significance level of 5%. Once a nonsignificant result was achieved, the results of all remaining key secondary endpoints were considered exploratory rather than confirmatory. Further details regarding statistical analysis are provided in the statistical analysis plan.

Results

Patients

The study enrolled 223 patients (109 treated with Oleogel-S10; 114 treated with control gel) (Figure S3; see Supporting Information) from 49 sites in 26 countries (April 2017 to March 2020). Baseline characteristics were similar between treatment groups (Table 1, Tables S1 and S2; see Supporting Information). Overall, 175 patients enrolled (78·5%) had a diagnosis of RDEB, 20 patients (9·0%) had
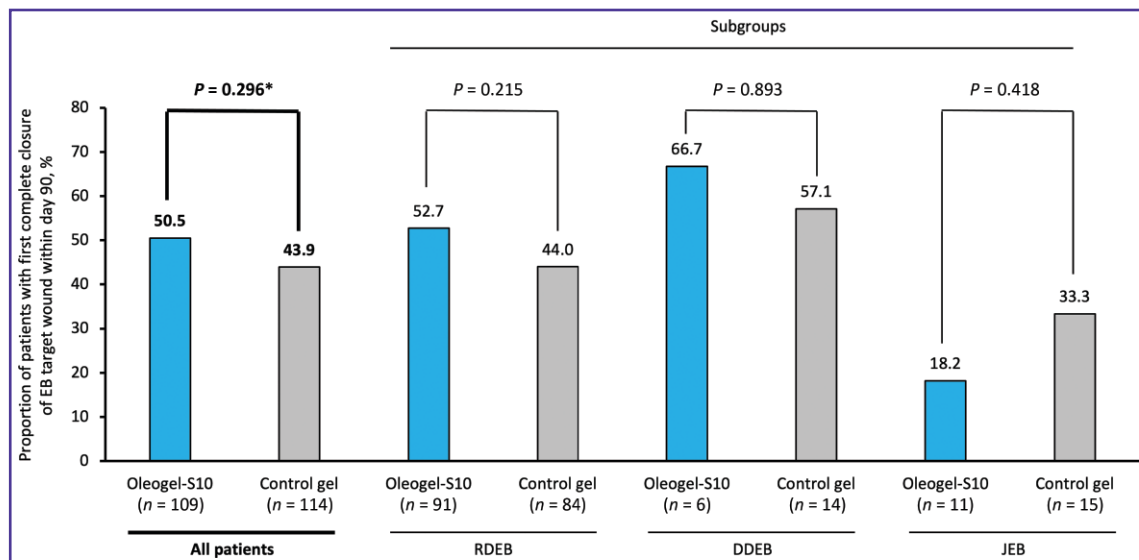
Figure 3 Proportion of patients with first complete closure of epidermolysis bullosa (EB) target wound within day 90 (all patients and by EB subgroup). DDEB, dominant dystrophic EB; JEB, junctional EB; RDEB, recessive dystrophic EB. *Cochran–Mantel–Haenszel test was used. The 'All patients' group includes two patients with EB simplex (one in each treatment arm).

dominant DEB (DDEB) and 25 patients (11·7%) had JEB. No patients with KEB were enrolled.

A total of 199 patients completed the DBP of the study to day 90 ± 7 days (100 patients treated with Oleogel-S10 and 99 patients treated with control gel; 91·7% and 86·8%, respectively; Figure S3). Frequency of dressing change is shown in Table S3 (see Supporting Information).

Efficacy results

EASE met its primary endpoint in relation to the proportion of patients with first complete closure of EB target wound by day 45. Complete target wound closure was achieved in 41·3% of target wounds treated with Oleogel-S10 and 28·9% of target wounds treated with control gel [relative risk (RR) 1·44, 95% confidence interval (CI) 1·01–2·05; $P = 0·013$ (Figure 1)]. This equates to a 44% increase in probability of wound closure with Oleogel-S10 vs. control gel. An independent panel assessment showed similar results (41·3% Oleogel S-10 vs. 28·1% control gel). This was further supported by the observed reduction in target wound size via clinical assessments over 90 days (available in Figure S4 and Tables S4 and S5; see Supporting Information).

Data from the CCC assessment support the observations from the primary endpoint. However, among the patients who were eligible to attend this visit (those with first complete target wound closure across both treatment arms within day 45; $n = 78$), the number of patients who completed the assessment was low and imbalanced between both treatments (30 of 45 patients treated with Oleogel-S10, 13 of 33 patients treated with control gel).

A subgroup analysis by EB subtype demonstrated that patients with RDEB, the largest group, were the only subgroup to demonstrate a statistically significant benefit from Oleogel-S10 treatment (Figure 1). Among the patients with RDEB (91 patients treated with Oleogel-S10; 84 patients treated with control gel), complete target wound closure

by day 45 was achieved in 44·0% of wounds treated with Oleogel-S10 and 26·2% of target wounds treated with control gel (RR 1·72, 95% CI 1·14–2·59; $P = 0·008$) (Figure 1). In patients with JEB ($n = 26$) and dominant DEB ($n = 20$), differences between treatment groups did not reach statistical significance, albeit with very small sample sizes. Further subgroup analyses are available in Figure S5 (see Supporting Information).

An analysis of time to first target wound closure up to day 90 was conducted over the key timepoints during the DBP (Figure 2, Figure S6 and Table S5; see Supporting Information). By day 30, the proportion of patients with complete target wound closure was 31·2% with Oleogel-S10 and 21·9% with control gel (RR 1·44, 95% CI 0·93–2·21; $P = 0·098$). A smaller difference between treatment groups was observed by day 90 (Figure 2). The difference in the time to first target wound closure over the 90-day double-blind period in the two arms was not statistically significant (log-rank test, $P = 0·302$) (cumulative incidence of first target wound closure computed using the Kaplan–Meier method; Figure S6). By day 90, the cumulative proportion of patients with first target wound closure was 50·5% for Oleogel-S10 vs. 43·9% for control gel (RR 1·16, 95% CI 0·88–1·52; $P = 0·296$) (Figure 3 and Table S4; see Supporting Information). A similar trend was observed in the subgroup analysis of RDEB by day 90 (Figure 3).

There were six patients with target wound infections during the DBP: one patient (0·9%) in the Oleogel-S10 arm compared with five patients (4·4%) on control gel (Table 2). A lower incidence and lesser severity was observed with Oleogel-S10. Differences in total wound burden measured by EBDASI skin activity and BSAP for the Oleogel-S10 arm compared with control gel did not reach statistical significance (Table 2).

Improvements in the Itch Man Scale (patients aged 4–13 years) were observed with both treatments, with a significant improvement observed only at day 60 with

Table 2 Key secondary efficacy outcomes from EASE

	Oleogel-S10	Control gel	P-values[a]
Target wound closure	*n* = 109	*n* = 114	
Proportion of patients with first complete closure of EB target wound within day 90, %	50·5	43·9	0·296
Relative risk (95% CI)	1·16 (0·88–1·52)		–
Time to first complete target wound closure, mean days (SD) (95% CI)	37·7 (21·7) (31·9–43·6)	44·5 (26·2) (37·1–51·9)	0·302
Total body wound burden			
EBDASI skin activity score (max score 100)			
Baseline, mean ± SD	19·6 ± 11·3 (*n* = 108)	19·6 ± 12·6 (*n* = 113)	–
Mean change from baseline at day 30 (95% CI)	−2·3 (−3·6 to −0·9) (*n* = 99)	−2·2 (−3·5 to −0·8] (*n* = 99)	0·95
Mean change from baseline at day 60 (95% CI)	−3·1 (−4·7 to −1·5) (*n* = 91)	−2·0 (−3·4 to −0·5] (*n* = 96)	0·20
Mean change from baseline at day 90 (95% CI)	−3·4 (−4·9 to −1·8) (*n* = 84)	−2·8 (−4·4 to −1·2] (*n* = 85)	0·89
Total body surface area (BSAP)			
Baseline, mean ± SD	12·1 ± 10·0 (*n* = 109)	12·2 ± 12·2 (*n* = 113)	–
Mean change from baseline at day 30 (95% CI)	−2·6 (−4·0 to −1·1) (*n* = 98)	−2·6 (−3·9 to −1·3) (*n* = 98)	0·82
Mean change from baseline at day 60 (95% CI)	−2·9 (−4·6 to −1·2) (*n* = 92)	−1·7 (−3·5–0·11) (*n* = 96)	0·11
Mean change from baseline at day 90 (95% CI)	−4·3 (−5·8 to −2·8) (*n* = 86)	−2·5 (−4·4 to −0·6) (*n* = 85)	0·11
Procedural pain			
Wong Baker Faces© (participants ≥ 4 years)			
Baseline, mean ± SD	3·7 ± 3·1 (*n* = 98)	3·0 ± 3·0 (*n* = 100)	–
Mean change from baseline at day 14 (95% CI)	−1·4 (−1·9 to −0·9) (*n* = 90)	−0·8 (−1·3 to −0·2) (*n* = 95)	0·02
Mean change from baseline at day 30 (95% CI)	−1·0 (−1·7 to −0·4) (*n* = 90)	−0·3 (−0·9–0·3) (*n* = 90)	0·15
Mean change from baseline at day 45 (95% CI)	−0·9 (−1·6 to −0·2) (*n* = 84)	−0·8 (−1·4 to −0·1) (*n* = 85)	0·81
Mean change from baseline at day 60 (95% CI)	−1·3 (−1·9 to −0·6) (*n* = 84)	−0·6 (−1·2–0·1) (*n* = 86)	0·10
Mean change from baseline at day 90 (95% CI)	−1·3 (−2·0 to −0·6) (*n* = 76)	−0·2 (−0·8–0·5) (*n* = 78)	0·05
FLACC (participants < 4 years)			
Baseline (mean ± SD)	4·7 ± 3·4 (*n* = 7)	2·7 ± 3·2 (*n* = 10)	–
Mean change from baseline at day 14 (95% CI)	−2·6 (−5·1 to −0·1) (*n* = 7)	−0·9 (−4·0–2·2) (*n* = 9)	NE
Mean change from baseline at day 30 (95% CI)	−2·0 (−4·6–0·6) (*n* = 7)	−2·1 (−5·6–1·3) (*n* = 8)	NE
Mean change from baseline at day 45 (95% CI)	−1·6 (−5·3–2·1) (*n* = 5)	−2·0 (−5·4–1·4) (*n* = 8)	NE
Mean change from baseline at day 60 (95% CI)	−2·0 (−6·5–2·5) (*n* = 7)	−1·6 (−5·1–1·8) (*n* = 8)	NE
Mean change from baseline at day 90 (95% CI)	−2·6 (−5·3–0·1) (*n* = 7)	−1·2 (−3·7–1·4) (*n* = 6)	NE
Target wound infections	*n* = 109	*n* = 114	–
Infection, *n* (%)[b]	1 (0·9)	5 (4·4)	–
Severity of infection, *n* (%)[c]			
Mild	0	0	–
Moderate	0	3 (2·6)	–
Severe	0	1 (0·9)	–
Life-threatening	0	0	–
Death	0	0	–

BSAP, body surface area percentage; CI, confidence interval; EBDASI, Epidermolysis Bullosa Disease Activity and Scarring Index; FLACC, Face, Legs, Activity, Cry, Consolability; NE, not estimable. [a]Oleogel-S10 vs. control gel. [b]The incidence of wound infection was evidenced by adverse events (AEs) and/or use of topical and/or systemic antibiotics (related to wound infection). [c]Severity of target wound infection between baseline and day 90 was evaluated if a participant had a wound infection event evidenced by AE. For target wound closure at day 90, parameter and model estimates based on a Cochran–Mantel–Haenszel test stratified by epidermolysis bullosa (EB) subtype and target wound size class. For EBDASI and BSAP, parameter and model estimates based on an analysis of covariance (ANCOVA) for the change from baseline with treatment group was utilized. For FLACC and Wong Baker Faces background and procedural pain rating, parameter and model estimates based on a two-sided Wilcoxon rank sum test using the van Elteren extension stratified by EB subtype and target wound size class.

the control gel (*P* = 0·016) (Figure S7; see Supporting Information). Procedural pain (pain associated with dressing changes) data are reported in Table 2, with a reduction in procedural pain observed for Oleogel-S10 vs. control gel in patients ≥ 4 years old [day 14: −1·4 (95% CI −1·9 to −0·9) vs. −0·8 (95% CI −1·3 to −0·2); *P* = 0·02]. At day 90, Oleogel-S10 reduced procedural pain by −1·3 (95% CI −2·0 to −0·6) vs. −0·2 (95% CI −0·8–0·5) with control gel (*P* = 0·051; Table 2). Differences in procedural pain at other timepoints were not statistically significant.

Analysis of dressing change frequency showed that throughout the DBP, patients treated with Oleogel-S10 had a reduced requirement for daily dressing changes compared with those who received control gel (Figure S3). At day 90, the change with Oleogel-S10 equated to one less dressing change every 2 weeks (*P* = 0·001) (Figure S8; see Supporting Information).

Other patient-reported outcomes including background pain, Wound-QoL, sleep, work days/school days missed and Treatment Satisfaction Questionnaire for Medication are reported in the Supporting Information (Figures S9–12, Tables S6 and S7; see Supporting Information).

Safety results

A similar percentage of patients in the Oleogel-S10 and control gel groups reported AEs, most of which were of mild or moderate intensity (Table 3) and there were no clinically meaningful differences between the treatment groups. A similar proportion in both groups were considered to be related to treatment, with a low number leading to drug withdrawal. There was also one patient in the control gel arm who prematurely discontinued the study because of pregnancy. The most frequently reported events for

Table 3 Adverse events (AEs)

AE category/system organ class preferred term	Oleogel-S10 (*n* = 109)	Control gel (*n* = 114)	All patients (*N* = 223)
Summary of AEs			
Any AEs	89 (81·7)	92 (80·7)	181 (81·2)
Any serious AEs[a]	7 (6·4)	6 (5·3)	13 (5·8)
Any severe AEs[a,b]	13 (11·9)	6 (5·3)	19 (8·5)
Any related AEs[a]	27 (24·8)	26 (22·8)	53 (23·8)
Any serious related AEs[a]	1 (0·9)	0 (0·0)	1 (0·4)
Any AEs leading to study withdrawal[a]	3 (2·8)	2 (1·8)	5 (2·2)
Any serious AEs leading to study withdrawal[a]	2 (1·8)	0 (0·0)	2 (0·9)
Any serious related AEs leading to study withdrawal[a]	1 (0·9)	0 (0·0)	1 (0·4)
Any serious AEs leading to death	0 (0·0)	0 (0·0)	0 (0·0)
AEs occurring in ≥5% of patients			
Number of events	282	277	561
Any AEs	89 (81·7)	92 (80·7)	181 (81·2)
Injury, poisoning and procedural complications	69 (63·3)	66 (57·9)	135 (60·5)
Wound complication[c,d]	67 (61·5)	61 (53·5)	128 (57·4)
Infections and infestations	37 (33·9)	36 (31·6)	73 (32·7)
Wound infection	8 (7·3)	10 (8·8)	18 (8·1)
General disorders and administration site conditions	21 (19·3)	25 (21·9)	46 (20·6)
Pyrexia	9 (8·3)	15 (13·2)	24 (10·8)
Skin and subcutaneous tissue disorders	11 (10·1)	15 (13·2)	26 (11·7)
Pruritus	8 (7·3)	6 (5·3)	14 (6·3)
Blood and lymphatic system disorders	8 (7·3)	6 (5·3)	14 (6·3)
Anaemia	8 (7·3)	4 (3·5)	12 (5·4)

[a]Single patient with wound haemorrhage (probably related, severe, serious, led to withdrawal); wound infection bacterial (unlikely related, severe, serious, led to study withdrawal). [b]Overall, 26 AEs (4·6%) were classified as severe of 561 AEs reported in the DBP. [c]Refers to any AEs with preferred term or low-level term of 'wound complication'; there are other AEs involving wounds (e.g. wound haemorrhage, wound secretion). [d]Included changes in wound size and wound reopening. Data are provided as *n* (%), unless otherwise stated.

Oleogel-S10 and control gel were wound complications, occurring at a similar frequency in both treatment arms (Table 3 and Table S8; see Supporting Information).

Changes in wound size from visit to visit are expected in patients with EB who have fragile skin. The patients treated with control gel had more events of increase from baseline with respect to wound size. A higher proportion of patients treated with Oleogel-S10 had healed wounds or decreased wound size, and therefore in these patients the increase in size was either relative to the previous visit or reopening of previously closed wounds. As the Medical Dictionary for Regulatory Activities term of 'wound complication' did not reflect these differences in changes of wound size, the subcategories of wound complication were specific to this study.

Serious AEs were reported in 6·4% of patients treated with Oleogel-S10 compared with 5·3% in those treated with control gel (Table S9; see Supporting Information). Only one serious AE, a wound haemorrhage in a patient treated with Oleogel-S10, was considered to be related to study treatment, and also led to withdrawal. One patient (adult RDEB, generalized severe) was diagnosed with SCC (Oleogel-S10 arm). However, no study treatment had been applied to the lesion, which was observed as suspicious at enrolment with subsequent biopsy leading to the diagnosis. Exposure to Oleogel S-10 did not result in any systemic accumulation of betulin (Table S10; see Supporting Information).

Discussion

The EASE phase III trial met its primary endpoint and is the largest randomized controlled study in EB (*N* = 223; from 26 countries). The majority of patients had severe disease, with 78·5% being diagnosed with RDEB (generalized severe RDEB was the most common form). This may be a function of the study inclusion criteria, including wound sizes and duration, which are characteristic of these subtypes, but it represents those patients with the greatest unmet need.

Accelerating wound healing/closure has been recently rated as an important attribute for potential EB treatments by caregivers and patients.[2] In EASE, the primary endpoint showed that Oleogel-S10 resulted in acceleration of wound healing with 41·3% of target wounds treated with Oleogel-S10 achieving first complete closure within 45 days compared with 28·9% for control gel. Therefore, patients who were treated with Oleogel-S10 were 44% more likely to achieve complete closure of their target wound within 45 days than those treated with control gel (*P* = 0·013). Recessive DEB (*n* = 175) was the most frequent subtype of EB enrolled in the trial and was characterized by a substantial treatment effect. In patients with JEB (*n* = 26) and dominant DEB (*n* = 20), the analysis was hindered by the small size of these groups. In addition, there was an imbalance within the DDEB group where only six patients were allocated to Oleogel-S10 compared with 14 patients allocated to control gel.

Further examination of target wound closure in the DBP showed that the difference between the two arms narrowed by day 90. This is due to a higher proportion of first target wound closures with Oleogel-S10 at early timepoints. This pattern reflects previous observations from another phase III study in EB, where the authors suggest application of good wound care during the study and a possible unforeseen benefit of the vehicle control eventually enables more wounds to heal over a longer period of treatment.[26] Closing wounds faster and reducing their size results in fewer, less

severe wounds, which is an obvious benefit to patients with EB, and is therefore an outcome that would be considered meaningful for patients, their caregivers, and healthcare professionals. Indeed, accelerating wound healing/closure was rated as important by 71·4% of patients and 80·6% of caregivers in a 2020 review by Bruckner *et al.*[2]

A reduction in overall wound burden using two different measures, the skin activity component of the validated EBDASI and the BSAP, was observed within the EASE study. As Oleogel-S10 is a topical medication, only the Section I skin activity evaluation (and not skin damage) of the EBDASI was completed.[27] Skin activity was assessed in terms of erosions, blisters and crusting. The mean change from baseline in the skin activity score was −3·1 at day 60 and −3·4 at day 90 for patients treated with Oleogel-S10 vs. −2·0 at day 60 and −2·8 at day 90 for control gel (Table 2). Therefore, although the difference vs. control gel is not statistically significant, at both timepoints, patients treated with Oleogel-S10 exceeded the clinically important threshold of a 3-point reduction.[21] In contrast, even at 90 days, patients with the control gel fell short of a 3-point reduction. Oleogel-S10 also reduced mean BSAP affected by EB PTWs consistent with the improvement observed using the EBDASI skin activity evaluation. In the Oleogel-S10 group, the mean BSAP at day 90 was 7·41%, an absolute change of −4·32% (36%) from baseline. In the control gel group, a smaller reduction in the BSAP was observed at day 90 with a mean score of 8·14% reflecting a −2·53% (21%) change from baseline.

Wound infections are particularly problematic in EB, adversely impacting the ability of wounds to heal, which increases the potential transformation to SCC in addition to affecting the patient's quality of life.[28,29] The incidence of target wound infections in EASE was low and therefore underpowered for effective analysis. The incidence and severity of both target and nontarget wound infections was lower in the Oleogel-S10 arm compared with control gel.

Dressing changes are typically daily, painful, time-consuming and result in psychological distress for both patients and caregivers.[30] Analysis of dressing change frequency in EASE showed a reduction in dressing changes that equated to one less dressing change every 2 weeks (for patients treated with Oleogel-S10 compared with no change observed for control gel) ($P = 0·001$).

Procedural pain associated with dressing changes was also analysed. Compared with control gel, Oleogel-S10 reduced the procedural pain at day 14 ($P = 0·022$) in participants ≥4 years of age. Differences numerically favoured Oleogel-S10 but were not statistically significant at other timepoints.

Improvements in itch were observed in both treatment groups; as itch is a diffuse, multifaceted symptom,[31] the degree of change was inconsistent between the scoring domains and there was no difference between treatment arms.

The majority of AEs were mild or moderate in severity, with similar proportions of treatment-related AEs in the two treatment groups. The patients with EB enrolled in the study had significant morbidity, and Oleogel-S10 was demonstrated to be safe and well tolerated. Most of the AEs in patients treated with Oleogel-S10 were either expected owing to their EB or resulted from the focus on clinical assessment of wound closure, as reporting AEs of

wound complication was specifically required by the clinical study protocol in case the wound worsened or increased in size. Only one serious AE for Oleogel-S10 was assessed as related by the investigator.

A limitation for EB studies is the lack of core outcome sets for EB. Unfortunately, these are still ill defined and there are no disease-specific endpoints for EB that are accepted by the regulators as proof of wound-healing efficacy. Indeed, this is recognized by the recent FDA guidance.[19] As a result, the primary endpoint of the EASE study was mandated by the FDA in its published guidance for the design of clinical trials on chronic cutaneous wounds,[32] and this guidance set the ambitious target of complete wound closure, which does not account for the recurrence and chronicity of wounds in EB.

Limitations of the EASE trial were largely related to the challenges of performing randomized clinical trials in rare diseases as stratification cannot balance all confounding factors, and important subgroup analyses and secondary endpoints are underpowered. In this trial, only 20 patients with DDEB and 26 patients with JEB were enrolled; consequently the small sample size of these subgroups makes interpretation difficult.[18,19] With respect to the secondary outcome assessing wound burden using the EBDASI, only the skin activity component of this tool was utilized as it was considered the most appropriate element to help assess response to therapy. The EASE DBP is additionally limited by the length of follow-up. Efficacy endpoints in severe chronic skin diseases are difficult to assess over a short timeframe and an additional long-term open-label phase (OLP) is under way that will provide additional data on the long-term effectiveness of Oleogel-S10 in EB. Indeed, a recent publication reporting the unplanned interim analysis from the OLP confirmed tolerability and long-term treatment effects of Oleogel-S10.[33]

While additional research is ongoing, and includes gene therapeutic approaches,[6,7,34] current patient care is centred on protection from minor trauma and friction, wound management, and prevention of infection in this devastating group of rare skin conditions.[9] Therefore, EASE is an important phase III study in patients with severe forms of EB in which Oleogel-S10 was shown to accelerate wound healing within 45 days, together with other positive findings. As of 23 June 2022, the approval of Oleogel-S10 by the European Commission will provide a new treatment option in the management of EB wounds.[35] As with all randomized controlled trials, real-world evidence will be an important source of data regarding the clinical effectiveness of this treatment in EB.

Supporting Information

Additional Supporting Information can be found in the online version of this article at the publisher's website.

Acknowledgments

Conflicts of interest

J.S.K. has received grants and/or fees for consultancy in the last 12 months from Amryt. E.S. has received grants for consultancy in the last 12 months from Amryt, Kamari Pharma Ltd, and BiomX, and as CMO of Sol-Gel Technologies Ltd. F.S., C.B. and M.F.F. have received grants and/or fees for consultancy in the last 12 months from Amryt. T.C., S.L. and M.S. are employees of Amryt Research Ltd. C.D. is a paid contractor for Amryt Research Ltd. A.L.B. has received grants and/or fees for consultancy in the last 12 months from Amryt, Amicus/Scioderm, Castle Creek, Fibrocell, ProQR/Wings and Phoenix Tissue Repair. D.F.M. has received grants and/or fees for consultancy in the last 12 months from Amryt and Amicus, and is a co-owner of the patent for topical sirolimus for epidermolysis bullosa simplex. A complete list of investigators in the EASE trial is provided in the Supporting Information.

Data availability

The study protocol, statistical analysis plan, and consent form, and selected subgroup level data, figures and listings can be made available on request via medinfo@amrytpharma.com. These data will be available from 1 year after completion of the trial and in perpetuity.

Ethics statement

EASE was approved by the institutional review boards of the participating sites.

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