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Betulin wound gel accelerated healing of superficial partial thickness burns: Results of a randomized, intra-individually controlled, phase III trial with 12-months follow-up

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ABSTRACT

Objective: Acceleration of wound healing promises advantages for patients and caregivers in reducing the burden of disease, avoiding complications such as wound infections, and improving the long-term outcome. However, medicines that can accelerate wound healing are lacking. The objective of this open, blindly evaluated, randomized, multicenter phase III study was to compare intra-individually the efficacy and tolerability of Oleogel-S10 with fatty gauze dressing versus Octenilin® wound gel with fatty gauze dressing in accelerating the healing of superficial partial thickness burn wounds.

Methods: Acute superficial partial thickness burn wounds in adults caused by fire, heat burn or scalding were divided into 2 halves and randomly assigned to treatment with Oleogel-S10 or Octenilin® wound gel. Photos for observer-blinded analysis of wound healing were taken at each wound dressing change. Percentages of reepithelialization were assessed at defined intervals. Efficacy and tolerability were evaluated based on a 5-point Likert scale.

Results: Of 61 patients that were enrolled, 57 received the allocated intervention and 48 completed treatment. The percentage of patients with earlier wound healing was significantly higher for Oleogel-S10 (85.7%, n=30) compared to Octenilin® wound gel (14.3%, n=5, $p<0.0001$). The mean intra-individual difference in time to wound closure was

Abbreviations: AE, adverse event; CI, confidence interval; CTCAE, common terminology criteria of adverse events classification; EoT, end of treatment; GCP, good clinical practice; ICH, International Council on Harmonisation; MedDRA, medical dictionary for regulatory activities; POSAS, Patient and Observer Scar Assessment Scale; SAE, serious adverse event; SSD, silver sulfadiazine; STSG, split-thickness skin graft; TBSA, total body surface area.

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−1.0 day in favour of Oleogel-S10 (−1.4, −0.6; 95% CI, $p < 0.0001$). Most investigators (87.0%) and patients (84.8%) evaluated the efficacy of Oleogel-S10 to be 'better' or 'much better' than that of Octenilin® wound gel. Long-term outcome 3 months and 12 months post injury was improved in some patients.

Conclusions: Oleogel-S10 (Episalvan) significantly accelerated the healing of superficial partial thickness burn wounds. It was safe and well tolerated.

1. Introduction

1.1. Early wound closure reduces risk of scarring

It has been a long-standing notion that the time needed to close a burn wound is correlated with long-term scar outcome, with longer healing times increasing the risk for visible scars. Recent studies provide quantitative support and evidence: the risk of hypertrophic scarring in paediatric burns with conservative treatment [1,2] increases from 0% in wounds healed within 8 days [1] to 10 days [2] and reaches as high as 56% [1] and 88% [2] for wounds that require more than 30 days to heal. A study in adults using split-thickness skin graft donor sites, that are comparable in wound depth to partial thickness burns, showed similarly an increase of a visual scar score (considering scar height, surface and colour) with time to healing [3].

Superficial partial thickness burns regenerate from proliferative keratinocytes in the basal skin layer and its appendages. Reepithelialization usually occurs within 2 weeks [5]. In deep partial thickness burns on the contrary, only a partial recovery based on connective tissue is possible. Split-thickness skin grafting is necessary to avoid scarring and contractures. An accurate distinction of superficial and deep partial thickness burns using imaging devices is therefore relevant, as it impacts management and prognosis [6]. Regular assessments are necessary, as burn depth can change and deepen following initial injury, if superficial and partial thickness wounds dry out or become infected [7].

1.2. Standard of care in superficial partial thickness burns

A dressing for treatment of superficial partial thickness burns should maintain a moist wound healing environment [8]. Partial thickness burns are either treated with traditional wound dressings, such as a combination of paraffin-impregnated gauze and an absorbent cotton wool layer or with advanced wound dressings. Advanced wound dressings absorb fluid while maintaining a moist environment, provide a bacterial barrier to prevent infection and need to be changed less frequently, but do not appear to offer advantages with regard to time to wound closure [7].

In a study using extracorporeal shock wave therapy for superficial partial thickness burns [12] the treatment reduced the time to wound closure compared to the standard of care control group, but to date no pharmacological active treatment is available that accelerates wound healing [7,8].

One of the major concerns in burn treatment is prevention and management of infection that delays wound healing and increases the length of hospital stays, costs, and mortality [9]. Silver sulfadiazine (SSD) cream is often used to reduce the risk of wound infection, but delays wound healing [7]. Antiseptic hydrogels containing polihexanide or octenidine are also used to prevent wound infections [10,11].

For the present study an octenidine hydrogel combined with fatty gauze dressing was selected as standard of care treatment.

1.3. Oleogel-S10

Oleogel-S10 is a sterile wound gel for topical use containing 10% refined triterpene dry extract from birch bark (quantified to 72%–88% betulin) and 90% refined sunflower oil. Additional components of birch bark extract include betulinic acid, lupeol, oleanolic acid, and erythrodiol. The active pharmaceutical ingredient of Oleogel-S10 modulates chemokines in the inflammation phase of wound healing and promotes the migration and differentiation of keratinocytes, thus accelerating reepithelialization and wound closure [13,14]. More recently it was shown that fibroblasts too are stimulated by birch bark extract and its main constituents [15]. For triterpenes present in birch bark extract, namely betulin, betulinic acid and oleanolic acid, antiviral, antibacterial, antimycotic, and anti-inflammatory effects have been described [16–18].

At the time of the study, Oleogel-S10 was still an investigational medicinal product. Recently it has received regulatory approval by the European Medicines Agency as a new medicine for the treatment of partial thickness wounds in adults (tradename: Episalvan).

1.4. Rationale for the study

Oleogel-S10 accelerated the reepithelialization of split-thickness skin graft (STSG) donor sites in an open, blindly evaluated, randomized, intra-individually controlled phase II trial in 24 patients who required skin grafting due to burns, trauma, chronic venous ulcers, or surgical removal of cutaneous malignancies. Oleogel-S10 administration was safe and well tolerated [19].

Since STSG donor sites are partial thickness 'model' wounds, this data was suggested proof of concept for accelerated healing of partial thickness wounds in general. The acceleration of wound healing in superficial partial thickness burns would meet an important medical need, as it might prevent wound infection, progression of wound depth, and delayed or compromised wound healing.

Therefore, an open, blindly evaluated, randomized, intra-individually controlled, multicenter phase III study has been initiated to investigate whether Oleogel-S10 with fatty gauze dressing accelerate the healing of superficial partial thickness burns compared with standard of care defined as octenidine

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hydrochloride gel (Octenilin® wound gel, Schülke & Mayr GmbH, Germany) with fatty gauze dressing. The primary outcome was the intra-patient comparison of wound healing in two comparable wound halves that were randomized to either treatment, Oleogel-S10 or Octenilin® wound gel. Here, we present the results of this study.

2. Methods

2.1. Study design

This open, blind evaluated, randomized, intra-individually controlled, multicenter phase III study (EudraCT No. 2012-000362-38) was conducted in 10 centers in 4 countries (Germany, n=4; Sweden, n=2; Switzerland, n=1; UK, n=3).

2.2. Ethics

Local or regional ethics committees of each study site approved the protocol. The study was conducted in compliance with the study protocol, ethical principles originating in or derived from the Declaration of Helsinki, ethics committee informed consent regulations, and International Council on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Informed consent was obtained from all patients before enrollment. All investigators and study team members were trained in the study protocol and the standardized acquisition of photographs.

2.3. Patient population

Adults with acute superficial partial thickness burns caused by fire burn, heat burn or scalding within 48 h of injury were eligible for enrollment if they had either a single superficial partial thickness burn wound >80 cm^2 and <25% of their total body surface area (TBSA) or 2 comparable wounds of >40 cm^2 and <12.5% TBSA each. Experienced surgeons assessed burn wound depth, additionally aided by Laser Doppler Imaging (LDI) or Multispectral Imaging (MSI) to distinguish between superficial partial thickness and deep partial thickness burns.

As a standard safety measure, women of childbearing potential had to use an effective form of birth control with failure rates <1% per year during participation in the study, pregnant or breastfeeding women were not eligible. Further exclusion criteria comprised chemical, electrical, or sunburns, pre-treatment with SSD, positive blood cultures, and a medical history of allergy including hypersensitivity to any of the drugs or dressings used in the trial.

2.4. Interventions

The eligible study wound was divided into 2 halves that were marked as 'proximal' or 'distal' and 'right' or 'left' related to the center of the body. When 2 comparable wounds were treated, they were marked correspondingly. An overview photo of both wound halves including markings and anatomical landmarks was taken. The upload of this overview photo to an interactive web response system (IWRS) initiated a tamper-proof randomisation process assigning the wound halves either to treatment with Oleogel-S10 (Birken AG, Niefern-Oeschelbronn, Germany) or with Octenilin® wound gel (Schülke & Mayr GmbH, Norderstedt, Germany). The healthy skin next to the wound half treated with Oleogel-S10 was marked with 'V', while the skin adjacent to the control wound was marked with '-'(Fig. 1).

The study wound was cleaned with octenidine hydrochloride or polyhexanide, before study treatment was administered to the respective wound halves according to randomization. Oleogel-S10 or Octenilin® wound gel were

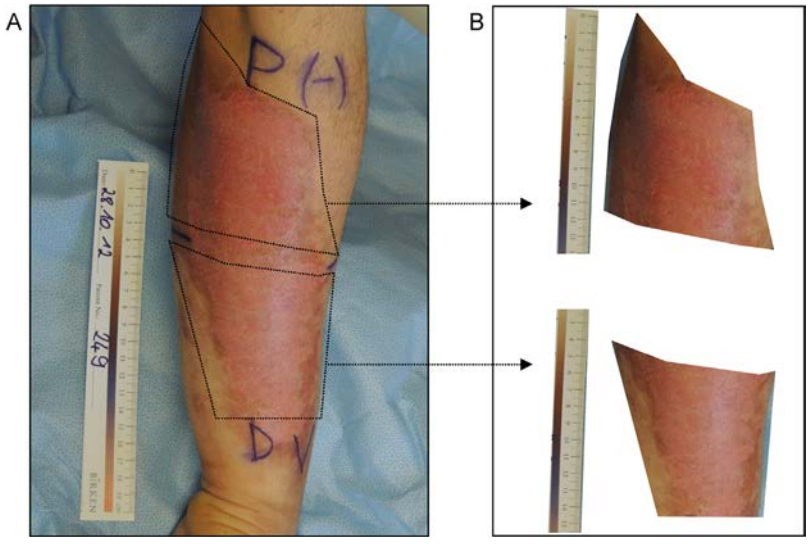

Fig. 1 – (A) Overview photo showing both study wound halves including markings for 'proximal' (P) or 'distal' (D) and 'V' for Oleogel-S10 treatment and '-' for control. (B) Wound halves for blinded read: chronological series of cropped and coded photographs by wound (half). Only photos that were confirmed by a medical expert not involved in efficacy or safety assessments to be free of markings or gel residues were considered for a blinded read.

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applied at a thickness of approximately 1 mm or 0.04 inch and covered with fatty gauze each. The wounds were cleaned, study treatments were administered, and dressings were changed at least every second day to avoid trauma to the new epithelium. Oleogel-S10 and Octenilin® wound gel were applied at every dressing change until full wound closure of both wound halves was observed by the investigator. For wounds not healed at Day 21, the investigator decided whether the treatment was continued, discontinued or changed.

2.5. Outcomes

2.5.1. Efficacy endpoints

The primary efficacy endpoint was the percentage of patients with earlier healing (≥95% epithelialization) of the wound half treated with Oleogel-S10 compared to Octenilin® wound gel as evaluated by the majority decision of 3 blinded experienced surgeons.

Secondary efficacy endpoints comprised sensitivity analyses of the primary efficacy endpoint, including separate results by each blinded evaluator. In addition, the time to wound closure and the intra-individual difference in time to wound closure between wound halves treated either with Oleogel-S10 or with Octenilin® wound gel was analyzed. The percentages of patients with wound healing and the percentages of wound epithelialization at different points in time were both investigated. Finally, the assessment of efficacy by investigators and patients was evaluated.

Endpoints for the follow-up period after 3 and 12 months were the cosmetic outcome in relation to texture, redness, growth of hair, and pigmentation based on blinded photo evaluation and observer, patient as well as total POSAS scores.

2.5.2. Evaluator-blinded assessments

At each wound dressing change after cleaning of the wound halves photos were taken using a Nikon COOLPIX P510 (Nikon Corporation, Tokyo, Japan) at fixed settings. Chronological photo series were assembled for observer-blinded analysis of wound healing progression. The markings for "proximal" (P) or 'distal' (D) and 'V' for Oleogel-S10 treatment and '-' for control were cropped from the photographs (see Fig. 1). Cropped and coded photographs were assembled to chronological series by wound half without providing data on day of treatment. A medical expert neither involved in safety nor in efficacy assessments checked whether the photo series lacked markings and gel residues that would have been indicative of Oleogel-S10 treatment. Eligible, paired photo series by patient were randomly presented on a web-based electronic read tool to 3 independent, experienced surgeons who were blind to treatment. If the readers considered the photo series evaluable, they assessed which wound half healed faster and reached wound closure first (≥95% epithelialization) or whether wound closure was not observed. In case wound closure was not observed, the exact day of wound closure was not known, only that it occurred after the day of the last evaluable photo. It was assumed that the wound closed 1 day after the point in time the last photo was taken. This "Day+1 approach" minimized the effect size between treatments and therefore was conservative. If there was no majority decision for a patient among the 3 blinded reviewers, the corresponding photo series was labelled 'undecided'. Similarly, if at least 2 readers considered the photo series not evaluable, it was labelled 'undecided'. Primary and several secondary efficacy endpoint analyses were based on blinded photo evaluation.

Cosmetic outcome, such as texture, hair growth, pigmentation, and redness of the skin was evaluated for the similarity to the surrounding healthy skin based on blinded photos acquired at 3- and 12-months follow-up visits.

2.5.3. Investigator direct assessments

At each wound dressing change, the investigator estimated the percentage of reepithelialization in percent of the initial wound half size. Patients and investigators both were asked to assess the efficacy of treatment based on a 5-point Likert scale at Day 7±1, Day 14±1, Day 21±1, and at EoT. At 3- and 12-months follow-up, investigators and patients assessed the appearance of the skin in both former wound halves based on the 'Patient and Observer Scar Assessment Scale' (POSAS) [20].

2.5.4. Safety and tolerability

Safety endpoints consisted of the incidence, severity, and relatedness of AEs. At each wound dressing change, the investigator assessed adverse events (AEs). AEs and serious adverse events (SAEs) were reported according to ICH GCP guidelines and were coded using the Medical Dictionary for Regulatory Authorities (MedDRA), Version 15.1. The investigators assessed causality to treatment either as 'unrelated' or as 'possibly', 'probably', and 'definitely' related to treatment, respectively. The severity of (S)AEs was rated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

The betulin serum concentration and the microbial colonization of both wound halves at Day 7±1, Day 14±1, and Day 21±1 were further safety endpoints. Serum samples were analyzed at a central laboratory for betulin concentration. Wound swabs were analyzed by the local laboratories and the investigator assessed the microbial colonisation results on whether there was a clinically significant difference between wound halves.

Finally, tolerability was assessed by investigators and patients on a 5-point Likert scale at Day 7±1, Day 14±1, Day 21±1, and at EoT.

2.6. Sample size estimate

The sample size was calculated using nQuery 7.0 (Statistical Solutions, Boston MA, USA) based on the assumption that wound halves treated with Oleogel-S10 healed earlier in a proportion of 0.715 of patients, an assumption estimated upon the results of an earlier clinical study in STSG donor sites [19]. The sample size was calculated to be N=45 with a power of 80% to reject the null-hypothesis of $s_0 \leq 0.5$. A total of N=60 patients was planned to be enrolled to account for the assumption that no difference in wound healing would be observed in 25% of patients.

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2.7. Randomisation

Within each patient, two comparable wound halves were defined (see Interventions above). A photo upload to the IWRS triggered assignment of one of the wound halves to verum treatment (Oleogel-S10) and the other wound half to standard of care control treatment. Randomisation by the IWRS was central, non-dynamic, using fixed blocks (block-size=4) and was stratified by sites.

2.8. Blinding

Treatment assignment was open to investigators and patients. Some assessments for secondary endpoints were performed as direct investigator assessments (see above).

Blinded evaluation of wound photographs was used for the assessment of the primary endpoint as well as several secondary endpoints (see Evaluator-blinded assessments above).

2.9. Statistical analysis

The statistical analyses were conducted using SAS® 9.3 (SAS Institute Inc., Cary NC, USA) based on the intent-to-treat analysis set that included all patients who were treated at least once with Oleogel-S10 or Octenilin® wound gel according to randomization.

The primary, confirmatory analysis tested the hypotheses H_0: $s_0 \leq 0.5$ versus H_1: $s_0 > 0.5$ with s_0 being the rate of superiority of Oleogel-S10 amongst decided cases using a 1-sided, exact binomial test with a significance level of $\alpha = 0.025$. SAS® procedure 'PROC FREQ' was applied specifying the statistic option 'BINOMIAL' in the 'EXACT' statement. Hence, Oleogel-S10 was considered significantly better than Octenilin® wound gel if the 1-sided p-value was ≤ 0.025 and the proportion of patients with earlier healing of the wound half treated with Oleogel-S10 was >0.5.

Sensitivity analyses consisted of the primary, confirmatory analyses in the per-protocol analysis set (intent-to-treat analysis set without any major protocol deviations), completer analysis set (intent-to-treat analysis set that completed the study), safety analysis set (all patients who were treated at least once, as treated), and as-randomized analysis set (all patients who were treated at least once and treated as randomized). Exact, 2-sided 95% Confidence Intervals (CI) were calculated. The 1-sided, non-parametric Sign test with $\alpha = 0.025$ tested whether the median intra-individual difference in time to wound closure between wound halves was ≥ 0 versus the alternative of <0, which meant an earlier healing of the wound half treated with Oleogel-S10. Oleogel-S10 was considered significantly better compared with Octenilin® wound gel if the 1-sided p-value was ≤ 0.025 and the test statistic 'M' was <0.

Time to wound closure per treatment was analyzed descriptively including 95% CI for the mean using t-test statistic. Kaplan–Meier estimates and the median 'time-to-event' were calculated using censoring information.

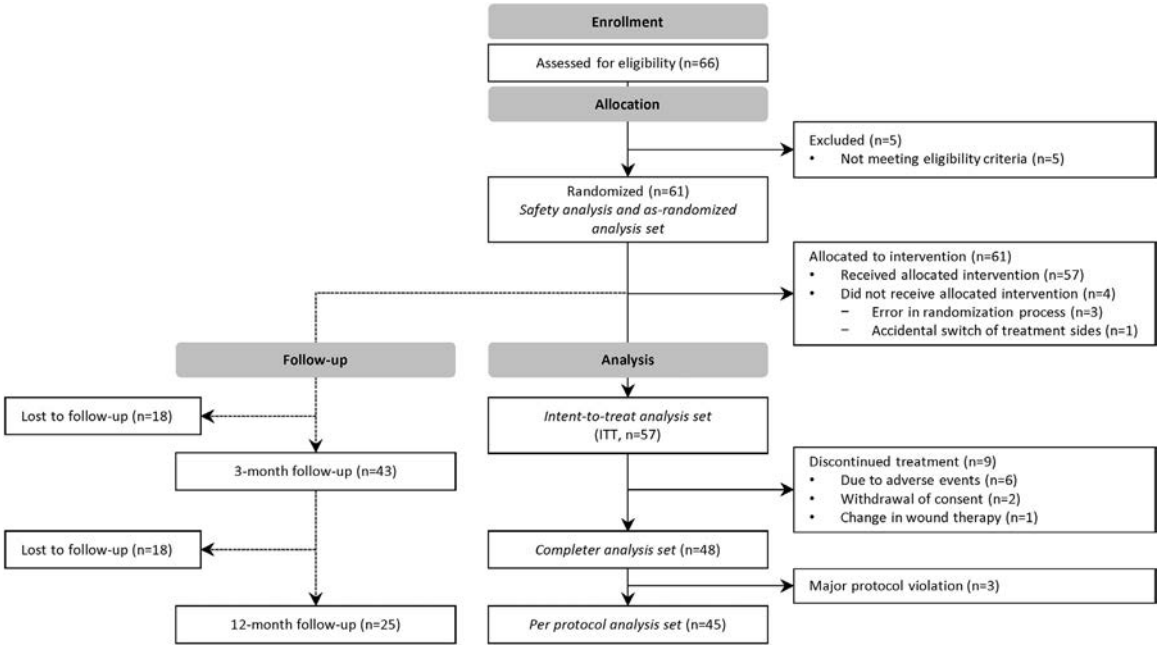

Fig. 2 – Disposition of patients according to CONSORT flow diagram recommendations.
66 patients were assessed for eligibility of whom 5 did not meet all eligibility criteria (wound size 3×, burn within 48 h 2×, birth control 1×, investigator opinion 1×) and were not enrolled into the study. The safety analysis set (SAF) included all 61 patients who were treated at least once with Oleogel-S10 or Octenilin® wound gel. The intent-to-treat (ITT) analysis set included all patients who were treated at least once with Oleogel-S10 or Octenilin® wound gel according to randomization. The completer analysis set was a subset of the ITT set comprising all patients who completed treatment; 6 patients discontinued treatment due to adverse events (see Table 4, footnote f); 2 patients withdrew consent on study day 2 and day 3, respectively; 1 patient discontinued due to a change to a different wound dressing. The per-protocol analysis set was a subset of the completer analysis set including all patients who completed treatment per protocol.

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Table 1 – Baseline characteristics.

Baseline Characteristic	Category	Patients (N=61)	
		n	%
Sex	Male	42	68.9
	Female	19	31.1
Race	Caucasian	51	83.6
	African American	4	6.6
	Asian	5	8.2
	Other	1	1.6
Fitzpatrick	Type I	7	11.5
	Type II	30	49.2
	Type III	13	21.3
	Type IV	5	8.2
	Type V	2	2.3
	Type VI	4	6.6
Cause of burn injury	Flame	24	39.3
	Heat	6	9.8
	Scalding	31	50.8
Severity of burn injury	Grade 2a	55	90.2
	Grades 2a and 2b	3	4.9
	Grades 2a, 2b, and 3	3	4.9
Size of burn injury (% of TBSA)		5.8	5.2
		Median	**Range**
Age	Years	41	18 to 79
		Mean	**SD**
Body mass index	Male	28.2	4.9
	Female	24.4	3.4
Number of study wounds treated	1 coherent wound	54	88.5
	2 comparable, separate wounds	7	11.5
Size of grade 2a study burn wound (cm^2)	1 coherent wound	210.0	140.5
	2 comparable, separate wounds, first wound	133.0	188.9
	2 comparable, separate wounds, second wound	133.0	188.9

N=total number; n=number of a subgroup; SD=standard deviation; TBSA=total body surface area.

Differences in time to wound closure were compared using a 2-sided, paired t-test evaluating the mean difference from 0 at $\alpha=0.05$.

The percentage of patients with wound closure at different points in time was calculated using a last observation carried forward (LOCF) approach if full wound closure was achieved for both wound halves before Day 21 or for wound halves without wound closure.

Baseline characteristics and safety data were analyzed descriptively based on the safety analysis set, i.e. in all patients who were treated at least once, as treated.

3. Results

3.1. *Patients*

Between 31 August 2012 and 17 July 2013, 66 patients were assessed for eligibility and 61 patients were enrolled into the study and randomized for treatment with study medication. Of those, 4 patients did not receive the allocated intervention due to errors in the randomization process (N=3) or accidental switches of treatment sides (N=1). The remaining 57 patients

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constituted the ITT analysis set. Overall, 9 patients discontinued treatment prematurely due to AEs (N=4), for other safety reasons (N=3), or due to withdrawal of consent (N=2). The 'completer analysis set' comprised 48 patients of which 3 patients were excluded because of major protocol violations. During follow-up, 43 patients were seen at 3 months and 25 patients presented at 12 months (Fig. 2).

Most patients were male (n=42, 68.9%), Caucasians (n=51, 83.6%), and had a Fitzpatrick Skin Type II (n=30, 49.2%). The median age was 41 years (range of 18 to 79 years). Burn injuries were most frequently caused by scalding (n=31, 50.8%) or flame (n=24, 39.3%) and were most commonly superficial partial thickness burns (n=55, 90.2%). The total wound size covered 5.8±5.2% of the Total Body Surface Area (TBSA) or was 210.0 cm^2 in size on average and consisted of 1 coherent wound in 88.5% of cases (n=54) (Table 1). Wound dressings were changed every 2.0 days (mean, standard deviation: 0.3 days).

3.2. *Photographs*

For more than half of the patients (38, 67%) one or more photos had to be excluded from the blinded read, in most cases due to gel residues.

3.3. *Efficacy*

3.3.1. *Intra-patient difference in time to wound closure*

Efficacy results are presented for the ITT analysis set (N=57). Observer-blinded assessment revealed a difference in wound healing in 35 of 57 patients. Thepercentage of patients with earlier healing of the wound half treated with Oleogel-S10 (85.7%, n=30) was significantly higher compared to the percentage of patients with earlier healing of the wound half treated with Octenilin® wound gel (14.3%, n=5, $p<0.0001$, 1-sided exact binomial test) (Table 2,Fig. 3). Sensitivity analyses confirmed the superiority of Oleogel-S10. The percentages of patients with earlier healing of the wound half treated with Oleogel-S10 were significantly higher than 50% in the per-protocol and completer analysis sets ($p<0.0001$, 1-sided exact binomial test). Stratified analyses by assessor ($p\leq0.015$, 2-sided exact binomial test), gender ($p<0.02$, 1-sided exact binomial test) or center ($p<0.02$, 1-sided exact binomial test) supported the evidence for the superiority of Oleogel-S10.

The mean intra-individual difference in time to wound closure between wound halves either treated with Oleogel-S10 or with Octenilin® wound gel was −1.0 day (−1.4, −0.6; 95% CI, $p<0.0001$, 2-sided paired t-test) (Table 2).

The percentages of wound epithelialization were significantly higher in wound halves treated with Oleogel-S10 compared with Octenilin® wound gel at all points in time as

Table 2 – Observer-blinded assessment of wound closure.

Blinded expert assessment	N=57, n (%)	P-value
Wound halves with a difference	35	
- Earlier healing of Octenilin®-treated wound half	5 (14.3)	<0.0001[a]
- Earlier healing of Oleogel-S10-treated wound half	30 (85.7)	
No difference observed, thereof	22	
- Missing data (only Day 0 photo available)	7	
- Wound healing not observed (both wound halves)	7	
- Wound healing observed in the same photo	8	
	Mean (95% CI)	
Days to wound closure		
- Oleogel-S10	7.6 (6.5, 8.6)	
- Octenilin® wound gel	8.8 (7.6, 10.0)	
- Difference	−1.0 (−1.4, −0.6)	<0.0001[b]

Intent-to-treat analysis set; CI=confidence interval; N=total number; n=number of a subgroup.
[a] One-sided exact binomial test at a significance level of 0.05 for the superiority of Oleogel-S10.
[b] Two-sided paired t-test evaluating the mean difference as different from 0.

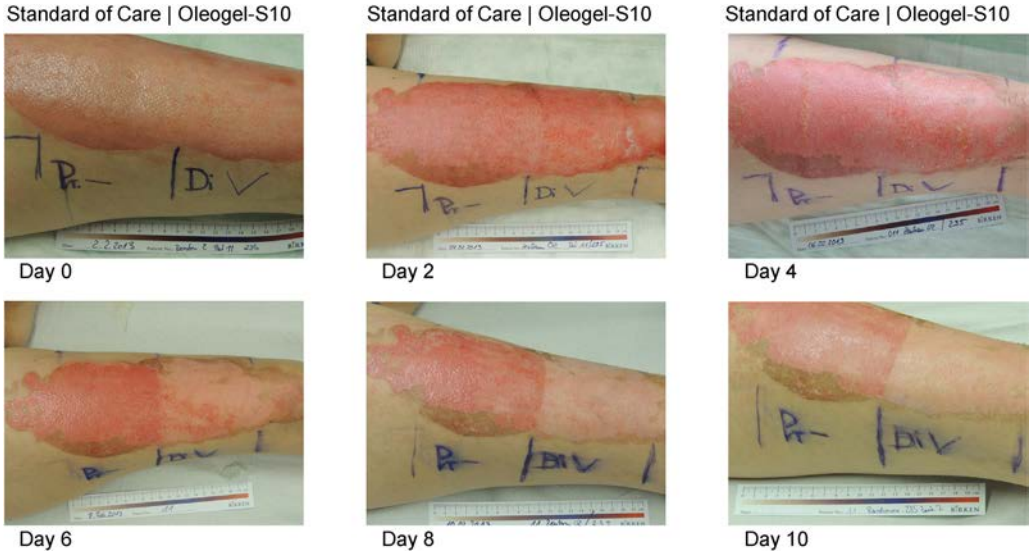

Fig. 3 – Patient example of the healing progression over time, photo-documented at every wound dressing change in 2-day intervals. Note the difference in inflammation (redness) between treatments.

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assessed by the investigators (Fig. 4). The difference in epithelialization was highest at Day 6, when the percentage of wound epithelialization was 78.9% in Oleogel-S10-treated wound halves and 60.9% in Octenilin®-treated wound halves (−18.0%, $p<0.0001$, paired t-test).

Investigators and patients evaluated the efficacy of Oleogel-S10 to be 'better' or 'much better' for 73.7% and 71.9% of patients, respectively; the opposite was reported with 1.8% by investigators and 0.0% by patients (Fig. 5).

3.3.2. *3-month follow-up*

In all categories of cosmetic outcome at 3 months, 'both former wound halves' were rated most frequently to be similar in appearance to the healthy surrounding skin except for pigmentation that was most commonly 'more similar to healthy skin in the Oleogel-S10 treated half' (Table 3, Fig. 6).

The total scores of both the observer and the patient scale of the POSAS range from 6 to 60 with lower values indicating towards normal skin. The investigator, patient, and total POSAS score assessments at Month 3 consistently showed outcomes that were more favourable for Oleogel-S10 compared with Octenilin® wound gel (Table 3).

3.3.3. *12-month follow-up*

At 12 months after injury, both wound halves appeared equal to the blinded photo-evaluators for most patients, although Oleogel-S10 was still superior to Octenilin® wound gel for some patients concerning the cosmetic outcomes texture (16.7%), pigmentation (20.8%) and redness (12.5%) (Table 3). Similarly, the POSAS showed a difference between treatments, though the scores where lower compared to the 3-month time point and the difference between treatments also decreased (Table 3).

3.4. *Safety and tolerability*

Safety results are presented for the safety analysis set of N=61 patients who received at least one dose of study medication. Twenty patients (32.8%) reported 29 AEs during the study, most of them were mild to moderate in severity (n=20, 68.9%). Seven AEs in 6 patients were evaluated as being severe (CTCAE Grade 3) and most commonly comprised aggravations of the condition or wound infections (Table 4). In 7 AEs being reported for 6 patients, the relationship to treatment with study medication could not be ruled out; these included wound inflammation, wound complication, pruritic rash, pain of the skin, wound necrosis and purpura.

Adverse events judged by the investigator to be application site reactions were reported by wound half (Oleogel-S10 or Octenilin® wound gel) or labelled with the term 'general' if both wound halves were affected or if a precise identification was not possible (Table 5). Overall, 17 mainly 'general' application site reactions in 14 patients were reported. In 5 patients, application site reactions were assessed as at least 'possibly' being related to study medication.

Investigators and patients evaluated the tolerability of Oleogel-S10 to be 'better' or 'much better' than that of Octenilin® wound gel for 65.6% of all patients; the opposite was reported with 0.0% by investigators and 1.6% by patients (Fig. 5).

Notably, no difference in microbial colonization between wound halves was observed (16 of 18 patients assessed on Day 7), although Octenilin® wound gel contains octenidine hydrochloride, an antiseptic that is active against Gram-positive and Gram-negative bacteria.

The potential absorption of betulin into the blood was assessed in plasma samples taken during the study. The lower limit of quantification for the betulin assay was 1 ng/mL. Out of

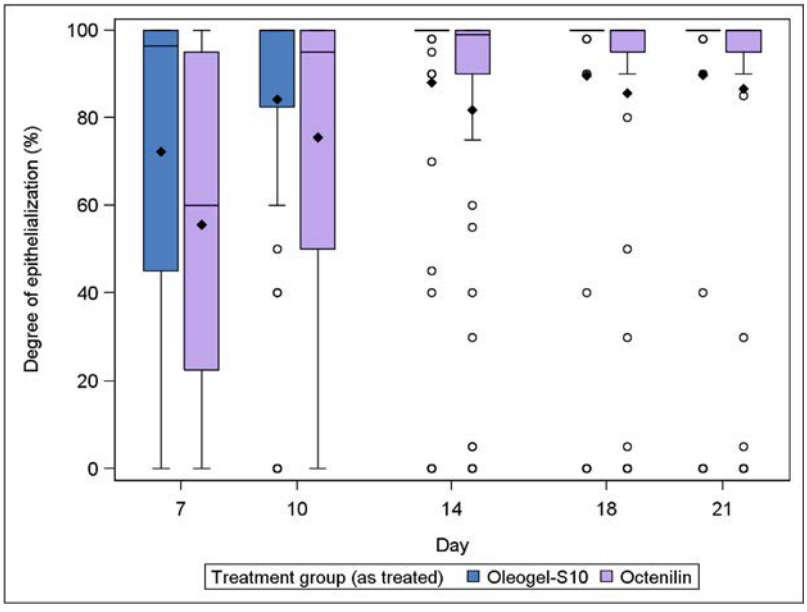

Fig. 4 – Kaplan–Meier analysis for the median time to wound closure (days) of wound halves treated with Oleogel-S10 versus Octenilin® wound gel in the ITT analysis set (N=57 excluding n=7 undecided cases, i.e., no difference between treatments, photo series not evaluable, or majority decision could not be reached) based on the blinded experienced surgeon assessment.

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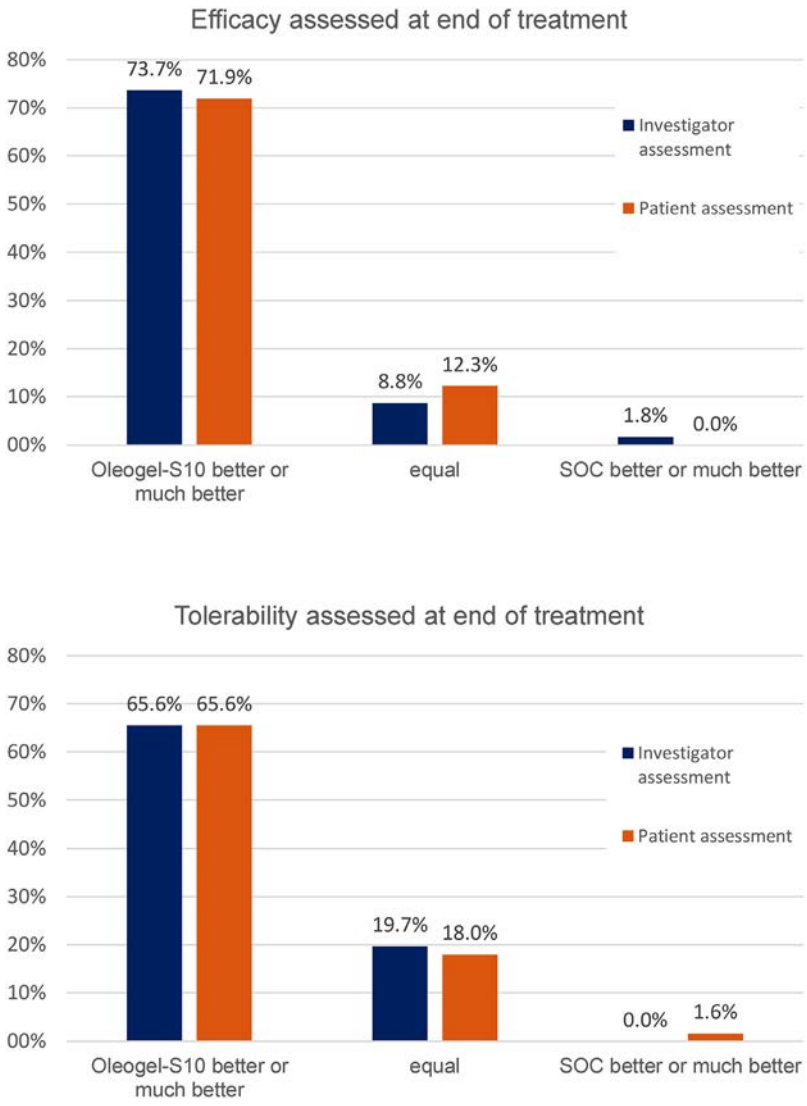

Fig. 5 – At the end of treatment, investigators and patients were asked to assess efficacy and tolerability of both treatments based on a 5-point Likert scale ('Oleogel-S10 much better', 'Oleogel-S10 better', 'No difference', 'Octenilin® wound gel better', 'Octenilin® wound gel much better'). Results of the efficacy assessment comprise the ITT analysis set (N=57, n=9 missing data), data for the tolerability assessment derive from the safety analysis set (N=61, n=9 missing data).

the 139 plasma samples taken only 17 (13.9%) had quantifiable betulin concentrations: 10 samples taken before the first dose of Oleogel-S10 was applied and 7 samples during the treatment period. The betulin concentrations from the pre-dose samples ranged from 1.1 to 7.6 ng/mL; and the betulin concentrations from samples collected during treatment ranged from 1.4 to 6.6 ng/mL.

4. Discussion

4.1. *Summary*

In this study, we provide evidence that Oleogel-S10 accelerates the healing of superficial partial thickness burns compared with standard of care defined as octenidine hydrochloride gel (Octenilin® wound gel). We found that in patients with a difference in wound healing the percentage of patients with earlier healing of the wound half treated with Oleogel-S10 (85.7%) was significantly higher compared to the percentage of patients with earlier healing of the wound half treated with Octenilin® wound gel (14.3%). Oleogel-S10 accelerated wound healing by 1.0 day on average based on a conservative approach of wound photography assessments by blinded experienced surgeons. In our study, Oleogel-S10 was shown to be safe and well tolerated.

4.2. *Robustness of evidence*

This study was randomized to avoid bias, was based on intra-individual comparison to reduce confounding factors, and was controlled by a standard of care comparator. Wound closure

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Table 3 – Long-term outcome and scarring.

Category	Assessment	3-Months follow-up (N=37)			12-Months follow-up (N=24)		
		n	(%)	95% CI (%)	n	(%)	95% CI (%)
Texture	Oleogel-S10 half most similar to healthy skin	11	(29.7)	15.9, 47.0	4	(16.7)	4.7, 37.4
	Octenilin® half most similar to healthy skin	1	(2.7)	0.1, 14.2	–	–	–
	Both sides equal	15	(40.5)	24.8, 57.9	18	(75.0)	53.3, 90.2
	No majority decision	6	(16.2)	6.2, 32.0	1	(4.2)	0.1, 21.1
	Not evaluable	4	(10.8)	3.0, 25.4	1	(4.2)	0.1, 21.1
Hair growth	Oleogel-S10 half most similar to healthy skin	–	–	–	–	–	–
	Octenilin® half most similar to healthy skin	–	–	–	–	–	–
	Both sides equal	33	(89.2)	74.6, 97.0	23	(95.8)	78.9, 99.9
	No majority decision	–	–	–	–	–	–
	Not evaluable	4	(10.8)	3.0, 25.4	1	(4.2)	0.1, 21.1
Pigmentation	Oleogel-S10 half most similar to healthy skin	14	(37.8)	22.5, 55.2	5	(20.8)	7.1, 42.2
	Octenilin® half most similar to healthy skin	–	–	–	–	–	–
	Both sides equal	13	(35.1)	20.2, 52.5	17	(70.8)	48.9, 87.4
	No majority decision	6	(16.2)	6.2, 32.0	1	(4.2)	0.1, 21.1
	Not evaluable	4	(10.8)	3.0, 25.4	1	(4.2)	0.1, 21.1
Redness	Oleogel-S10 half most similar to healthy skin	9	(24.3)	11.8, 41.2	3	(12.5)	2.7, 32.4
	Octenilin® half most similar to healthy skin	1	(2.7)	0.1, 14.2	–	–	–
	Both sides equal	16	(43.2)	27.1, 60.5	19	(79.2)	57.8, 92.9
	No majority decision	7	(18.9)	8.0, 35.2	1	(4.2)	0.1, 21.1
	Not evaluable	4	(10.8)	3.0, 25.4	1	(4.2)	0.1, 21.1

		3-Months follow-up (N=40)		12-Months follow-up (N=24)	
		Median	Range	Median	Range
POSAS	Investigator assessment				
	Oleogel-S10	9	6.0, 40.0	7	6.0, 28.0
	Octenilin®	14	7.0, 46.0	7	6.0, 47.0
	Patient assessment				
	Oleogel-S10	10	6.0, 32.0	7.5	6.0, 26.0
	Octenilin®	13	6.0, 51.0	8	6.0, 30.0
	Total score				
	Oleogel-S10	19	12.0, 67.0	14	12.0, 38.0
	Octenilin®	30	13.0, 97.0	16	12.0, 64.0

CI=confidence interval; N=number of patients in the analysis set; n=number of patients in the subgroup; POSAS=patient and observer scar assessment scale.

was assessed complementary by both blinded experienced surgeons and the investigators who treated the patients.

The analyses of the primary and most secondary efficacy endpoint data were based on the majority decision of 3 blinded, experienced surgeons. Blinded photographic analysis of wound closure was demonstrated to be a reliable method correlating satisfactorily with clinical judgment. The intra- and interrater variability of the rater panel that assessed efficacy data of this study was examined for 2 other randomized controlled clinical studies. The results demonstrated that the mean intraclass correlation coefficient was excellent (r=0.79), the interrater correlation coefficient was good (r=0.67), and the agreement between remote visual assessment and clinical assessment at the time of healing was good (r=0.64) [21]. Intra- and interrater reliability was confirmed for the assessment of epithelialization based on photography of split-thickness skin grafts in burn wounds [22,23] and other indications [24].

The validity and reliability of observer-blinded photography assessment was complemented by a conservative approach of statistical analysis. In case wound closure was not observed, it was assumed that the wound closed 1 day after the point in time the last photo was taken. This 'Day+1 approach' minimized the effect size between treatments and was conservative assuming that healing with Oleogel-S10 was faster than that with Octenilin® wound gel. Hence, differences in wound closure times underestimated the real difference.

Some photos had to be excluded from efficacy analysis due to gel residues, which would have been indicative for Oleogel-S10 treatment. Further, photo series were labelled 'undecided' if there was no majority decision by patient or if >2 readers considered the photo series not evaluable. Despite these limitations, Oleogel-S10 was superior to Octenilin® wound gel as confirmed by several sensitivity analyses in different analysis sets and stratified by assessor, gender, or center.

The superiority of Oleogel-S10 was even more pronounced based on the clinical judgment of the investigators that observed significantly higher percentages of epithelialization in Oleogel-S10 treated wound halves at all points in time.

Long-term follow-up revealed Oleogel-S10 to be superior to Octenilin® wound gel concerning the cosmetic outcomes 'texture', 'pigmentation', and 'redness of the skin'. Consistently lower observer, patient, and total POSAS scores at Month 3 and Month 12 confirmed this data for Oleogel-S10. Notably, the effect size decreased towards Month 12. It remains to be

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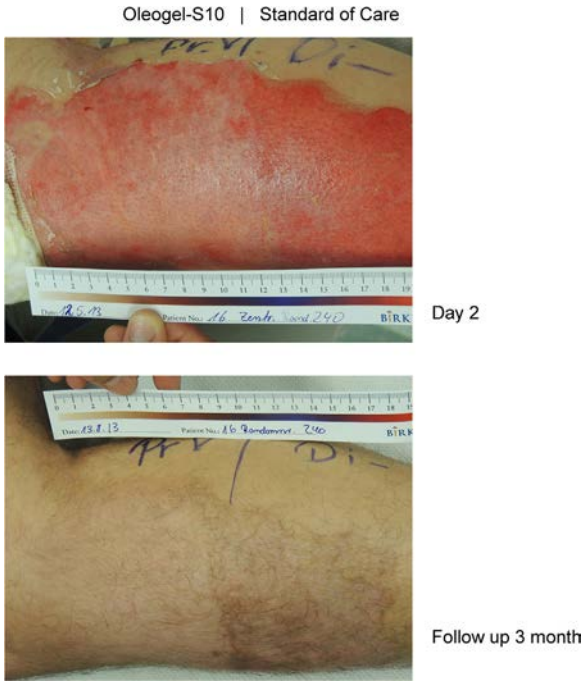

Fig. 6 – Patient example of the difference in inflammation (redness) and pigmentation in the long-term follow-up.

tested whether prolonged treatment with Oleogel-S10 after wound closure would further improve the long-term outcome of scars. Alternatively, the improved long-term outcome may be secondary to earlier wound closure, as faster healing is thought to be associated with improved long-term skin appearance.

It has been a long-standing dogma in burn medicine that partial thickness burns that do not heal within 21 days should be surgically covered with STSGs to avoid hypertrophic scarring. This underlines the importance of treatments that accelerate the endogenous healing of partial thickness wounds, in particular if they require more than a week to reepithelialise. For such patients acceleration of healing promises to reduce the need for surgical intervention. Thus even a modest acceleration of healing is of significant medical relevance.

The risk of wound healing complications is similarly related to the duration of the healing process — earlier healing reduces the risk for complications. The observed lower number of wound complications in the Oleogel-S10-treated wound halves in the present study supports this notion and underlines the relevance of therapies that speed up wound healing.

4.3. *Relation to other relevant studies and treatment options*

The goal in treatment of superficial partial thickness burns is wound healing without complications, in particular to avoid infections, to reduce the pain associated with these wounds, and to achieve a good long-term outcome in skin appearance. No defined standard of care exists, though all wound treatments should provide a moist wound healing environment [8] and antimicrobial treatments are widely used to clean wounds, namely polyhexanide and octenidine [10,11,25]. Infection prevention is considered so important that even SSD creams are still in use despite knowledge that SSD slows down wound healing [7,26].

Time of healing, more specific the time to wound closure, varies with severity of the injury and constitution of the patient. Predominant factor however is the depth of the wound and how many dermal structures remain present which offer a reservoir of basal keratinocytes that can regenerate the epidermis and close a superficial partial thickness wound. The observed mean time to wound closure of approximately 8 days in the present study is typical for a superficial partial thickness burn. A mean acceleration of time to wound closure by 1.0 days may appear modest, however, it represents a remarkable result in light of the chosen comparator octenidine hydrogel. Most often found as comparator in clinical studies is SSD for historical reasons — this has well established that SSD slows down wound healing by a couple of days [7,26], rendering it a poor comparator for studies investigating speed of wound healing.

In the setting of this study the wound dressings have been changed every two days, yet in parallel studies in STSG donor sites longer intervals (every 3–4 days) were successfully used [29]. Thus it is likely that the regular wound dressing interval of a wound dressing does not need to be adjusted in standard practice if Oleogel-S10 is added to the treatment.

4.4. *Safety and tolerability*

Our results indicate that Oleogel-S10 is safe and well tolerated. Few treatment-related AEs occurred that were mild to moderate in severity and disease-inherent. All SAEs were considered unrelated to treatment except for 1 case of wound necrosis CTCAE Grade 2 in the Oleogel-S10 treated wound half for which relationship to study treatment was assessed as 'unknown'. A

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Table 4 – Overview of adverse events.

Category	Preferred term (MedDRA)	Patients		Events	
		n	(%)[a]	n	(%)[b]
Total AEs		20	32.8	29	100.0
- AEs of CTCAE Grade 1		9	14.8	13	44.8
- AEs of CTCAE Grade 2		7	11.5	7	24.1
- AEs of CTCAE Grade 3		6	9.8	7	24.1
	Aggravated condition	2	3.3	2	6.9
	Pyrexia	1	1.6	1	3.4
	Soft tissue infection	1	1.6	1	3.4
	Urinary tract infection	1	1.6	1	3.4
	Wound infection	2	3.3	2	6.9
- Related AEs		6	9.8	7	24.1
	Wound inflammation[c]	1	1.6	1	3.4
	Wound complication[c]	1	1.6	1	3.4
	Wound necrosis[d]	1	1.6	1	3.4
	Pain of skin[e]	2	3.3	2	6.9
	Purpura[d]	1	1.6	1	3.4
	Pruritic rash[c]	1	1.6	1	3.4
- AEs leading to discontinuation[f]		6	9.8	6	20.7
- Application site reactions		14	23.0	17	58.6
SAEs[g]		8	13.1	8	27.6
- Related SAEs	Wound necrosis[d]	1	1.6	1	3.4

AE=adverse event; CTCAE=common terminology criteria of adverse events classification; MedDRA=medical dictionary for regulatory activities; N=total number; n=number of subgroup; SAE=serious adverse event.

[a] Percentages are based on total number of patients in the safety analysis set (N=61).

[b] Percentages are based on total number of events in the safety analysis set (N=29).

[c] Possible relationship.

[d] Unknown relationship.

[e] Probable relationship.

[f] 5 of the 6 AEs leading to premature discontinuation of treatment were SAEs, namely 'wound necrosis', 'soft tissue infection', 'wound infection', 'aggravated condition', and 'tonsil cancer'. Another AE was the 'pruritic rash' CTCAE Grade 1 that was assessed as 'possibly' being related to study medication. 5 of these 6 AEs resolved except for 'tonsil cancer'.

[g] 8 SAEs included 2 aggravated conditions, 2 wound infections, 1 case each of soft tissue infection, pyrexia, and tonsil cancer that were all considered unrelated to treatment. In 1 SAE of wound necrosis, the relationship to study treatment was 'unknown'.

further application site reaction in the wound half treated with Oleogel-S10 was a pruritic rash CTCAE Grade 1 that was observed 12 days after wound closure. For the majority of patients (65.6%), investigators and patients evaluated the tolerability of Oleogel-S10 to be 'better' or 'much better' compared with Octenilin® wound gel. Since there was no difference in microbial colonization between wound halves, Oleogel-S10 was comparable to the antiseptic Octenilin® wound gel containing octenidine hydrochloride that is active against Gram-positive and Gram-negative bacteria.

Although the superficial partial thickness burns in this study had a mean size of 210.0 cm^2 (1 coherent wound) or 133.0 cm^2 (2 comparable, separate wounds) and were treated for 10.4 days on average, the systemic availability of betulin was negligible. Betulin occurs naturally in foods, for example in olives [27] and lingonberries [28]. The low baseline concentrations probably derived from betulin-containing food consumption and the application of Oleogel-S10 to superficial partial thickness burns did not result in plasma betulin levels that were higher than diet-induced levels.

Further investigations may distinguish whether the lower number of wound complications and the improved long-term outcome in particular with regards to skin pigmentation are solely a secondary effect of faster wound healing or whether pharmacologic effects of birch bark extract contribute to these treatment benefits of Oleogel-S10. With regard to wound infections, it is important to note that the hydrophobic triterpenes of the birch bark extract are no antiseptics. On the other hand, the oleogel formulation may act as physical barrier to protect the wound from external infections. The total number of wound infections observed in this study was too low to draw far-reaching conclusions, nevertheless the lower number of infected wounds under Oleogel-S10 treatment compared to the standard of care antiseptic octenidine hydrogel suggests that Oleogel-S10 may have some ability to prevent wound infections.

4.5. *Limitations of the study*

Superficial partial thickness burns treated in the present study represent very common, but also relatively easy to treat burn

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Table 5 – Application site reactions.

System organ class Preferred term (MedDRA)	n	(%)[a]	n (%) Application site[b] (Relationship to study medication)		
			Octenilin®	Oleogel-S10	General
Any	14	(23.0)	5 (8.2)	2 (3.3)	9 (14.8)
General disorders and administration site conditions	2	(3.3)			
- Condition aggravated	2	(3.3)	–	–	2 (No)
Infections and infestations	4	(6.6)			
- Soft tissue infection	1	(1.6)	1 (No)	–	–
- Wound infection	3	(4.9)	–	–	3 (No)
Injury, poisoning and procedural complications	4	(6.6)			
- Inflammation of wound	1	(1.6)	1 (Possible)	–	–
- Wound complication	2	(3.3)	1 (No)	–	1 (Possible)
- Wound necrosis	1	(1.6)	–	1 (Unknown)	–
	5	(8.2)			
Skin and subcutaneous tissue disorders					
- Pain of skin	3	(4.9)	1 (No) 1 (Probable)	–	1 (Probable)
- Pruritus	1	(1.6)	–	–	1 (No)
- Purpura	1	(1.6)	–	–	1 (Unknown)
- Rash pruritic	1	(1.6)	–	1 (Possible)	–

n=number of patients with the respective AE; MedDRA=medical dictionary for regulatory activities.
[a] Percentages are based on the total number of patients in the safety analysis set (N=61).
[b] Application site: Octenilin® wound gel, Oleogel-S10, or general — location cannot be further differentiated.

wounds. Further studies are necessary to understand whether more severe partial thickness burns benefit from Oleogel-S10 therapy too, in particular deep partial thickness burns that a burn surgeon nevertheless decides to treat conservatively.

5. Conclusion

In conclusion, our results indicate that Oleogel-S10 is superior to Octenilin® wound gel in the treatment of superficial partial thickness burn wounds. This data suggest that Oleogel-S10 might improve the outcome of superficial partial thickness burn wounds due to the acceleration of wound healing, as shorter healing-times correlate with better outcomes in burn patients.

While many products are in use to treat superficial partial thickness burns, no defined standard of care exists. This may be a reflection of a generally low level of evidence that would allow to single out individual products over others and to establish a standard. The present study was part of a larger development program that included also clinical studies in STSG donor site wounds for a combined number of more than 300 patients. This comparatively broad evidence led 2016 to the approval of Oleogel-S10 in 2016 under the tradename Episalvan as a new medicine by the European Commission, the first in the indication 'treatment of partial thickness wounds'.

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Conflicts of interest

HOR reports personal fees from Birken AG/Amryt Pharma and personal fees from Moelnlycke Healthcare unrelated to the submitted work; TZ is a former employee of Birken AG, member

of the supervisory board of Amryt AG and owns shares in Amryt Pharma; BH reports personal fees from Birken AG.

Appendix A. BBW-11 Study Group

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