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Accelerated re-epithelialization of partial-thickness skin wounds by a topical betulin gel: Results of a randomized phase III clinical trials program

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ABSTRACT

The clinical significance of timely re-epithelialization is obvious in burn care, since delayedwound closure is enhancing the risk of wound site infection and extensive scarring. Topical treatments that accelerate wound healing are urgently needed to reduce these sequelae. Evidence from preliminary studies suggests that betulin can accelerate the healing of different types of wounds, including second degree burns and split-thickness skin graft wounds.

The goal of this combined study program consisting of two randomized phase III clinical trials in parallel is to evaluate whether a topical betulin gel (TBG) is accelerating re-epithelialization of split-thickness skin graft (STSG) donor site wounds compared to standard of care.

Two parallel blindly evaluated, randomised, controlled, multicentre phase III clinical trialswere performed in adults undergoing STSG surgery (EudraCT nos. 2012-003390-26 and 2012-000777-23). Donor site wounds were split into two equal halves and randomized 1:1 to standard of care (a non-adhesive moist wound dressing) or standard of care plus TBG consisting of 10% birch bark extract and 90% sunflower oil (Episalvan, Birken AG, Niefern-Oeschelbronn, Germany). The primary efficacy assessment was the intra-individual difference in time to wound closure assessed from digital photographs by three blinded experts.

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A total of 219 patients were included and treated in the two trials. Wounds closed faster with TBG than without it (15.3 vs. 16.5 days; mean intra-individual difference = −1.1 days [95% CI, −1.5 to −0.7]; $p < 0.0001$).
This agreed with unblinded direct clinical assessment (difference = −2.1 days [95% CI, −2.7 to −1.5]; $p < 0.0001$). Adverse events possibly related to treatment were mild or moderate and mostly at the application site.
TBG accelerates re-epithelialization of partial thickness wounds compared to the current standard of care, providing a well-tolerated contribution to burn care in practice.

1. Introduction

Cutaneous wound healing is a complex biological process leading to re-establishment of the epidermal barrier. The clinical significance of timely wound closure is obvious in extensive wounds like burns, when delayed healing can lead to infection of the wound site and scarring. Topical treatments that accelerate wound healing are urgently needed to reduce these sequelae.

Growth factors, stem cells, nanoparticles, platelet-rich plasma, cold atmospheric pressure physical plasma [1] and many other topical treatments have been investigated [2–5], but none have proven effective in clinical trials and no treatment or pharmaceutical is currently available to accelerate the secondary closure of open superficial surgical sites or other partial-thickness wounds. Therefore, the current standard of care for open superficial surgical sites remains a moisture-regulating dressing, which promotes re-epithelialization by preventing desiccation [6,7].

Betulin is a pentacyclic triterpene found in the outer bark of white barked birches (*Betula*) [8]. Betulin has been reported to promote healing in a porcine ex vivo wound healing model and to modulate inflammatory mediators and promote keratinocyte differentiation and migration in vitro [9,10]. Evidence from preliminary studies suggests that betulin can improve the healing of different types of skin lesions, including second-degree burns [11] and necrotizing herpes [12]. A proof-of-concept phase II clinical study showed that topical betulin gel (TBG) consisting of 10% birch bark extract and 90% sunflower oil (Episalvan, Birken AG, Niefern-Oeschelbronn, Germany) significantly accelerates re-epithelialization of split-thickness skin graft (STSG) donor sites [13]. This water-free oleogel is thixotropic: when agitated TBG becomes less viscous making it easy to spread, and at rest it thickens again providing a stable occlusive cover [14,15]. Herein, we describe the results of a study program consisting of two related phase III clinical trials including a total of more than 200 patients confirming the clinical effectiveness and safety of TBG in healing of STSG donor site wounds.

2. Methods

2.1. Study design

The program design is consisting of two open, blindly evaluated, prospective, controlled, randomised, multi-centre phase III clinical trials, both using the same protocol. Study BSG-12 (EudraCT no. 2012-003390-26) was performed in Spain (6 centres), Greece (3 centres), Latvia (2 centres), and France (3 centres), and study BSH-12 (EudraCT no. 2012-000777-23) was performed in Germany (8 centres), Czech Republic (2 centres), Poland (1 centre), Finland (1 centre), Austria (2 centres), and Bulgaria (4 centres). The principal objective of the study was to examine the efficacy and tolerability of TBG. The primary efficacy endpoint was the intra-individual difference in time to wound closure (≥95% epithelialization) between two equal halves of STSG donor site wounds treated with either a standard moist wound dressing alone or a standard moist wound dressing containing TBG. The assessment was based on photo evaluation by a remote panel of three blinded experts. Study protocols were approved by the local or regional ethics committee for each centre (for the leading study centres: Ethic Committee of the Greifswald University Medicine, Greifswald, Germany and Ethic Committee of Vall d'Hebron University Hospital, Barcelona, Spain) and the studies were performed in compliance with International Conference on Harmonisation guidelines for Good Clinical Practice and the principles in the Declaration of Helsinki. All investigators and study team members received training in the study protocol and in the standardized acquisition of photographs. Informed consent was obtained from patients before inclusion in each study.

2.2. Patients

Adults with STSG donor site wounds ≥15 cm^2 and ≥3 cm wide were considered for enrolment. As a routine safety measure all study participants had to be using a highly effective method of birth control. Exclusions included skin disorders that could affect the outcome of the trial; clinically significant hypersensitivity to any of the treatments used in the trial; multiple allergic disorders; or other diseases or conditions that could interfere with the study assessments. Women could not be pregnant or breastfeeding.

2.3. Interventions

Prior to STSG surgery, the donor site was divided into two equal halves. After STSG harvest and marking of the wound halves, an overview photo was taken with a digital camera using the same standard settings at all participating centres. Once the overview photo was uploaded, the two wound halves were randomised 1:1 to TBG (other names: Oleogel-S10, Episalvan) combined with a non-adhesive moist wound dressing as

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standard of care or the wound dressing alone. Dressings were trimmed to the appropriate size for the wound and then cut in half, and after cleaning, TBG was applied approximately 1 mm thick to the appropriate wound half on the wound-facing side of the dressing or directly onto the wound (Fig. 1). Every 3 or 4 days according to protocol or more frequently if medically necessary, the wound dressing was changed, the wound was cleaned, and medication was applied for the appropriate wound half. Treatment continued up to complete closure of both halves of the wound or, if complete closure of both wound halves was not observed, until day 28.

2.4. Assessments

For observer-blinded analysis of wound closure, at each wound dressing change and after cleaning the wound, photos were taken with a Nikon Coolpix P510 camera with fixed settings at all participating centres. For evaluation of long-time outcome, photos were taken 3 and 12 months after treatment. For the unblinded analysis, investigators estimated the degree of epithelialization (% of the original wound half size) for each wound half.

Investigators collected adverse events (AEs) in accordance with International Committee for Harmonisation guidelines for Good Clinical Practice. AEs were encoded using MedDRA version 16.0 (MedDRA MSSO, McLean, VA, USA). Causality as unrelated or as unknown, unlikely, possibly, or probably related to the treatment. AE severity was graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0.

At days 7, 14, and 21 and at the end of treatment, patients and investigators answered questionnaires about the efficacy and tolerability of the two treatments on a 5-point Likert scale (which treatment was more effective/which treatment was better tolerated) [16,17].

2.5. Randomisation and masking

Randomisation was via an interactive web response system. For photo evaluations, observers were blinded by using a web-based electronic blinded read tool.

2.6. Analysis of photos

Markings were cropped from the photo, and photos were checked by investigators not involved in safety or efficacy assessments (Fig. 1). Only photos confirmed to be free of markings were considered for a blinded read of efficacy and tolerability. Eligible photographs were independently evaluated by three wound experts (experienced surgeons or dermatologists) via a web-based electronic blinded read tool. All available photos from one wound half comprising a photo series were presented to each blinded expert without information about the treatment, and the order of series was randomised. Within each series, photos were presented in chronological order but with no information on the specific treatment day at which each photo was taken. For photo series that the reader considered evaluable, readers assessed which series was the first to show wound closure (epithelialization of $\geq$95% of the wound half) or whether wound closure could not be detected in any of the photos. When wound closure was not observed, it was assumed to have closed 1 day after the last observation. Long-term outcomes were estimated using the same method and included determination of which wound half was most similar to surrounding healthy tissue in terms of texture, hair growth, pigmentation, and redness.

2.7. Sample size

Each study planned to enrol 105 subjects to reach a total of more than 200 patients for the TBG safety database. This was estimated to allow detection of a primary outcome (mean intra-individual difference in time to wound closure) of 1.9 days in each study at an alpha of 0.05 and 90% power, given a standard deviation of 6.0 days.

2.8. Statistical analysis

Statistical analysis was performed using SAS version 9.3 (Cary, NC). A p-value below 0.05 was considered statistically significant. Efficacy was initially analysed within the intent-to-treat analysis set, which included all patients who signed informed consent and who were treated at least once with TBG. The primary endpoint (intra-individual difference in time to wound closure) was calculated from the means of the values for each of the three blinded experts. Median time to wound closure was used for Kaplan–Meier analysis. If more than one expert considered a photo series as not evaluable, the corresponding wound half was not included in the analysis. The percentage of patients with wound closure over time was determined using a last observation carried forward approach. The percentage of wound epithelialization as assessed by investigators during dressing change was compared at each time point by a paired t-test and a non-parametric sign test. Baseline characteristics and safety were analysed within the safety analysis set, which included all patients who received at least one treatment.

3. Results

3.1. Patients and studies

Study BSG-12 was conducted between April 5 and September 25, 2013 and enrolled 113 adult patients of whom 112 were treated. Study BSH-12 was performed between August 3, 2012 and August 23, 2013 and enrolled 111 adult patients of whom 107 were treated. The patients were on average 52.6 years of age (Table 1). Nearly two-thirds (64.1%) were men. Overall, just over half of the patients (54.4%) had Fitzpatrick skin type I or II, although this was much more common in study BSH-12 (79.4%) than in study BSG-12 (30.0%), consistent with the different regions in which the studies were performed. Wounds were on average $81.5 \pm 66.4\,cm^2$. Mepilex (Mölnlycke Health Care, Goteborg, Sweden), a siliconized foam dressing, was selected for most (78%) patients as the standard-of-care control. For other patients, Allevyn Gentle or Allevyn Non-Adhesive (Smith & Nephew, Hull, United Kingdom) was used as the standard-of-care control.

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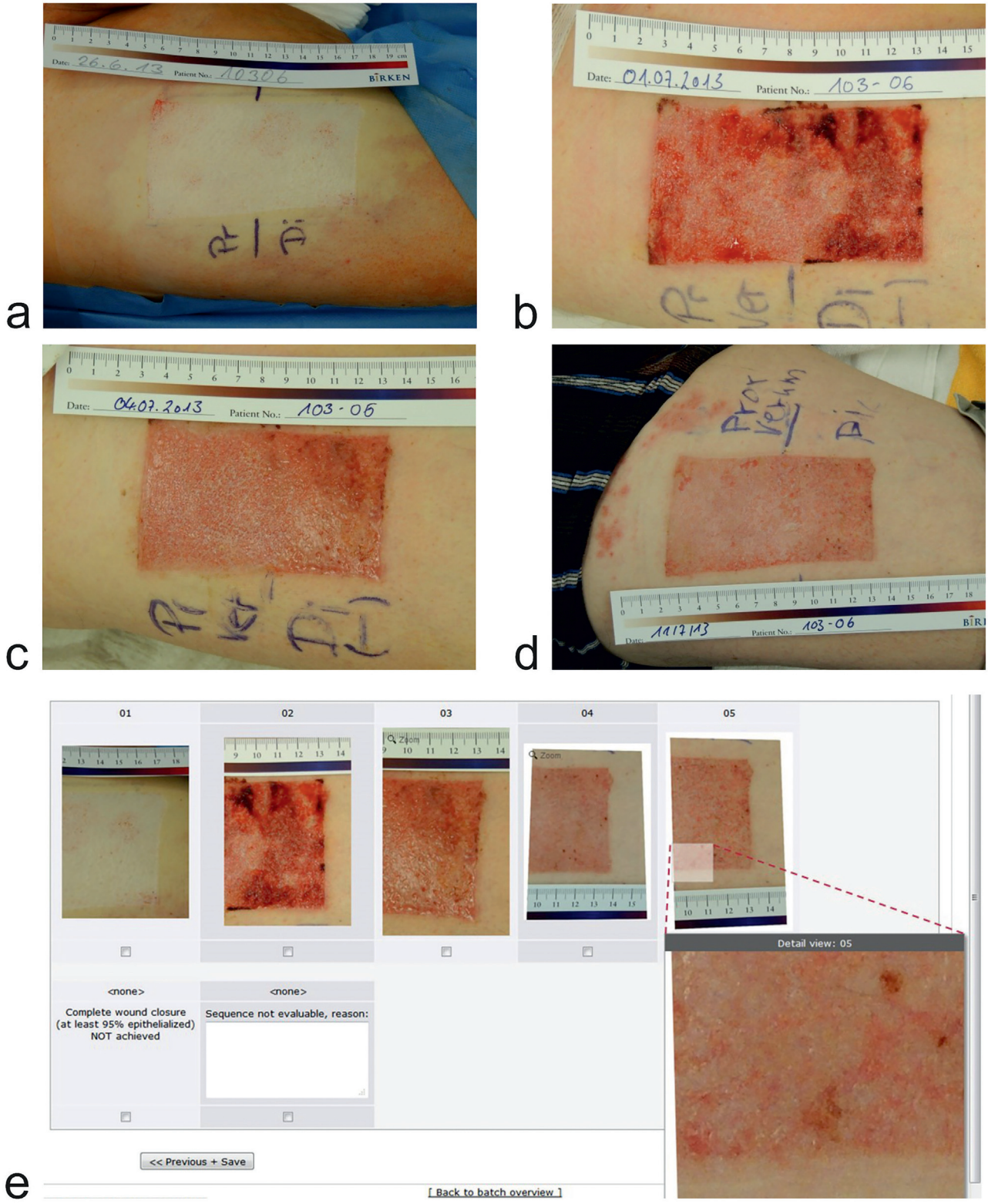

Fig. 1 – Marking, blinding, and reading of wound halves.
Original photo series taken on days 0 (a), 2 (not shown), 5 (b), 8 (c) and 15 (d). Immediately after split-thickness skin harvest, the donor site wound was divided in two halves, marked 'Pr' for proximal and 'Di' for distal (a). Randomisation then assigned treatments to the wound halves. Skin next to the wound half to be treated with topical betulin gel was marked as 'Ver' (verum) and skin next to the control wound half was marked as '-' (b-d).Prior to the blinded read, markings were cropped from the photo and checked by a medical expert. Only photos that were confirmed to be free of markings or other details that could have compromised blinding (e.g., gel residue) were considered for a blinded read. Eligible photographs were divided into two halves based on the skin markings, then photo series of separate wound halves were evaluated by three wound experts via a web-

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Table 1 – Baseline characteristics.

Characteristic	BSH-12 (N=107)	BSG-12 (N=110)	Pooled (N=217)
Age (y), mean±SD	54.0±18.1	51.2±17.3	52.6±17.7
Sex, n (%)			
Male	68 (63.6)	71 (64.5)	139 (64.1)
Female	39 (36.4)	39 (35.5)	78 (35.9)
Fitzpatrick skin type			
I-II	85 (79.4)	33 (30.0)	118 (54.4)
III-V	22 (20.6)	77 (70.0)	99 (45.6)
Wound size (cm^2), mean±SD	76.4±74.4	86.5±57.4	81.5±66.4

Abbreviation: SD, standard deviation.

Of the 219 patients who were treated, 174 (79.5%) completed the treatment period and achieved full wound closure by day 28 or before (Fig. 2). Seventeen patients (7.8%) discontinued early, 6 (2.7%) of whom discontinued because of AEs. The remaining 28 (12.8%) patients did not have full wound closure on both halves.

3.2. *Time to wound closure*

For about one-third of the patients (35.0%), wound closure was observed for both halves, and for another one-third (31.8%), full wound closure was not observed for either half (Table 2). More of the remaining patients had full wound closure with TBG +wound dressing (22.6%) than with the wound dressing alone (3.2%). For a few patients (7.4%), results differed between the three blinded experts, so whether closure occurred could not be established.

For the primary analysis, when wound closure was not observed, it was assumed to have closed 1 day after the last observation. Using this conservative assessment, wound closure was faster with TBG+wound dressing than with the wound dressing alone (15.3 vs. 16.5 days; mean intra-individual difference=−1.1 days [$p<0.0001$]) (Fig. 3). In addition, more patients had earlier closure of the wound half treated with TBG+wound dressing than had earlier closure of the wound half treated with wound dressing alone (73.9% vs. 26.1% of the 157 patients with a difference in time to wound closure). Faster wound closure with TBG was also found in each of the two studies, although the difference was larger for study BSH-12 (mean, 15.5 vs. 17.1; difference=−1.4 days [$p<0.0001$]) than for study BSG-12 (mean, 15.1 vs. 16.0 days; difference=−0.8 days [$p=0.0232$]). Results were also similar when the analysis was repeated using different analysis sets (e.g. all patients completing the study and patients completing according to protocol), as well as for each of the three blinded experts independently and according to country or centre (data not shown). Using a less conservative analysis, in which the mean time passed between the last observation and the day of wound closure (3.1 days) was used for cases where wound closure was not observed, the mean intra-individual difference in time to wound closure was −1.5 days ($p<0.0001$). Applying this analysis to a second blinded read of all photos (i.e., without removal of photos with ointment residue) resulted in a difference of −2.2 days ($p<0.0001$). Finally, in unblinded assessments, investigators reported wound closure to be 2.1 days faster for areas treated with TBG+wound dressing than for areas treated with the wound dressing alone ($p<0.0001$).

3.3. *Safety*

During both the treatment and follow-up periods in the two studies, AEs were reported by 86 (39.3%) patients (thereof reported by 78 patients within the treatment period), although only 17 (7.8%) patients had AEs that the investigator considered related or possibly related to the treatment, all of which were rated as mild or moderate severity (Table 3). The most common related or possibly related AEs were skin pain, pruritus, post-procedural complication, wound complication, and pain.

Thirty-nine patients (17.8%) had AEs at the application site (Tables 3 and 4). One patient (0.5%) had pruritus and one patient (0.5%) a skin infection limited to the TBG-treated wound half. Thirteen patients (5.9%) had application-site AEs limited to the standard of care-treated wound half, the most common of which was skin infection (four cases) and two cases each of skin pain and wound haemorrhage. In 27 (12.3%) patients, the AE occurred on both wound halves, the most common of which were infections (five patients with skin infections, four with wound infections).

SAEs included wound infection in two patients and bacteraemia, sepsis, post-operative wound complication, mania, bronchospasm, and diabetic foot, each in one patient. Both cases of serious wound infection, the severe post-procedural complication, and the case of mania resulted in early discontinuation of the study. None of these SAEs were considered related or possibly related to treatment.

Administration of TBG to STSG donor site wounds did not lead to plasma levels of betulin higher than natural background levels (data not shown).

3.4. *Patient and investigator assessment of efficacy and tolerability*

In most cases, investigators (60.2%) and patients (56.8%) considered TBG+wound dressing more or much more effective than wound dressing alone (Table 5). Only 6.7% of investigators and 6.3% of patients considered wound dressings alone to be more effective than wound dressings+TBG. Also, for almost half of all cases, investigators (44.8%) and patients (46.1%) considered TBG+wound dressing to be better tolerated than wound dressing alone, whereas only 1.9% of investigators and 3.9% of patients considered wound dressing alone to be better tolerated.

3.5. *Long-term outcome*

At 3 and 12 months after treatment, wound halves treated with TBG+dressing were more often similar to the surrounding skin

based electronic blinded read tool (e). Readers could magnify areas of interest using a zoom tool (e). The blinded readers assessed which of the photos in the series was the first to show full wound closure, as defined by ≥95% epithelialization.

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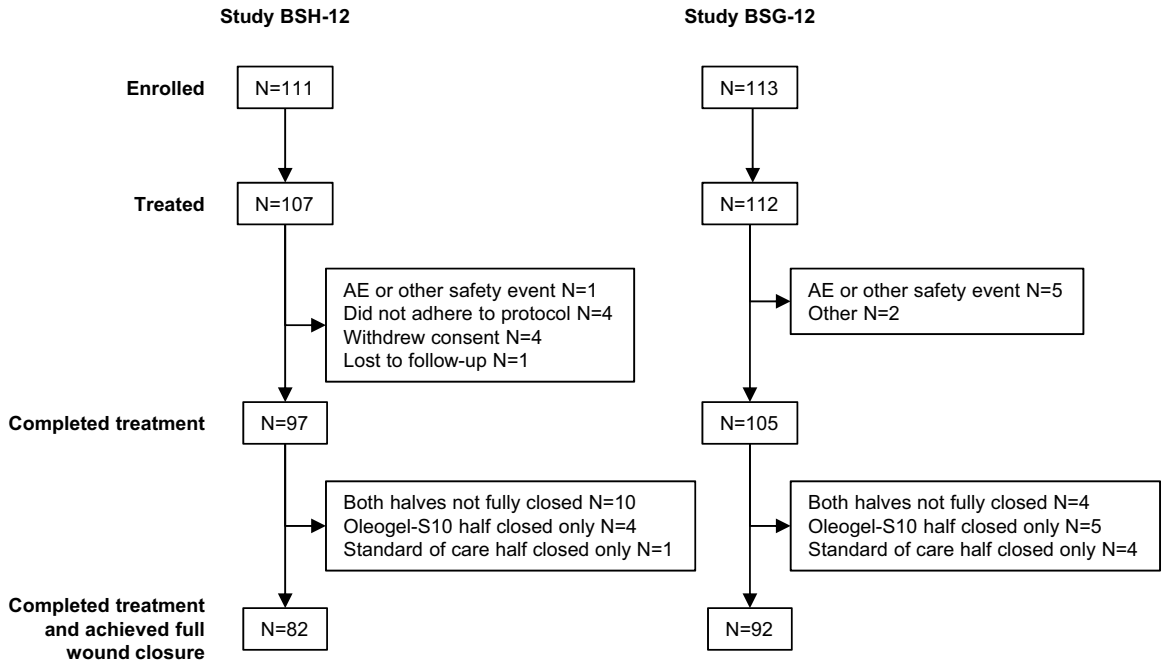

Fig. 2 – Flow diagram/disposition.
Two studies (BSG-12 and BSH-12) were performed with the same protocol. In study BSH-12, 111 patients were enrolled, and 107 were intra-individually randomized for the wound-half to be treated with TBG and treated. All 107 patients were included in the analysis (safety analysis set and intent-to-treat analysis set). In study BSG-12, 113 patients were enrolled, and 112 were intra-individually randomized for the wound-half to be treated with TBG and treated. All 112 patients were included in the safety analysis set, 2 patients were excluded from the intent-to-treat analysis set related to informed consent documentation. Of the total of 219 patients who were treated in the two studies, 219 were analysed in the safety analysis set and 217 in the intent-to-treat analysis set. 174 patients completed the treatment and achieved full wound closure for both wound halves on or before day 28.

than would halves treated with the dressing alone in terms of texture (27.5% vs. 7.1% at 3 months [$p<0.001$], 13.5% vs. 2.7% at 12 months [$p=0.002$]), redness (28.0% vs. 10.4% [$p<0.001$] at 3 months, 12.8% vs. 4.1% at 12 months [$p=0.015$]), and especially pigmentation (36.8% vs. 10.4% at 3 months [$p<0.001$], 23.6% vs. 8.9% at 12 months [$p=0.002$]) (Table 6). Hair growth was not affected by TBG (98.4% at 3 months, 98.0% at 12 months equal for both wound halves).

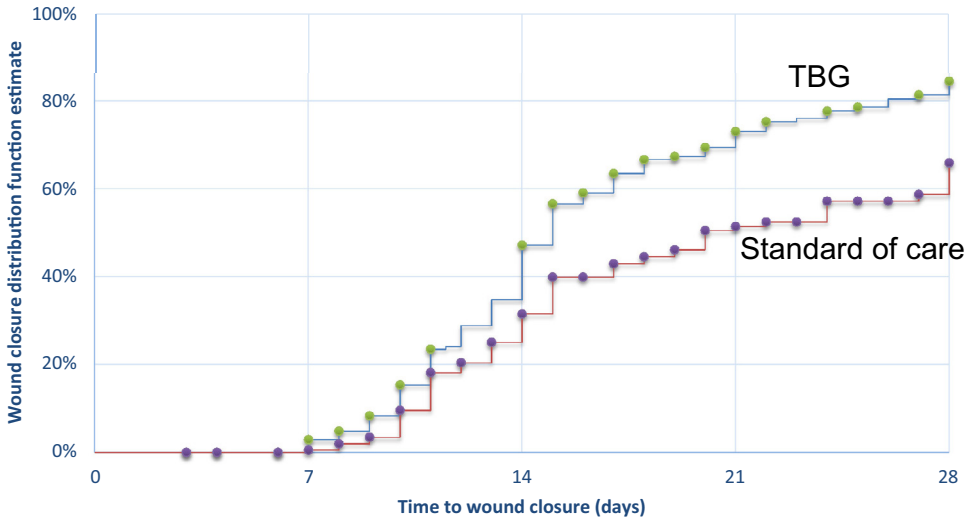

Fig. 3 – Time to first observation of wound closure.
For each patient, time to wound closure was determined from the median time to wound closure from the three blinded experts. For each of the three expert readers, the day of closure was the day on which the first photograph in the photo series showed full wound closure, as defined by ≥95% epithelialization. Results are for the intent-to-treat analysis set (N=217).

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Table 2 – Assessment of wound closure.

Measure	BSH-12 N=107	BSG-12 N=110	Pooled N=217
Intra-patient difference in days to wound closure[a]			
Mean (95% CI)	−1.4 (−1.8, −0.9)	−0.8 (−1.5, −0.1)	−1.1 (−1.5, −0.7)
P-value vs. no change	<0.0001	0.0232	<0.0001
Days from surgery to wound closure[a]			
TBG, mean (95% CI)	15.5 (14.2, 16.8)	15.1 (14.1, 16.1)	15.3 (14.5, 16.1)
Standard of care, mean (95% CI)	17.1 (15.8, 18.5)	16.0 (14.8, 17.1)	16.5 (15.7, 17.4)
Wound closure, n (%)			
For both wound halves	22 (20.6)	52 (47.3)	76 (35.0)
For TBG-treated half only	33 (30.8)	16 (14.5)	49 (22.6)
For standard of care-treated half only	2 (1.9)	5 (4.5)	7 (3.2)
For neither half	43 (40.2)	26 (23.6)	69 (31.8)
Inconclusive	5 (4.7)	11 (10.0)	16 (7.4)
Difference in rate of wound closure, n (%)			
No difference between wound halves	33 (30.8)	27 (24.5)	60 (27.6)
Earlier closure for TBG-treated half	66 (61.7)	50 (45.5)	116 (53.5)
Earlier closure for standard of care-treated half	8 (7.5)	33 (30.0)	41 (18.9)
Intra-patient difference in days to wound closure based on mean time between dressing changes[b]	−2.0 (−2.5, −1.4)	−1.1 (−1.9, −0.3)	−1.5 (−2.0, −1.1)
P-value vs. no change	<0.0001	0.0063	<0.0001
Intra-patient difference in days to wound closure based on mean time between dressing changes[b], secondary blinded read with all photos presented[c]	−2.7 (−3.4, −2.0)	−1.7 (−2.6, −0.8)	−2.2 (−2.8, −1.6)
P-value vs. no change	<0.0001	0.0002	<0.0001
Difference in days to wound closure according to investigator (unblinded) assessment	−2.5 (−3.3, −1.6)	−1.8 (−2.6, −1.0)	−2.1 (−2.7, −1.5)
P-value vs. no change	<0.0001	<0.0001	<0.0001

Abbreviations: CI, confidence interval; TBG, topical betulin gel.

[a] For wound halves for which wound closure was observed in the blinded read, the day of the photo at which wound closure was first observed was used. For wound halves in which closure was not observed, the wound half was assumed to have closed one day after the last available photograph. For 5 patients in study BSH-12 and 2 patients in study BSG-12, data for this analysis were missing because photo series were rated as 'not evaluable' by the majority of readers (for other endpoints, intra-patient analyses, these patients were rated as no difference).

[b] A sensitivity analysis was carried out in which wound halves for which wound closure was not observed were assumed to have healed by the time of the next dressing change (3-4 days) after the last available photo.

[c] In the primary blinded read evaluation, a rigorous quality check was implemented to ensure blinding of the observers. As a result, many photographs were excluded and not presented in the primary blinded read because of apparent gel residue. The secondary blinded read was conducted with all photographs presented to the blinded observers.

4. Discussion

The physical, chemical, and pharmacological characteristics of oleogel-forming triterpenes, especially betulin, were described in 2006 [18]. Betulin has since been reported to promote healing in vivo and in vitro[9,10]. In a previous phase II study in which 24 Caucasian STSG patients were treated for 14 days with TBG plus a non-adhesive wound dressing or the wound dressing alone, re-epithelialization was more often rated as faster for the TBG-treated half than for the control half (83.3% vs. 8.3%; $p<0.0001$) [13].

The two open-label phase III clinical trials described here extend these findings and confirm that STSG donor sites heal significantly faster when TBG is added to the current standard of care, moist dressings lacking pharmacological, antimicrobial, or other agents. Efficacy was assessed in these two trials using a blinded, remote photographic analysis, which correlates well with direct clinical assessment by investigators [19,20] and is feasible for clinical studies. For the primary analysis, we used a conservative estimate of time to wound closure: when wound closure was not observed, the time to wound closure was assumed to be 1 day after the last observation, even though at least 2 or 3 days typically passed between each observation. This meant that the differences in closure times were underestimated. Indeed, when using the mean time between visits instead 1 day after the last observation, the difference increased from 1.1 to 1.5 days. Both of these calculations underestimate the real difference because some detail is lost when using photos instead of direct observation. Using investigators' direct observations of re-epithelialization, wound closure was estimated to be approximately 2 days faster with TBG. Together, the different efficacy assessments strongly support the conclusion that TBG

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Table 3 – Number and percentage of patients with AEs reported during treatment period and follow-up period.

Measure	BSH-12 (N=107) n (%)	BSG-12 (N=112) n (%)	Pooled (N=219) n (%)
Any AE	23 (21.5)	63 (56.3)	86 (39.3)
At the application site	12 (11.2)	27 (24.1)	39 (17.8)
Probably or possibly related to treatment	3 (2.8)	14 (12.5)	17 (7.8)
Leading to discontinuation	1 (0.9)	4 (3.6)	5 (2.3)
Probably or possibly related to treatment and leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Any SAE	6 (5.6)	10 (8.9)	16 (7.3)
Related or possibly related to treatment	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AE, adverse event; SAE, serious adverse event.

significantly and substantially accelerated wound healing compared to this state-of-the-art wound dressing material.

From the clinical point of view there are two important results of benefit for the patients: The first result is the reduction of healing time by approximately 2 days, that means more than 10% less open skin surface period, reduced risk of contamination with pathogens, and reduced treatment need. Importantly, TBG was safe and well tolerated, with no serious adverse events (SAE) or discontinuations considered related to treatment. Both clinical investigators and patients considered the tolerability of TBG+the wound dressing to be better than the wound dressing alone. Only a single patient had AEs (pruritus and a skin infection) limited to the TBG-treated wound half. This was the only patient to have early signs of SSI on the TBG-treated wound half. In contrast, four patients had early signs of SSI on the wound half treated with the wound dressing alone. This is likely due to the faster wound healing with TBG because betulin itself has only modest antimicrobial activity [21].

The second result is the for many patients even more important finding of this study, that long-term aesthetic outcome was better with TBG. In particular, texture, redness, and pigmentation were better when TBG was applied. Hair growth, in contrast, was not affected by TBG, which is not surprising because the surgical removal of the STSG left the underlying hair follicles intact.

Moist, non-adhesive dressings are the current standard of care for partial thickness wounds [7,22–25]. Topical treatments that have been reported to accelerate healing include honey [26,27] and topical growth factors [28], but the comparator is generally not the current standard of care, and the studies have mostly been limited to burn wounds. A few other treatments (e.g. aloe, MEBO®, and RGD peptide) have been shown to improve healing of burn wounds, but the comparator

Table 4 – Number and percentage of patients with application-site adverse events.

Adverse events	BSH-12 (N=107)			BSG-12 (N=112)			Overall (N=219)		
	TBG	Std of care	General[a]	TBG	Std of care	General[a]	TBG	Std of care	General[a]
Impaired healing	–	–	1 (0.9)	–	–	–	–	–	1 (0.5)
Skin infection	–	2 (1.9)	1 (0.9)	1 (0.9)	2 (1.8)	4 (3.6)	1 (0.5)	4 (1.8)	5 (2.3)
Wound infection	–	1 (0.9)	1 (0.9)	–	–	3 (2.7)	–	1 (0.5)	4 (1.8)
Wound haemorrhage	–	1 (0.9)[b]	1 (0.9)	–	1 (0.9)	1 (0.9)	–	2 (0.9)	2 (0.9)
Skin pain	–	–	1 (0.9)	–	2 (1.8)	4 (3.6)	–	2 (0.9)	5 (2.3)
Pruritus	–	–	1 (0.9)	1 (0.9)	–	3 (2.7)	1 (0.5)	–	4 (1.8)
Hypersensitivity	–	–	–	–	–	1 (0.9)	–	–	1 (0.5)
Post-procedural complication	–	–	–	–	1 (0.9)	3 (2.7)	–	1 (0.5)	3 (1.4)
Procedural pain	–	–	–	–	–	2 (1.8)	–	–	2 (0.9)
Wound complication	–	–	–	–	–	2 (1.8)	–	–	2 (0.9)
Wound haematoma	–	–	–	–	–	2 (1.8)	–	–	2 (0.9)
Wound secretion	–	–	–	–	–	1 (0.9)	–	–	1 (0.5)
Dermatitis	–	–	–	–	1 (0.9)	–	–	1 (0.5)	–
Excessive granulation tissue	–	–	–	–	–	1 (0.9)	–	–	1 (0.5)
Haematoma	–	–	–	–	–	1 (0.9)	–	–	1 (0.5)
Skin ulcer	–	1 (0.9)[b]	–	–	–	–	–	1 (0.5)	–
Keratoacanthoma	–	1 (0.9)[b]	–	–	–	–	–	1 (0.5)	–
Any application site adverse event	0 (0.0)	6 (5.6)	6 (5.6)	2 (1.8)	7 (6.3)	21 (18.8)	2 (0.9)	13 (5.9)	27 (12.3)

Abbreviations: Std, standard; TBG, topical betulin gel.
[a] Not limited to a single wound half.
[b] Observed during the follow-up period.

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Table 5 – Investigator and patient assessment of efficacy and tolerability at the end of treatment.

Response	Efficacy, n (%)		Tolerability, n (%)	
	Investigator-assessed (N=209)[a]	Patient-assessed (N=206)[a]	Investigator-assessed (N=210)[a]	Patient-assessed (N=206)[a]
TBG much better	35 (16.7)	37 (18.0)	27 (12.9)	32 (15.5)
TBG better	91 (43.5)	80 (38.8)	67 (31.9)	63 (30.6)
No difference	69 (33.0)	76 (36.9)	112 (53.3)	103 (50.0)
Standard of care better	12 (5.7)	11 (5.3)	4 (1.9)	7 (3.4)
Standard of care much better	2 (1.0)	2 (1.0)	0 (0.0)	1 (0.5)

Investigators and patients answered questionnaires about the efficacy and tolerability of the two treatments. Shown are responses at the end of treatment. Abbreviation: TBG, topical betulin gel.
[a] For some patients, the assessment was missing (intent-to-treat analysis set N=217).

Table 6 – Long-term outcome.

Measure	Wound half more similar to neighbouring untreated skin	Month 3 (N=182)[a]		Month 12 (N=148)[a]	
		n (%)	p-Value[b]	n (%)	p-Value[b]
Pigmentation	TBG-treated wound half	67 (36.8)	<0.001	35 (23.6)	0.002
	Standard of care treated wound half	19 (10.4)		13 (8.9)	
	Both sides equal	89 (48.9)		96 (64.9)	
	No majority decision or not evaluable	7 (3.8)		4 (2.7)	
Redness	TBG-treated wound half	51 (28.0)	<0.001	19 (12.8)	0.015
	Standard of care treated wound half	19 (10.4)		6 (4.1)	
	Both sides equal	105 (57.7)		123 (83.1)	
	No majority decision or not evaluable	7 (3.8)		0 (0.0)	
Texture	TBG-treated wound half	50 (27.5)	<0.001	20 (13.5)	0.002
	Standard of care treated wound half	13 (7.1)		4 (2.7)	
	Both sides equal	113 (62.1)		124 (83.8)	
	No majority decision or not evaluable	6 (3.3)		0 (0.0)	
Hair growth	TBG-treated wound half	2 (1.1)	0.5	2 (1.4)	1.0
	Standard of care treated wound half	0 (0.0)		1 (0.7)	
	Both sides equal	179 (98.4)		145 (98.0)	
	No majority decision or not evaluable	1 (0.5)		0 (0.0)	

Long-term outcomes were assessed by blinded photo evaluation. Abbreviation: TBG, topical betulin gel.
[a] All patients attending follow-up visits were included in the analysis. The difference to N=217 (intent-to-treat analysis set), N=35 at the 3-months and N=69 at the 12-months time point, represent patients lost to follow-up.
[b] P-value determined by exact binomial test for [% for the TBG-treated half ÷ % for the standard of care-treated half] >0.5.

has usually been silver sulfadiazine, which is now well known to slow healing [22,29]. Furthermore, study quality has varied widely, and with the exception of our own previous phase II study [13], no other phase II or III clinical trials have examined the ability of topical agents to enhance wound closure or re-epithelialization.

5. Conclusion

TBG is a safe topical agent that accelerates epidermal barrier closure of split-thickness skin graft donor sites with faster secondary re-epithelialization of partial thickness wounds and reduced scarring, compared to the current standard of care. TBG is providing a well-tolerated contribution to burn care in practice.

Conflicts of interest

JPB reports grants and personal fees from Birken AG; FP declares no conflict of interest; HOR reports personal fees from Birken AG and personal fees from Moelnlycke Healthcare unrelated to the submitted work; HS reports personal fees from Birken AG and personal fees from Dr Ausbüttel & Co. GmbH unrelated to the submitted work; BL and ASB

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