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Original research article

Wound healing characteristics of a novel wound healing ointment in an abrasive wound model: A randomised, intra-individual clinical investigation

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ABSTRACT

Objective: Moist wound healing conditions are beneficial in a professional wound care setting as well as for self-treatment of acute, superficial wounds. The purpose of this randomized, controlled, investigator-blinded investigation was to determine the local tolerability, wound healing efficacy and cosmetic outcome of a novel wound healing ointment in an intra-individual comparison of 4 treatment regimens in an abrasive wound model.
Methods: Standardized abrasive wounds were induced on the inner forearms of 30 healthy subjects and 4 treatment regimens were randomly allocated to test areas (wound healing ointment covered with standard first aid dressing, wound healing ointment covered with gauze, standard first aid dressing alone, untreated area covered with gauze). Wounds were treated once daily for 11 days. Local tolerability and wound healing were assessed using visual scoring and digital photography on 5 different days. The cosmetic outcome was evaluated on a follow-up visit on Day 31.
Results: The wound healing ointment exhibited excellent local tolerability with superior assessments in comparison to treatment utilizing only dressings without ointment. Significant differences between AUC values for re-epithelization and overall wound healing efficacy were demonstrated in favor of treatment with the wound healing ointment in comparison to dry wound healing conditions. Wounds treated with the wound healing ointment showed a faster onset of healing and the cosmetic outcome was rated as being superior for the wound healing ointment both by the investigator and the subject.
Conclusion: Superficial cutaneous wounds treated with the novel wound healing ointment displayed a significant improvement of wound healing with an earlier onset of re-epithelization, faster wound closure and a better cosmetic outcome. Clinically relevant accelerated wound healing compared to traditional dry healing could be shown demonstrating the benefits of moist wound healing conditions also in the treatment of minor, superficial wounds (Clinical trial identification number: EUDAMED_CIV 17-04-019364).

1. Introduction

Acute, superficial wounds caused by abrasions, cuts or minor burns occur every day. Usually, these small injuries are not examined by a physician. Patients leave them unattended or treat the wounds themselves using first aid dressings. The first aid dressing provides a barrier against dirt, bacterial contamination and mechanical factors such as pressure and friction [1]. This conventional self-treatment at home usually generates a dry wound environment.

The first studies investigating moist wound healing concentrated on acute wounds [2,3]. However, the concept of moist wound healing has been broadened to include not only chronic wounds but the management of all wounds [4]. The healing process in superficial wounds is often considered self-evident but to prevent complications and to ensure a satisfactory cosmetic result, these wounds benefit from a moist environment designed to support optimal wound healing.

To create a moist healing environment in superficial wounds, dressings and ointments are utilized. Ointments form a semi-occlusive, breathable protective film that moisturizes and prevents the wound from drying out. External influences are kept to a minimum and the healing process is promoted.

However, clinical studies investigating standard wound treatment of

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minor everyday wounds are still rare [5–7]. Accordingly, the purpose of this controlled investigation was to determine the local tolerability (primary objective), wound healing efficacy (secondary objective) and cosmetic outcome of a novel wound healing ointment in an intra-individual comparison of 4 different treatment regimens. A wound model using an abrasive brush technique was used that created uniform abrasive wounds reflecting the clinical situation in superficial wounds [5].

2. Methods

This study was a single-center, randomized, investigator-blind clinical investigation. All volunteers provided written and informed consent. The novel wound healing ointment is classified as a medical device and meets the requirements of the European Council Directive 93/42 EEC. The investigation was approved by an independent ethics committee and performed according to the German medical device law MPG §§ 20–22, the German Regulation on clinical testing of medical devices MPKPV § 7 and ISO 14155-2011(E). It was conducted in compliance with Good Clinical Practice (GCP) and in accordance with the currently valid revision of the Declaration of Helsinki.

The clinical investigation was carried out from August to September 2017 at the bioskin GmbH, Hamburg, Germany.

2.1. Study population

Within 14 days prior to the first administration of the wound healing ointment, 34 volunteers came to the clinical investigation site (bioskin GmbH, Hamburg, Germany) for an initial screening. Thirty healthy subjects (5 male, 44–70 years of age; 25 female, 21–80 years of age) meeting all inclusion criteria with intact, undamaged skin at the test areas and belonging to Fitzpatrick skin types I–III [8] were enrolled into the investigation. The main exclusion criteria were as follows: acne, suntan, eczema, scars, excessive hair, acute skin infection or skin disease, hyper- or hypopigmentation or tattoos in the test fields, Fitzpatrick skin types IV–VI [8], diabetes mellitus, psoriasis, atopic dermatitis, lichen ruber planus, a history of plaster sensitivity, a history of keloids, hypertrophic scars or wound healing disorders, treatment with systemic medications or medications acting locally in the test field areas (e.g. antihistamines or glucocorticosteroids) within two weeks before the baseline visit as well as during the investigation.

2.2. Randomization and blinding

The investigation was carried out investigator-blind. To apply this condition, treatments were coded and randomly allocated to test areas. Codes A–C, respectively, were assigned to treatment 1–3 (see section Investigational product, Fig. 1A). The untreated control field (treatment 4) was assigned the code D. Randomization was performed by permutation of the treatment codes A to D. The treatment listed first in the respective permutation was assigned to test field A, the second to test field B, etc.

To create the random allocation sequence, a randomized complete block design (RCBD) was used. The randomization list was generated by bioskin statistics and the investigator enrolled the participants. Volunteers meeting the inclusion criteria received their 3-digit randomization number at randomization on Day 1 (baseline) by the investigator. The treatment of the respective test fields followed the randomization list which included the assignment of the 4 treatments to test fields per randomization number.

The design of this investigation included no separate treatment group, each subject received all treatments. But since the 4 treatment regimens differed, subjects and the study nurse involved in the application were not blinded. To keep the investigator, who performed the clinical assessments, blinded, he/she was not involved in the performance of treatments. The unblinded study nurse removed the patches and product residues 30 min prior to the assessment and applied the treatments again after performance of the assessments.

2.3. Induction of abrasive wounds

On Day 1, two small, superficial, abrasive wounds were induced on the right volar forearm and two on the left volar forearm of each subject using a sterile surgical hand brush [5]. Before wounding, the forearms were disinfected with a standard alcohol-based antiseptic. A disinfected template (robust foil) was then applied to the skin. The template for the right and for the left forearm contained two holes with a diameter of approximately 1.2 cm having a distance of at least 5 cm A trained study nurse then induced epidermal abrasive wounds under visual control by repeatedly scrubbing the skin with a sterile surgical hand brush using moderate pressure until first signs of uniform glistening and punctuate redness were observed. At this point, the scrubbing was stopped to ensure that the lesion was superficial with only partial erosion of the papillary dermis (Fig. 1B). This procedure causes only minor pain, so that no anesthetic was necessary.

The length of the treatment (11 days) and of the observation period (31 days) are adequate for a superficial wound with this diameter to heal completely [5].

2.4. Investigational product

The investigational wound healing ointment is classified as medical device containing white petrolatum, thin paraffin oil, ceresin wax, glycerin, panthenol, and glyceryl stearate.

On Day 1, after induction, wounds were photographed. Each wound was then treated with one of the 4 treatment regimens randomly allocated to the 4 test areas once daily for 11 days:

Treatment 1: 0.2 g wound healing ointment covered with gauze (e.g. Gazin®, Lohmann & Rauscher, Rengsdorf, Germany).

Treatment 2: 0.2 g wound healing ointment covered with standard first aid dressing (Hansaplast Sensitive Plaster, Beiersdorf AG, Germany).

Treatment 3: Test field covered with standard first aid dressing alone.

Treatment 4: Test field covered with gauze alone.

The tested non-invasive investigational medical device is a ready-to-use wound healing ointment. The test fields were covered with fabric gauze that was fixed if necessary by the outside with adhesive patches (e.g. Fixierpflaster Hansaplast Sensitive, Beiersdorf AG, Germany) or plaster (Hansaplast Sensitive, wound plaster, Beiersdorf AG, Germany).

The use of topical products other than the wound healing ointment and coverings in the test fields was prohibited during the clinical investigation. Also, bathing, sauna, sunbathing or solarium were not allowed. To exclude any influence on wound healing, showering was only allowed as long as the test fields were shielded from water. Out of the same reason, subjects were asked to avoid exercise associated with excessive sweating.

On the following ten days (Day 2 to Day 11), wounds were treated daily by the study nurse at the clinical investigation site. In case plasters were loosened, subjects were allowed to cover the respective test field according to the treatment regimen at home.

On Days 2, 6, 8, 10 and 12, clinical and global assessment of tolerability and wound healing efficacy assessments as well as determination of signs of infection were performed. On Day 12, a physical examination of the skin in the test fields was carried out and subjects filled out a questionnaire pertaining the treatment regimens. On Day 31 ± 2, the cosmetic outcome was assessed by the investigator and the subject. Photographic documentation of the induced wounds was performed on Days 1, 4, 6, 8, 10, 12 and 31 ± 2 for all subjects. For 5 subjects, photographic documentation was additionally carried out on Days 2, 3, 5, 7, 9 and 11.

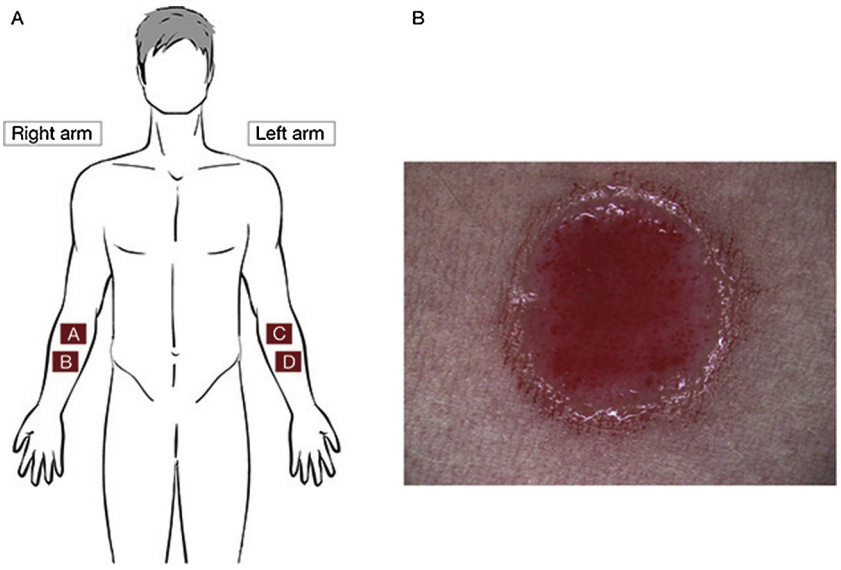

Fig. 1. A: Four treatment regimens were randomly allocated to the 4 test areas (A–D); B: Standardized superficial wounds induced on the forearm of healthy volunteers.

2.5. Determination of local cutaneous tolerability and global assessment of tolerability

Local cutaneous tolerability was evaluated by the investigator only on healthy skin in close proximity to the 4 test fields using the following 5-point-erythema score [9]: 0 = no reaction, 1 = slight uniform or spotty erythema or slight diffuse, partial or follicular erythema, 2 = clear, sharply demarcated erythema, 3 = severe erythema with infiltrate, 4 = severe erythema with infiltrate and/or epidermal defect (blisters, blebs, erosions). Individual treatments were discontinued in the event of assessment with a score for erythema greater than 2. The observer continued with the assessment of the dermal reactions (erythema) after discontinuation of this test field. Treatment in other test fields was continued.

Additionally, the local tolerability was globally assessed by the investigator and the subject by means of the following 5-point-scale: 0 = very good, 1 = good, 2 = acceptable, 3 = poor, 4 = very poor. Individual treatments were discontinued in the event of assessment with a score for tolerability greater than 3. The observer did not continue with the assessment of the dermal reactions after discontinuation of the test field. Treatment in other test fields was continued.

2.6. Assessment of signs of infection

The investigator assessed whether the wounds showed signs of infection by answering a closed question (Yes/No), considering the following parameter: erythema, pain, malodor, delayed wound healing, excessive exudate, and heat.

2.7. Clinical assessment of wound healing - re-epithelialization and crust formation

Wound healing efficacy was assessed by the investigator for the 4 test fields by means of the following 6-point-re-epithelialization score. Re-epithelialization 0 = 0% healing, 1 = 1–25% re-epithelialization, 2 = 26–50% re-epithelialization, 3 = 51–75% re-epithelialization, 4 = over 75% but not complete re-epithelialization, 5 = 100% complete healing.

Crust formation was clinically assessed by the investigator for the 4 test fields using the following 6-point scale: Crust formation 0 = 100% crust formation, 1 = over 75% crust formation but less than 100% crust formation, 2 = 51–75% crust formation. 3 = 26–50% crust formation, 4 = 1–25% crust formation, 5 = 0% crust formation, 99 = wound is completely re-epithelialized.

Additionally, the investigator evaluated whether the crust formation developed as expected and showed no signs of clinical relevance by answering a closed question (Yes/No), considering the following parameter: bleeding, adhesion to the test field, removal or loosening (complete or partially) e.g. during the change of the wound plaster.

Wound healing was globally assessed by the investigator and the subject in the test fields using the following 5-point score: Efficacy 0 = very good, 1 = good, 2 = acceptable, 3 = poor, 4 = very poor.

2.8. Assessment of cosmetic outcome

The cosmetic outcome was assessed by the investigator and the subject by means of a visual analog scale ranging from 0 (poor) to 10 (excellent) on Day 31 ± 2 for each of the 4 test fields. The investigator and the subject were asked to place a mark along the horizontal scale that indicated the overall aesthetic appearance of the wound healing. Numeric scores were then obtained by measuring the horizontal distance from the low end of the scale to the marking and rounded to the nearest millimeter. All values had to be rounded to whole numbers.

2.9. Patient questionnaires

On Day 12, subjects filled out a questionnaire assessing product performance and product traits using a 4-tiered rating scale: 1 = no, not at all, 2 = no, 4 = yes, 5 = yes, absolutely. Additionally, a “don’t know” (99) was allowed. The questions regarded distribution/spreading of the ointment, skin feeling after application, support of pain free wound healing, reliability of wound protection, wound healing conditions when using the ointment compared to the untreated wound only covered with gauze, wound healing conditions when using the ointment compared to the wound only treated with the standard first aid dressing, suitability of the ointment for regular treatment of minor injuries and satisfaction with the efficacy of the ointment.

2.10. Photographic documentation

High quality digital photographic documentation of the 4 test fields was performed using a Canon EOS 5D Mark II (21.1 M P) equipped with a DermLite Photo II Pro dermoscopy lens. The photographs were taken under standardized conditions (e.g. distance, illumination,

background). Camera settings were as follows: Exposure Mode: manual; Exposure time: 1/60 s; ISO 400; White balance: custom (set with white page and actual lighting); Image recording quality: Raw (CR2) + JPEG fine. Lens settings were as follows: Lighting: Non-polarized; Zoom: Fully wide (image height: 20 mm); Contact plate removed (distance ring instead).

Due to potential slight transient erythema visible immediately after removal of wound coverage, the test field had to be exposed to air between 30 and 60 min before beginning of photographic documentation and assessments.

2.11. Statistics

The sample size estimation was not based on a formal sample size calculation. Following the guidance for industry on skin irritation and sensitization testing of generic transdermal drug products as advised by the FDA [10], a sample size of 30 subjects was considered to be sufficient to meet the objectives of the clinical investigation. As a consequence, 34 subjects were screened to ensure the enrollment of 30 subjects to be randomized.

The statistical evaluation was conducted using the software program SAS (Statistical Analysis System, Cary, NC). Descriptive statistics were given for raw data. Descriptive two-sided p-values were provided. If appropriate, two-sided hypothesis testing with 95%-confidence intervals was performed. For the re-epithelialization score and global assessment of wound healing efficacy scores, the area under the curve (AUC) was calculated using the trapezoid form. Comparisons between treatments regarding the AUC of scores were assessed by means of an analysis of variance (ANOVA) model. With respect to the 95% confidence interval, the effect of the comparison of treatments was determined with an unstructured covariance matrix.

The answers to the subject questionnaire on product traits 'yes, absolutely' and 'yes' were combined to 'agreement', while the answers 'no',' no, not at all' and 'do not know' were combined to 'no agreement'. A two-sided binomial test for null hypothesis proportion $p = 0.5$ was performed to test if the agreement level differed from 50%. The descriptive significance level was defined as 5%.

3. Results

3.1. Study population

All 30 subjects completed the clinical investigation (Fig. 2). There were no dropouts and no treatment discontinuation due to erythema score > 2 or local tolerability score > 3 during this investigation.

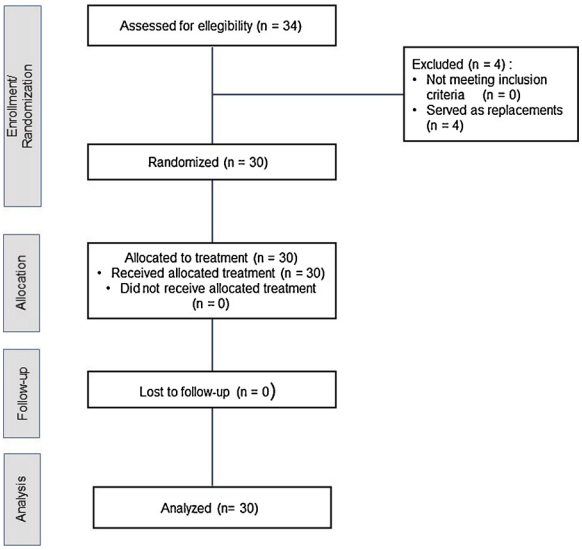

Fig. 2. Disposition of subjects.

3.2. Primary objective: Clinical and global assessment of local tolerability

The majority of the subjects (73.3%) showed 'no erythema' (score 0) in the respective test fields either treated with the wound healing ointment covered with standard first aid dressing or gauze or in the test field covered with the standard first aid dressing alone. In the untreated control field protected with gauze 'no erythema' was reported in 50% of the subjects.

The investigator did not detect any signs of wound infection in any test field under the 4 different treatment types in any patient at any point in time. No adverse event was reported.

According to the investigator's clinical assessment the wound healing ointment demonstrated excellent local tolerability. The investigator assessed the local tolerability as predominantly 'very good' (score 0) or good (score 1) in all 4 test fields of all 30 subjects at each assessment point (Days 2, 6, 8, 10 and 12) with the exception of 1 subject where 'acceptable' (score 2) was rated in the test field covered with the standard first aid dressing alone on Days 6, 8 and 10.

The mean sum score for clinical assessment of tolerability was lowest for the treatment with the wound healing ointment covered with standard first aid dressing (0.3 ± 0.5), followed by wound healing ointment covered with gauze (0.5 ± 1.1) and test field covered with the standard first aid dressing (0.6 ± 1.3). A higher mean sum score was reported for the untreated test field covered with gauze (1.2 ± 1.6).

This evaluation was confirmed by the investigator's global assessment of tolerability (mean sum score: Wound healing ointment covered with standard first aid dressing (0.1 ± 0.3), wound healing ointment covered with gauze (0.0 ± 0.2), test field covered with the standard first aid dressing (0.4 ± 1.4), untreated test field covered with gauze (0.1 ± 0.3). Subjects rated the global tolerability as follows (mean sum score): Test areas treated with the wound healing ointment covered with the standard first aid dressing (3.1 ± 2.7), the wound healing ointment covered with gauze (4.4 ± 2.7), test field covered with the standard first aid dressing (7.4 ± 3.3), untreated test field covered with gauze (8.2 ± 5.0). The sum of scores on Days 2, 6, 8, 10 and 12 is presented in Fig. 3. Generally, the rating by subjects tended to be less good than the investigator's rating.

3.3. Secondary objectives

3.3.1. Re-epithelialization and wound healing

In the test field treated with the wound healing ointment covered with the standard first aid dressing, re-epithelialization of wounds was already noted in all subjects after 5 days of treatment on Day 6 (Fig. 4). In more than half of the subjects (53.4%) over 75% re-epithelialization was assessed. 100% re-epithelialization was already achieved by 2 subjects (6.7%) on Day 6, in over one-third of the subjects (36.7%) on Day 8, by almost all subjects (96.7%) on Day 10 and by all subjects (100%) on Day 12. In the test field treated with the wound healing ointment covered with gauze, 83.3% of the subjects showed re-epithelialization of wounds on Day 6 mainly of smaller extent (25%–50% re-epithelialization). 100% re-epithelialization was already reached by 1 subject (3.3%) on Day 6, by 3 subjects (10.0%) on Day 8, by 17subjects (56.7%) on Day 10 and by 27 subjects (90.0%) on Day 12 (Table 1, Fig. 5).

Re-epithelialization of wounds was also observed in all subjects in the test field covered with the standard first aid dressing alone on Day 6, but the extent of wound healing was less pronounced (25%–50% re-epithelialization). 100% re-epithelialization was accomplished by 2 subjects (6.7%) on Day 10 and by more than half of the subjects (60.0%) on Day 12. In 40.0% of subjects complete re-epithelialization exceeded 12. Assessment of wounds in the untreated test fields covered

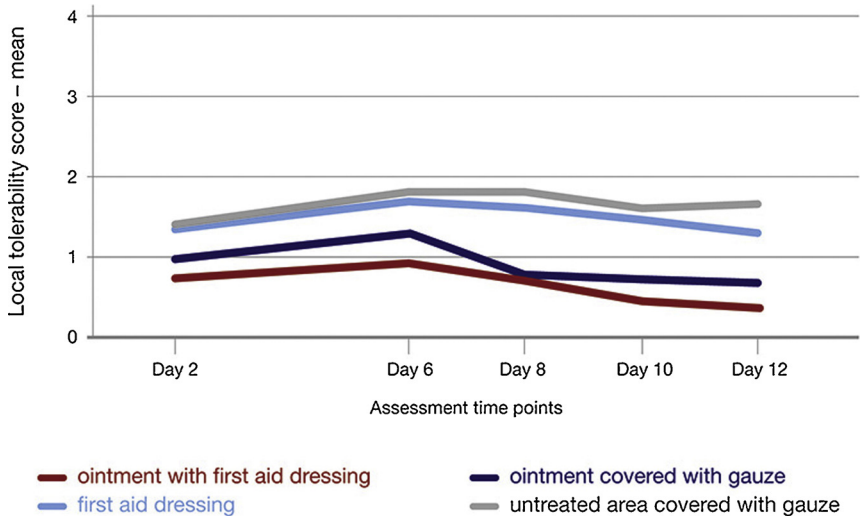

Fig. 3. Clinical assessment of local tolerability assessed by the subject. Sum score is calculated as the sum of scores on Days 2, 6, 8, 10 and 12 on the scale: 0 = very good, 1 = good, 2 = acceptable, 3 = poor, 4 = very poor. Possible values of sum score range from 0 to 20.

with gauze revealed that only 6 subjects (20.0%) had reached 100% re-epithelialization on Day 12. In the majority of subjects (80.0%) the re-epithelialization process continued past Day 12.

The Kaplan-Meier-estimates and their 95%-confidence intervals determined for the expected time to reach 100% re-epithelialization in areas treated with the wound healing ointment covered with the standard first aid dressing were 10 days (8.0, 10.0) and 10 days (10.0, 12.0) in areas treated with the wound healing ointment covered with gauze. For the traditional treatment with standard first aid dressing alone 12 days (10.0, -) were reported and for the treatment with gauze no interval could be obtained (-, -) (Table 2).

As illustrated in Fig. 5, the mean AUC regarding re-epithelialization calculated on scores assessed on Days 2, 6, 8, 10 and 12 showed a value of 33.6 ± 3.9 for the wound healing ointment covered with the standard first aid dressing and 24.3 ± 8.6 for the wound healing ointment covered with gauze. The test fields covered with standard first aid dressing alone and the untreated test fields covered with gauze displayed scores of 20.2 ± 4.2 and 4.1 ± 4.9, respectively.

The treatments utilizing the wound healing ointment covered with the standard first aid dressing or covered with gauze and the treatment using coverage with the standard first aid dressing alone showed significantly larger $AUCs_{Days\ 2–12}$ values than the treatment which applied only gauze. Compared with the untreated test fields covered with gauze only, the wound healing ointment covered with the standard first aid dressing or covered with gauze as well as the standard first aid dressing alone demonstrated significantly larger $AUCs_{Days\ 2–12}$ values (Table 2). For the test area treated with the wound healing ointment covered with the standard first aid dressing or covered with gauze no or only minor crust formation was reported. The test area treated with the standard first aid dressing alone, showed crust formation in 40% of subjects but only to a minor degree. The untreated test area covered with gauze displayed crust formation in all subjects. In 70% of subjects a much larger wound area was affected.

Both the investigator's and the subject's global assessments of the treatment with the wound healing ointment covered with the standard first aid dressing or covered with gauze were evaluated as 'very good' or 'good'. The rating was 'acceptable' for the test area covered the standard first aid dressing alone. In contrast, the untreated test area covered with gauze was mainly assessed as 'poor' at all points in time.

Regarding the investigator's global assessments of the treatment with the wound healing ointment covered with standard first aid dressing or covered with gauze the mean $AUCs_{Days2–12}$ were reported to be 0.7 ± 1.7 and 7.3 ± 5.1, respectively. The test fields covered with standard first aid dressing alone and the untreated test fields covered with gauze exhibited values of 10.0 ± 3.7 and 21.8 ± 2.9, respectively. Compared to the test fields covered with gauze the sites treated

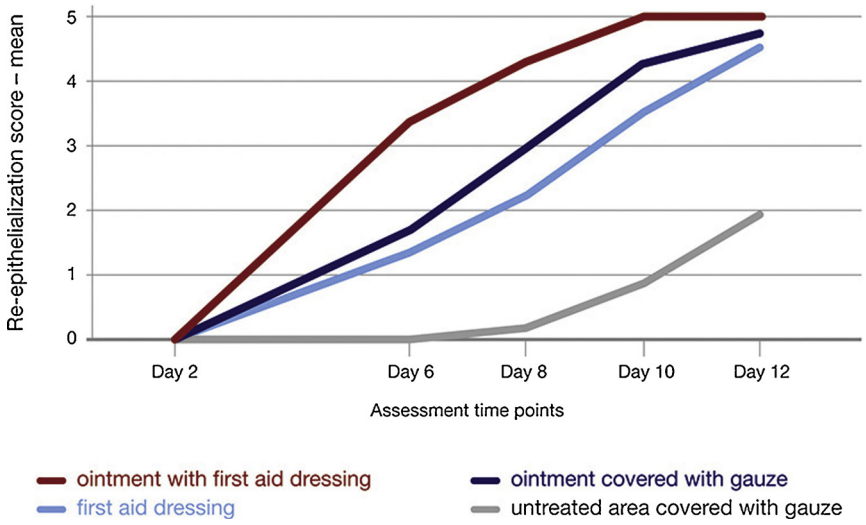

Fig. 4. Mean values for re-epithelialization assessed by the investigator using visual scoring on Days 2, 6, 8, 10 and 12. Scores from 0 to 5 indicate: 0 = no healing; 1 = resurfacing > 0 up to 25%; 2 = resurfacing > 25 up to 50%; 3 = resurfacing > 50 up to 75%; 4 = resurfacing > 75% but not complete; 5 = complete closure of surface 100%.

Table 1
Re-epithelialization assessed by the investigator: Mean re-epithelialization scores.

Treatment	Day 6 mean ± SD	Day 8 mean ± SD	Day 10 mean ± SD	Day 12 mean ± SD
Wound healing ointment covered with standard first aid dressing	3.4 ± 1.0	4.3 ± 0.6	5.0 ± 0.2	5.0 ± 0.0
Wound healing ointment covered with gauze	1.7 ± 1.3	3.0 ± 1.4	4.3 ± 1.1	4.7 ± 0.9
Untreated test field covered with standard first aid dressing	1.4 ± 0.6	2.2 ± 0.7	3.5 ± 0.8	4.5 ± 0.7
Untreated test field covered with gauze	0.0 ± 0.0	0.2 ± 0.6	0.9 ± 1.3	1.9 ± 2.1

with the wound healing ointment covered with the standard first aid dressing or covered with gauze or the standard first aid dressing alone displayed significantly lower $AUCs_{Days\ 2–12}$ scores. The treatment with the wound healing ointment covered with the standard first aid dressing or covered with gauze demonstrated significantly smaller $AUCs_{Days\ 2–12}$ values than the treatment with the standard first aid dressing alone (Table 3). The sum of scores on Days 2, 6, 8, 10 and 12 is presented in Fig. 6. As exemplarily shown for one subject in Fig. 7, faster wound healing was seen after application of the wound healing ointment.

3.3.2. Cosmetic outcome

The cosmetic outcome of the treatment with the wound healing ointment covered with the standard first aid dressing was rated by the investigator and subject as overall 'good to very good' (Fig. 8). The investigator assessed the cosmetic outcome for this test field as 'good to excellent' in 83.3%% of the subjects as did 76.6% of subjects.

The evaluation of the cosmetic outcome for the test field treated with the wound healing ointment covered with gauze resulted in an overall 'good to acceptable' whereas the treatment with the standard first aid dressing alone led an overall 'acceptable' rating. In contrast, the coverage of wounds with gauze alone lead produced an overall 'acceptable tending to poor' outcome.

The results of the patient questionnaires on product performance, which were assessed on day 12, revealed an excellent rating of product properties with agreements 86.7%–100% (Table 4).

4. Discussion

The occurrence of minor wounds is much more frequent than the incidence of chronic wounds. A study of 2000 people in Britain e.g. revealed that the average person experiences 5 cuts a year [11]. Usually, in superficial wounds it is assumed that the healing process progresses in a normal way and no guidelines regarding wound management exist [12]. But to accelerate re-epithelization and to minimize the risk of infection, a proper wound management is advised. For the successful treatment of minor everyday wounds, a dressing should be applied encouraging fast wound closure. However, the use of a standard first aid dressing alone provides conventional dry wound care only [12,13]. The investigational wound healing ointment containing established lipophilic and humectant ingredients which exert semi-occlusive characteristics creates a moist wound surface. By applying this wound healing ointment to the wound before the wound is covered with a standard first aid dressing a moist wound environment is created.

The goal of this clinical investigation was to assess the local tolerability and wound healing efficacy of the novel wound healing ointment with intra-individual comparison of 4 different regimens using an abrasive wound model. According to the investigator's clinical assessment, the wound healing ointment demonstrated excellent local tolerability. This evaluation was confirmed by the investigator's global assessment of tolerability. With respect to safety, no signs of wound infection and no adverse events were reported for any treatment.

Both treatments with the wound healing ointment showed significantly higher AUC values with respect to re-epithelialization and overall wound healing efficacy as compared to the test area treated with the standard first aid dressing alone and the untreated area covered with gauze. A faster onset of healing could be demonstrated for the investigational product. In the test field treated with the wound healing ointment covered with standard first aid dressing more than half of the patients displayed over 75% re-epithelialization after 5 days of treatment. On Day 12, 100%/90% wounds were completely closed in test areas treated with the wound healing ointment covered with the standard first aid dressing and the wound healing ointment covered with gauze. In the test field covered with the standard first aid dressing alone 60% of the patients displayed complete healing while in the untreated test area covered with gauze only 20% of the patients showed complete healing. These results are further supported by the fact that in contrast to the wound healing ointment-treated areas, where no or only minor crust formation was reported, the untreated test area covered with standard first aid dressing alone or gauze displayed crust formation in many subjects.

The process and characteristics of wound healing are similar in all tissues and not influenced by the nature of injury. Wound healing always leads to scar formation. Out of that reason, even in minor wounds deviations from the normal healing process may yield undesired cosmetic results. But under moist conditions, both the inflammatory and

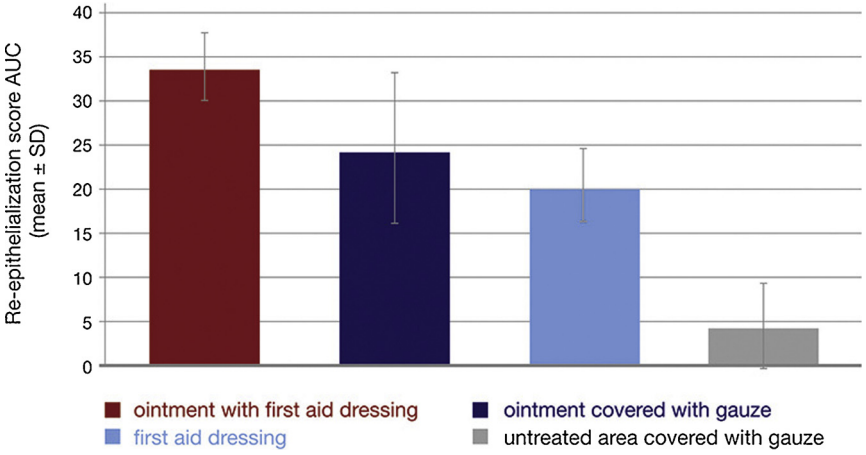

Fig. 5. Re-epithelialization assessed by the investigator. Mean AUC is calculated using the trapezoid form for scores on Days 2, 6, 8, 10 and 12 on the scale: 0 = 0% healing, 1 = 1–25% re-epithelialization, 2 = 26–50% re-epithelialization, 3 = 51–75% re-epithelialization, 4 = over 75% but not complete re-epithelialization, 5 = 100% complete healing. Possible values of AUC range from 0 to 50. Data are depicted as mean AUC ± SD.

Table 2
Re-epithelialization assessed by the investigator: Comparison between treatments regarding AUC.

Treatment	Difference to treatment	95%-Confidence interval	P-Value
Wound healing ointment covered with standard first aid dressing	Untreated test field covered with gauze	27.4, 31.7	< 0.0001
Wound healing ointment covered with gauze	Untreated test field covered with gauze	16.3, 24.1	< 0.0001
Untreated test field covered with standard first aid dressing	Untreated test field covered with gauze	13.8, 18.4	< 0.0001
Wound healing ointment covered with standard first aid dressing	Untreated test field covered with standard first aid dressing	1.0, 7.3	0.0122
Wound healing ointment covered with gauze	Untreated test field covered with standard first aid dressing	11.5, 15.4	< 0.0001

Table 3
Global wound healing assessed by the investigator: Comparison between treatments regarding AUC.

Treatment	Difference to treatment	95%-Confidence interval	P-Value
Wound healing ointment covered with standard first aid dressing	Untreated test field covered with gauze	−22.2, −19.9	< 0.0001
Wound healing ointment covered with gauze	Untreated test field covered with gauze	−17.0, −12.1	< 0.0001
Untreated test field covered with standard first aid dressing	Untreated test field covered with gauze	−13.4, −10.1	< 0.0001
Wound healing ointment covered with standard first aid dressing	Untreated test field covered with standard first aid dressing	−4.9, −0.6	0.0131
Wound healing ointment covered with gauze	Untreated test field covered with standard first aid dressing	−10.5, −8.1	< 0.0001

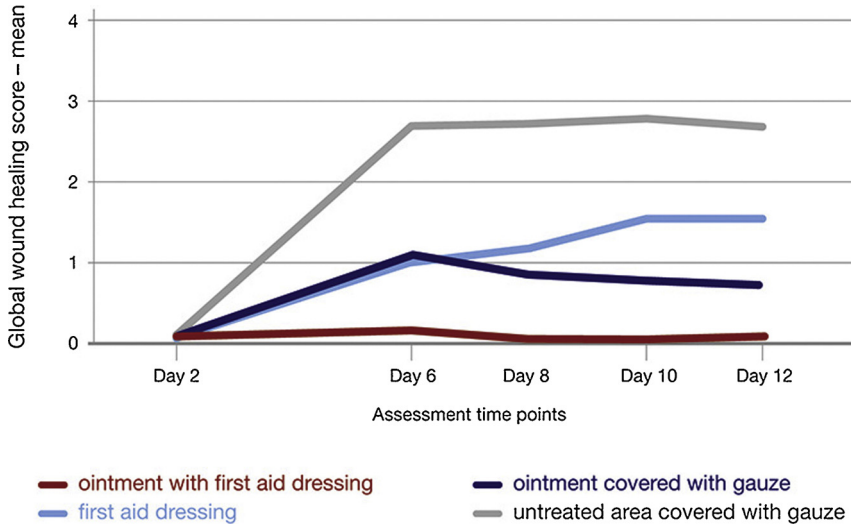

Fig. 6. Global wound healing assessed by the investigator. Global wound healing score: 0 = very good, 1 = good, 2 = acceptable, 3 = poor, 4 = very poor. Data are depicted as mean AUC ± SD. Significant differences are marked with an asterisk (*p ≤ 0.05, **p ≤ 0.001).

proliferative phases in wound healing are believed to be accelerated [14] leading to the formation of cosmetically more appealing scars [4,15,16].

Regarding the cosmetic outcome, the wound healing ointment covered with the standard first aid dressing and the wound healing ointment covered with gauze were graded as superior to the standard first aid dressing alone or the untreated test area covered with gauze by both the investigator and the subject.

These results are in line with research demonstrating that wounds that are kept moist show faster re-epithelialization, accelerated healing as well as a better cosmetic result compared to wounds that are exposed to air or dressed with conventional gauze [4,17].

However, the lack of a comparison between the new wound healing ointment and a well-established standard reference product might be regarded as a limitation to our investigation. On the one hand, the abrasive brush technique creates uniform and identical standardised wounds making it possible for each subject to receive all 4 treatment regimens and at the same time function as their own control. On the other hand, this clinical procedure represents a limitation to the investigation by providing optimal hygiene and thereby decreasing the risk of infection. Also, it should be mentioned that it was not possible to blind the subjects to the different treatment regimens.

5. Conclusion

Superficial cutaneous wounds treated with the novel wound healing ointment showed a significant improvement of wound healing. The best wound healing properties were seen for the wound healing ointment covered with the standard first aid dressing, followed by treatment with the wound healing ointment covered with gauze. These well tolerated treatment regimens showed the fastest onset and a better outcome of wound healing with superior rates of re-epithelialization and overall cosmetic outcome compared to traditional treatment (standard first aid dressing alone or gauze) providing a dry healing environment.

In conclusion, it could be demonstrated that minor, superficial wounds benefit from the moist wound healing conditions exerted by the novel wound healing ointment as shown by a clinically relevant accelerated wound healing in combination with a superior cosmetic outcome.

Declaration of interest

This clinical investigation was funded by Beiersdorf AG, Germany. Neither author has any interest in the sponsor's commercial activities.

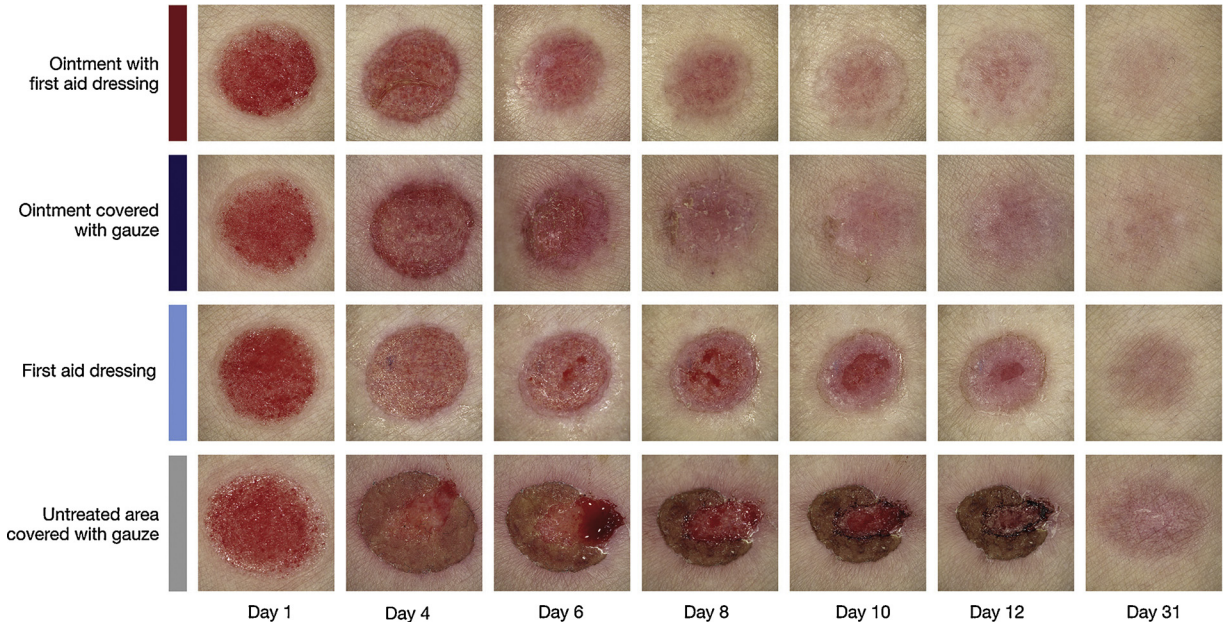

Fig. 7. Example photographic documentation.

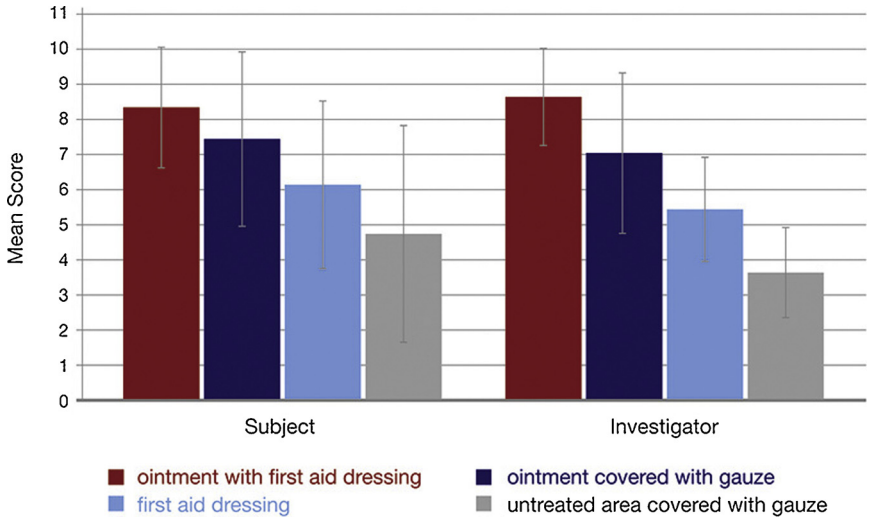

Fig. 8. Assessment of cosmetic outcome on a visual analogue scale (VAS) ranging from 0 (poor) to 10 (excellent) on Day 31 ± 2 – by subject and investigator. Data are depicted as mean ± SD.

Table 4
Results of patient questionnaires on product performance on Day 12.

Wound healing ointment	Wound healing ointment + standard first aid dressing	Wound healing ointment + gauze
… is easy and comfortable to spread / distribute over the wound	86.7%	86.7%
… supports pain free healing of the wound	96.7%	96.7%
… protects the wound reliably	100.0%	96.7%
… leaves a pleasant feeling after application	96.7%	96.7%
… provides good healing conditions compared to untreated test area	96.7%	96.7%
… provides good healing conditions compared to standard first aid dressing alone	96.7%	90.0%
… is suitable for regular use for the treatment of minor wounds	96.7%	96.7%
I am overall satisfied with the efficacy of the cream	100.0%	96.7%

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