2 SYNOPSIS

Sponsor: **MEDICE** **Arzneimittel Pütter** **GmbH & Co. KG** **Name of Finished Product:** Soventol® Wund- und Heilgel	*(For national Authority Use only)*
Name of Active Ingredients: none	

Title of Study:	A monocentric, observer-blind, randomized clinical study using an abrasive wound model with an intra-individual comparison to investigate the wound healing properties of a topical wound healing product in comparison to untreated and a reference product in 36 healthy subjects	
Principal Investigator:	Dr. med. Kirstin Deuble-Bente, D-22869 Schenefeld/Hamburg	
Investigators:	Dr. med. A. Heilemann	
Study Center(s):	proDERM Institut für Angewandte Dermatologische Forschung GmbH, Kiebitzweg 2, 22869 Schenefeld	
Publication (Reference):	---	
Phase of Development:	Not applicable	
Studied Period	Date of First Enrollment: 18JUN2014	Date of Last Terminated: 17JUL2014
Objectives:	<u>Primary Objective</u> The primary objective was the comparison of the investigational product versus untreated on the size of the open wound area/crusts assessed by quantitative image analysis at the different assessment time points (Area Under the Curve (AUC) over time on relative differences to Baseline). <u>Secondary Objectives</u> • Comparisons of reference product versus investigational product and versus untreated on the size of open wound area/crusts assessed by quantitative image analysis at the different assessment time points (AUC over time on relative differences to Baseline). • Pair-wise comparisons of the investigational product, reference product and untreated area on relative differences to Baseline of size of open wound area/crusts assessed by quantitative image analysis at each post-treatment assessment time point.	

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- Comparisons of size of open wound area/crusts assessed by quantitative image analysis at each post-treatment assessment time point versus Baseline for each treatment separately.
- Pair-wise comparisons of investigational product, reference product and untreated area on original/actual wound margin area (AUC over time calculated on ratio to Baseline wound area).
- Pair-wise comparisons of investigational product, reference product and untreated area on original/actual wound margin area (ratio to Baseline wound area) at each post-treatment assessment time point.
- Pair-wise comparisons of investigational product, reference product and untreated area on wound healing assessed by visual scoring at each assessment time point.
- Descriptive statistics (counts and frequencies) for visual assessment scores of inflammation/infection or allergy.
- Descriptive statistics (counts and frequencies) for discontinuations due to a score ≥ 3 for inflammation/infection and allergy.
- Descriptive statistics for quantity of product usage.
- Documentation and analysis of safety parameters.

Methodology:	Monocentric, randomized, observer-blind, intra-individual comparison	
Number of Subjects:	Enrolled: 42	Analyzed: 33 (FAS) 33 (PP)
Diagnosis and Main Criteria for Inclusion:	Male and female subjects with healthy skin (age 18-55) and Fitzpatrick skin type I to III	
Test Products and Batch Numbers:	Soventol® Wund- und Heilgel / Batch No. 5859 Bepanthen® Wund- und Heilsalbe / Batch No. 5859	
Method and Mode of Application:	<u>Induction of abrasive wounds:</u> Three standardized superficial abrasive wounds were induced at the left forearm with an autoclaved hand brush on three different test areas with a diameter of approx. 1 cm each (with a distance from each other of at least 2 cm).	

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	Application of test products: The investigational and reference products were applied twice daily (mornings and evenings) on the abrasive wounds on the left volar forearm. The test areas were then covered with a standard plaster. On study days with visits at the test center (Days 1, 3, 5, 8, 9, 10, and 12) the first daily application was done by a technician after instrumental measurements and visual assessments. The second daily application was done by the subjects at home (evening). On Days 2, 4, 6, 7, 11, 13, and 14 the test products were applied by the subjects themselves at home according to the instruction by a technician. Applications were always performed between 8 and 11 a.m. in the morning and 8 and 11 p.m. in the evening.	
Duration:	Duration of treatment: 14 days	Duration of study: 15 days
Instrumental Measurements:	Digital Photography: Pictures were taken after induction of the wounds and at each visit at the test center after removal of the standard bandages. Afterwards the open wound area (including areas covered with a crust) was marked on the picture and the size of the open wound area (including area with the crust) was calculated. Additionally, the original wound margin was marked and the size of the actual wound was calculated. Images of the wounds were taken with a handheld camera equipped with a ring flash as well as a tubular distance holder (complete extinction of light) to enable reproducible images with defined magnification. The captured test area was 3 cm in diameter. Relative change in the size of the wound was used as primary parameter.	
Assessment(s):	At study Days 1, 3, 5, 8, 9, 10, 12 and 15 (+ 1) wound healing was assessed according to visual scoring: 0 = No healing 0 % 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 %	

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Possible inflammations/infections were assessed at each visit at the test center regarding the signs (all signs were assessed together) erythema, pain, odor, non-healing, excessive exudates and hyperthermia according to the following scale:

0 = no
1 = mild
2 = moderate
3* = strong
4* = very strong

*In case of skin reactions ≥ 3 the respective test product application had to be discontinued. The last observation before discontinuation had to be carried forward for analysis (LOCF).

Possible allergic reactions were assessed at each visit regarding signs (all signs had to be assessed together) of erythema, edema and itching according to the following scale:

0 = no
1 = mild
2 = moderate
3* = strong
4* = very strong

*In case of skin reactions ≥ 3 the respective test product application had to be discontinued. The last observation before discontinuation had to be carried forward for analysis (LOCF).

Plan for Data Analysis / Statistics:

Primary endpoint:

The size of the open wound area (including area covered with crusts) was determined for defined time points by quantitative image analysis. The relative difference to Baseline was calculated. AUCs from Day 3 to Day 15 were calculated with the trapezoid formula for the three treatments on these relative differences to Baseline. The statistical analysis for the primary objective was done on the AUC values.

Secondary endpoints:

Relative differences to Baseline for open wound areas (including area covered with crusts) and actual wound size assessed by quantitative image analysis.

Original wound margin area ratio to Baseline wound size and AUC for original wound margin area ratio to Baseline wound size from Day 3 to Day 15 calculated with the trapezoid formula for

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	the three treatments. Visual assessment of wound healing at post treatment time points. Inflammation/infection and allergy signs at all time points.
Safety:	• Physical examination focused on the skin • Signs of inflammation/infection • Signs of allergic skin reactions • Monitoring of blood pressure and heart rate • HIV and Hepatitis testing • Documentation of adverse events • Pregnancy test (for women of child bearing potential)
Results:	The mean open wound area/crusts of the treatment areas were similar at Baseline with 0.896 cm^2 (investigational product), 0.901 cm^2 (reference product) and 0.910 cm^2 (untreated). The Bravais-Pearson coefficient of correlation was calculated between Baseline values and the AUC for each treatment. The absolute values of the Bravais-Pearson coefficient of correlation was clearly lower than 0.6 for the investigational product (0.18), the reference product (0.25) and for untreated (0.01) indicating that there was no sign for an influence of varying Baseline wound areas on AUC. A check for an effect of change of the type of bandage on treatment effect was done by ANOVA. The results showed no significant interaction between bandage group and treatment. At Day 15 the wounds treated with the investigational product were completely closed (quantitative image analysis) and the wounds treated with the reference product were almost closed (remaining wound area of 0.003 cm^2), while the remaining mean open wound area of the untreated wounds was 0.075 cm^2. The remaining open wound areas/crusts of the investigational product treated and the reference product treated areas were similar in size and the untreated wounds showed markedly larger remaining wound area/crusts. **Primary Objective** When comparing the AUC on relative differences to Baseline of the investigational product versus untreated over all assessment time points and for each assessment separately, lower p-values than

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0.01 were observed for the comparison of the investigational product vs. untreated.

Secondary Objectives

The reference product was compared to untreated and to the investigational product regarding relative differences to Baseline at all assessment time points and AUC for open wound area/crusts by quantitative image analysis at all assessment time points. p-values lower than 0.01 indicate differences in treatments. This was observed for the comparison of the reference product vs. untreated at all assessment time points, while there was no evidence for differences between the reference product and the investigational product at any assessment time point.

Lower mean values with a p-value < 0.001 were found for all assessment time points on wound areas treated with the investigational product and reference product and for the untreated area in comparison to Baseline.

The highest AUC, for original/actual wound margin area, with 1010.20 was found for the test areas treated with the investigational product, the second highest AUC with 982.72 for test areas treated with the reference product and the third highest AUC with 883.95 for the untreated test area. A significantly higher mean value for AUC values for the areas treated with the investigational product and with the reference product in comparison to untreated areas was seen. No statistically different AUC between the investigational product and the reference product was found.

The comparison of the investigational and the reference product on original/actual wound margin area at post-treatment time points showed better results for the investigational product at Day 9, Day 10, Day 12 and Day 15. Further the comparison to untreated showed better results for the investigational product at Day 3, Day 8, Day 9, Day 10, Day 12 and Day 15.

Visual scoring of wound healing showed identical values for the investigational product and the reference product with a complete closure of the surface from Day 10 on. A difference between the investigational product vs. untreated and the reference product vs. untreated was analyzed at Day 5, Day 8, Day 9, Day 10, Day 12, and Day 15. There was no indication for a difference in favor of the investigational product in comparison to the reference product.

Average product usage for the investigational product was 6.5 g, while for the reference product 4.0 g was used.

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Safety:	A total of 98 nonserious AEs, on one or multiple test areas, were documented for 31 subjects. No serious AE occurred. All but one AE were of mild severity, while one AE (sprain of right knee) was judged as of moderate severity. All but one subject recovered without sequelae, in one subject (sprain of right knee) the condition was improving and no follow-up was necessary. A possible relation to the treatment procedures was seen in 86 cases (signs of inflammation/infection and signs of allergic reactions). Since in this study abrasive wounds were induced, it is difficult to differentiate between an adverse reaction against the treatment procedures (including treatment with the investigational and reference product) and a reaction due to the induction of the wounds. Adverse effects due to the wound induction were expected (see protocol, section 12.2.3) and a specific score was therefore designed to quantitate these effects. The intensity of the events of inflammation/infection and signs of allergy were mild (score 1) or in rare circumstances moderate (score 2) and occurred mostly at the beginning, as expected. Unexpectedly another peak of occurrence could be observed around treatment days 9 and 10, which might be a hint that some of the events were more likely caused by trial course related examinations. Otherwise no higher safety risk for treated areas compared to untreated areas could be found. There were no relevant changes in pulse rate and blood pressure between Screening and Termination. All female women of childbearing potential had a negative pregnancy test at Screening and at Termination.
Conclusions:	Better results for wound healing were seen after application of the investigational product compared to untreated as measured by quantitative image analysis. Further, the comparison to untreated area showed better wound healing for the reference product by quantitative image analysis and for both treated areas by visual scoring. Although the investigational product performed slightly better in its ability to promote wound healing compared to the reference product, differences between the two products in favor of the investigational product were not statistically different (open wound area/crusts).

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Contraction of the wound is an unwanted effect in wound healing.

The comparison of post-treatment assessment time points for original/actual wound margin area (ratio between original and actual) showed differences between the investigational product and the reference product in favor of the investigational product at Day 9, Day 10, Day 12 and Day 15, indicative of reduced contraction of the wound areas.

A total of 98 nonserious AEs, on one or multiple test areas, occurred in 31 subjects. The majority of these AEs showed signs for inflammation/infection and signs for allergy. No higher safety risk for treated areas compared to untreated areas could be found.