Clinical Study Report

Sponsor:	**Almirall Hermal GmbH**
Study no.:	**H552000-0809/280502BS**
EudraCT-no.:	**2008-003362-26**
Title:	A phase IIa single-center, randomized, controlled, observer-blind study to investigate the antimicrobial efficacy of topical formulations containing octenidine and prednicarbate in an “expanded flora test” with healthy subjects
Study preparation:	**Study preparations:** 1) Octenidine cream (0.1 % octenidine) 2) Octenidine cream (0.25 % octenidine) 3) Octenidine/Prednicarbate cream (0.1 % octenidine, 0.25 % prednicarbate) 4) Active ingredient-free vehicle to study preparations 1-3 **Controls:** 1) Octenisept® (0.1 % octenidine, 2 % phenoxy ethanol) 2) Two untreated test fields
Clinical phase:	**IIa**
Indication:	Testing whether topical formulations containing octenidine and octenidine plus prednicarbate exerted an in vivo antibacterial action on skin surface bacteria multiplied by occlusion using the "expanded flora test”
Description:	This single-center study was controlled and observer-blind with random assignment of the treatments to the test fields. The study was performed in 20 male or female subjects with healthy skin in the test area. There were no drop outs. All 20 subjects were included in the intention-to-treat (ITT) and the per-protocol (PP) analyses. All subjects received all treatments. Altogether seven test areas on the back were occluded for 24 hours. Then 50 µl of the study preparations and controls were applied once per test area. Two occluded areas were left untreated as negative controls. After another 24 hours of occlusion the superficial flora was extracted and the number of CFUs (Colony forming units) of the skin surface bacteria was evaluated.
Principal Investigator:	[redacted], bioskin GmbH Burchardstrasse 17, 20095 Hamburg, Germany [redacted]
Clinical Trial Manager:	[redacted] bioskin GmbH Burchardstrasse 17, 20095 Hamburg, Germany [redacted]
Project Manager Sponsor:	[redacted] Almirall Hermal GmbH Scholtzstrasse 3, 21465 Reinbek, Germany [redacted]
GCP Compliance:	The study was conducted in compliance with Good Clinical Practice incl. the archiving of essential documents.
Study dates:	September 29 to October 9, 2008
Date of Report:	February 16, 2009

2. Synopsis

Name of Company: Almirall Hermal GmbH	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: n.a.		
Name of Active Ingredient: Octenidine, Octenidine plus Prednicarbate		

Title of Study:
A phase IIa single-center, randomized, controlled, observer-blind study to investigate the antimicrobial efficacy of topical formulations containing octenidine and prednicarbate in an “expanded flora test” with healthy subjects

Investigator(s):
[redacted]

Study center(s):
bioskin GmbH, Hamburg, Germany

Publication (reference):
Not applicable to this study

Studied period (years):	Phase of development:
2008	IIa

Objectives:
Testing whether topical formulations containing octenidine and octenidine plus prednicarbate exert an in vivo antibacterial action on skin surface bacteria multiplied by occlusion using the "expanded flora test”.

Methodology:
Altogether seven test areas on the back were occluded for 24 hours. Then 50 µl of the study preparations and controls were applied once per test area. Two occluded areas were left untreated as negative controls. After another 24 hours of occlusion the superficial flora was extracted and the number of CFUs (Colony Forming Units) of the skin surface bacteria was evaluated.

Number of subjects (planned and analyzed):
Twenty male or female subjects were included in the study. There were no drop outs. All 20 subjects were included in the ITT and the PP analyses.

Diagnosis and main criteria for inclusion:
Subjects with healthy skin in the area of the test fields, aged 18 to 45 years

Test product(s), dose and mode of administration, batch number:
1) Octenidine cream (0.1 % octenidine), batch no.: K0552/11
2) Octenidine cream (0.25 % octenidine), batch no.: K0552/71
3) Octenidine/Prednicarbate cream (0.1 % octenidine, 0.25 % prednicarbate), batch no.: K0552/21
4) Active ingredient-free vehicle to study preparations 1-3, batch no.: K0552/31
single topical occlusive application of approximately 50 µl formulation per test field (2.0 cm²)

Duration of treatment:
24 hours

Reference therapy or controls, dose and mode of administration, batch number:
1) Octenisept® (0.1 % octenidine, 2 % phenoxy ethanol), batch no.: 908K0187
single topical occlusive application of approximately 50 µl formulation per test field (2.0 cm²)
2) Two untreated test fields

Duration of treatment:
24 hours

2. Synopsis (continued)

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Criteria for evaluation:

Primary efficacy variable: Colony forming unit counts for skin surface bacteria was the primary variable.

Safety: Medical history and physical examination, recording of adverse events.

Statistical Methods:

Analyses populations

The Safety Set included all subjects who received any trial medication at least once; all safety analyses based on the Safety Set.

The Full Analysis Set included all randomized subjects who received at least one dose of study medication, and had a valid assessment of the primary parameter. The intention-to-treat (ITT) analysis was based on the Full Analysis Set.

The Valid-Cases Set included all subjects in the Full-Analysis Set, excluding subjects with major protocol violations or significant protocol deviations.

Major protocol violations included but were not limited to:

- inappropriate enrollment
- the use of prohibited concomitant medication
- reaching a major exclusion criterion during the trial

Significant protocol deviations included:

- identified protocol violations or significant deviations during the “Subject Data Inclusion” meeting

The per-protocol (PP) analysis was based on the Valid-Cases Set.

Statistical methods

Analysis variables

Subject characteristics:

- Demographic and background characteristics
- Concomitant medications

Efficacy part:

- Colony forming unit counts for skin surface bacteria is the primary variable

Safety data:

- Adverse events
- Physical examination
- Vital signs

Analysis of subject characteristics

Demographic and background data were summarized using descriptive statistical methods. Continuous data were summarized by mean, standard deviation, median and range. Categorical demographic data were summarized by frequency tables. Concomitant medications were listed only.

Analysis of efficacy data

The number of bacteria calculated for the test areas were given in relation to the average number of germs from the two negative control fields. Since bacteria numbers could be considered to have a logarithmic normal distribution, the bacteria numbers were expressed as logs.

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Statistical Methods (continued):

Per volunteer and test area the primary parameter was then calculated as:

Z = log (average of the bacteria number from the control fields +1)
– log (number of bacteria from test area + 1)

The primary variable was summarized by descriptive statistics (number of valid values, mean, standard deviation, median, interquartile range, minimum and maximum) for each treatment group.

The study preparations were compared with respect to the mean of the primary parameter. The null hypthesis

H_{01}: The two study preparations do not differ in their mean effectiveness

was tested against the alternate hypothesis:

H_{11}: The two study preparations differ in their mean effectiveness.

The two-sided hypotheses were tested applying the paired t-test at a significancy level of 5%. The following comparisons were performed:

1.	Octenidine cream (0.1 % octenidine)	vs.	Active ingredient-free vehicle
2.	Octenidine cream (0.25 % octenidine)	vs.	Active ingredient-free vehicle
3.	Octenidine/Prednicarbate cream (0.1 % octenidine, 0.25 % prednicarbate)	vs.	Active ingredient-free vehicle
4.	Octenisept® (0.1 % octenidine, 2 % phenoxy ethanol)	vs.	Active ingredient-free vehicle

Analysis of safety data

Tables with adverse events were presented as appropriate.

Vital signs were summarized by time point with number of valid values, mean, standard deviation, median, interquartile range, minimum and maximum. Physical examination outcomes were listed only.

Determination of sample size

It was planned to recruit 20 volunteers for this clinical study. The determination of the sample size was not based on biometric considerations. In the past a sample size of 18 had proved sufficient to uncover clinically relevant differences between formulations.

2. Synopsis (continued)

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Summary, conclusions:

Efficacy results:

Under the conditions in this "expanded flora test" with modified occlusion times all three active study preparations containing octenidine and octenidine plus prednicarbate exerted an in vivo antibacterial action on skin surface bacteria.

The greatest antimicrobial effect was noted for Octenidine cream 0.25 % (mean Z = 4.14).

A comparable, somewhat lower reduction of the number of CFUs (Colony forming units) of skin surface bacteria was noted for Octenidine cream 0.1 % and the combination Octenidine 0.1 %/Prednicarbate 0.25 % cream (mean Z = 2.75 and 2.87, respectively). The antimicrobial effect of these two formulations was comparable to the marketed product Octenisept® (mean Z = 2.80).

No relevant effect on skin surface bacteria was noted for the active ingredient-free vehicle (mean Z = -0.21).

In the statistical comparisons all four active formulations showed significantly greater mean log untreated control corrected numbers of bacteria per skin surface (mean Z-values) than the active ingredient-free vehicle ($p < 0.0001$, respectively).per skin surface (mean Z-values) than the active ingredient-free vehicle ($p < 0.0001$, respectively).

Safety results:

There were no adverse events or other relevant observations related to safety in this study.

Conclusion:

The aim of the study was to investigate the antimicrobial efficacy of topical formulations containing octenidine and prednicarbate in an "expanded flora test" in healthy subjects.

The three study preparations (Octenidine cream 0.25 % and 0.1 % and the combination Octenidine 0.1 % /Prednicarbate 0.25 % cream) exerted a clear, significant in vivo antibacterial action on skin surface bacteria under the conditions in this study. In this "expanded flora test" a bacterial reduction of 2 to 4 magnitudes was found which reflects a clear antibacterial action according to literature (3).

The study preparation with the highest octenidine concentration, Octenidine cream 0.25 %, showed the greatest antimicrobial effect with a bacterial reduction of 4 magnitudes.

A comparable, somewhat lower antimicrobial effect (reduction of 2 – 3 magnitudes) was noted for the two other study preparations with 0.1 % octenidine alone or in combination (Octenidine cream 0.1 %, the combination Octenidine 0.1 %/Prednicarbate 0.25 % cream). The reduction in skin surface bacteria of these two formulations was comparable to the reducing effect seen for the control Octenisept®. Both study preparations containing 0.1 % octenidine revealed a clear antibacterial action which was in the same range as the marked Octenisept® (0.1 % octenidine, 2 % phenoxy ethanol).

No relevant effect on skin surface bacteria was noted for the active ingredient-free vehicle. The number of skin surface bacteria was comparable to the untreated field (approx. 10^7, both). This was in accordance with the dense flora after 48 hours occlusion described in the respective literature (2).

There were no safety concerns based on the results of this study.

Date of the report: February 16, 2009