Clinical Study Report

Sponsor:	Almirall Hermal GmbH
Trial No.:	**H 552 000-0920 / 290505BS**
EudraCT-No.:	2009-016627-56
Title:	A phase IIa, multi-center, randomized, double-blind trial to evaluate the anti-mycotic and anti-inflammatory efficacy of topical combinational product LAS 41003 versus corresponding mono-substances in patients with candida infections in intertriginous areas at the trunk
Investigational Medicinal Product/s (IMPs):	**IMP 1:** Octenidine/prednicarbate cream (0.25 % octenidine, 0.25 % prednicarbate) **IMP 2:** Octenidine cream (0.25 % octenidine) **IMP 3:** Prednicarbate cream (0.25 % prednicarbate)
Clinical Phase:	IIa
Objectives:	To assess the efficacy of a combined octenidine/prednicarbate cream in comparison to creams with prednicarbate or octenidine alone after once daily treatment over a 2-week period in patients with inflammatory candida infections in intertriginous areas
Description:	This phase IIa trial was performed as a multi-center (six centers), randomized and double-blind trial with three parallel groups. In total, 137 male or female patients aged 18 years or older with candida infections in intertriginous areas on the trunk were included in this trial to determine the efficacy of a combined octenidine/prednicarbate cream in comparison to creams with prednicarbate or octenidine alone. Data of all 137 patients were valid for the safety and intent-to-treat (ITT) analyses. Ninety-four patients were included in the modified intent-to-treat (MITT) analysis. The MITT did not include delayed exclusions, i.e. patients who were found to have a negative baseline culture for mycology following randomization. There were 43 patients who prematurely discontinued the trial and were excluded from the MITT. All were symptomatic patients with negative culture for mycology. In addition, for two of them another reason for discontinuation was given (withdrawal of consent and protocol violation). Eighty-eight patients were valid for the per-protocol (PP) analysis. The 43 discontinued patients and a further six patients who were outside the time window for the Day 15 visit were excluded from the PP analysis. Treatment was performed in all affected intertriginous areas on the trunk once daily over a 2-week treatment period. Physician's assessment of signs and symptoms and physician's global assessment of the intertriginous areas were done on Days 1, 8 and 15. Samples for culture for mycology were taken on Days 1, 8 and 15. Pictures of all treated regions were taken for photographic documentation on Days 1 and 15.
Coordinating Investigator:	[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 clinical trial was conducted in compliance with Good Clinical Practice incl. the archiving of essential documents.
Trial Period:	10 February 2010 to 08 July, 2011
Date of Report:	23 March 2012

2. Synopsis

Name of Company: Almirall Hermal GmbH	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Not applicable (n.a.)	Volume: Page:	
Name of Active Ingredient: Octenidine, prednicarbate		

Title of Study:	
A phase IIa, multi-center, randomized, double-blind trial to evaluate the anti-mycotic and anti-inflammatory efficacy of topical combinational product LAS 41003 versus corresponding mono-substances in patients with candida infections in intertriginous areas at the trunk	
Investigator(s):	
The coordinating investigator was [redacted], bioskin GmbH, Burchardstrasse 17, 20095 Hamburg, Germany A list and description of investigators can be found in appendix 16.1.4.	
Study center(s):	
Six study centers in Germany	
Publication (reference):	
Not applicable to this trial	
Studied period (years): 2010-2011	Phase of development: IIa
Objectives:	
To assess the efficacy of a combined octenidine/prednicarbate cream in comparison to creams with prednicarbate or octenidine alone after once daily treatment over a 2-week period in patients with inflammatory candida infections in intertriginous areas	
Methodology:	
Application of approximately 2 - 3 mg per cm^2 of one of the three preparations once daily to all intertriginous areas on the trunk were performed by the patients at home or in the case of inpatients, this would be by a study nurse at the clinic once daily over a 2-week treatment period. No treatment had to be performed before the assessment at the center on Days 8 and 15. Physician's assessment of signs and symptoms and physician's global assessment of the intertriginous areas were done on Days 1, 8 and 15. Samples for culture for mycology were taken on Days 1, 8 and 15. Pictures of all treated regions were taken for photographic documentation on Days 1 and 15.	
Number of subjects (planned and analyzed):	
Ninety-six male or female patients were planned in three groups of 32 patients each. In reality a total of 137 patients were randomized. Octenidine/prednicarbate cream group: The data from 48 randomized patients were used for the safety and ITT analyses. Fifteen patients were excluded from the MITT analysis, which was therefore performed on 33 patients. There were two additional patients who were outside the time window on Day 15 and therefore excluded from the PP analysis. The data from 31 patients were valid for the PP analysis. Octenidine cream group: The data from 44 randomized patients were used for the safety and ITT analyses. Sixteen patients were excluded from the MITT analysis, which was therefore performed on 28 patients. There were three additional patients who were outside the time window on Day 15 and therefore excluded from the PP analysis. The data from 25 patients were valid for the PP analysis. Prednicarbate cream group: The data of 45 randomized patients were used for the safety and ITT analyses. Twelve patients were excluded from the MITT analysis, which was therefore performed on 33 patients. There was one additional patient who was outside the time window on Day 15 and therefore excluded from the PP analysis. The data of 32 patients were valid for the PP analysis.	
Diagnosis and main criteria for inclusion:	
Male or female patients aged 18 years or older were eligible for this trial if they suffered from candida infections in intertriginous areas confirmed by a positive culture for mycology.	

2. Synopsis (continued)

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Test product(s), dose and mode of administration, batch number:

IMP 1: Octenidine/prednicarbate cream (0.25 % octenidine, 0.25 % prednicarbate)
IMP 2: Octenidine cream (0.25 % octenidine)
IMP 3: Prednicarbate cream (0.25 % prednicarbate)

All IMPs had the same batch numbers (double-blind). Depending on time of shipment these were: 001kk03, 017kk04, 038k05 or 104k06.

Topical application of approximately 2 - 3 mg/cm^2 (up to approximately 2 g) formulation to all lesions on the trunk once daily

Duration of treatment:

2-week treatment period (14 treatments)

Reference therapy or controls, dose and mode of administration, batch number:

n.a.

Duration of treatment:

n.a.

Criteria for evaluation:

Primary efficacy variable: Treatment success (= negative culture for mycology and clinical success – see below for definition)

Secondary efficacy variables:

- Physician's assessment of signs and symptoms
- Physician's global assessment score (PGA)
- Total clinical score
- Change from baseline in total clinical score
- Culture
- Clinical success

These were scored as follows:

Physician's assessment of signs and symptoms

The overall (i.e. considering all affected areas) severity of each individual sign and symptom (erythema, papules, pustules and maceration) was assessed by the investigator according to the following 4-point scale (5):

0 = absent (normal)
1 = mild (barely abnormal)
2 = moderate (distinctly abnormal)
3 = severe (intense involvement or marked abnormality)

Physician's global assessment (PGA) score

The physician's global assessment was performed according to the following 4-point scale:

0 = clinical cure/clear: normal appearance of the target lesion. No signs and symptoms perceptible.
1 = almost clear: trace evidence of existent disease. At most, mild residual erythema and/or mild scaling notable without other signs and symptoms.
2 = notable signs and symptoms exist.
3 = prominent signs and symptoms exist.

2. Synopsis (continued)

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Criteria for evaluation (continued):

Mycologic assessment by microscopy and culture

The mycological assessment was performed on samples taken from a target lesion defined on Day 1. Photographic documentation of the agar plates was performed at the time point of evaluation.

For each patient and each visit the following variables were determined:

- Total clinical score was defined as the sum of all sign and symptom scores (erythema, papules, pustules and maceration)
- Change from baseline in total clinical score was determined by subtracting the baseline value from all post baseline assessments
- Culture:
  - negative = no fungi found
  - positive = fungi found
- Clinical success:
  - clinical success = all clinical sign and symptom scores ≤ 1 and total clinical score ≤ 3
  - no clinical success = any clinical sign and symptom score > 1 or total clinical score > 3
- Treatment success:
  - treatment success = culture negative and clinical success
  - no treatment success = culture positive or no clinical success.

Safety variables

- Medical history
- Physical examination including vital signs (blood pressure and pulse rate)
- Urine pregnancy test in female patients
- Recording of AEs

Statistical Methods

Study populations

Intent-to-treat (ITT)

The ITT population consisted of all randomized patients who received at least one dose of IMP and had at least one post-baseline assessment.

Modified intent-to-treat (MITT)

The MITT population consisted of all ITT patients who had positive culture results for mycology at baseline and who were dispensed drug. The MITT population did not include delayed exclusions, i.e. those patients who were found to have a negative baseline culture for mycology following randomization. (Note: patients were randomized based on investigator's baseline clinical assessment and the culture results for mycology were not available at time point of randomization.) The MITT analysis was based on the MITT population.

2. Synopsis (continued)

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Statistical Methods (continued):

Per-Protocol (PP)

The PP population comprised the MITT patients after excluding those patients with major protocol violations, including patients:

- with any major violation of inclusion criteria;
- who missed more than two treatments, except for treatment discontinuation due to treatment related adverse events or lack of efficacy;
- who were outside the time window (±1 day) for the Day 15 visit;
- with any missing values of the primary variables, i.e. with no imputed values except for treatment discontinuation due to treatment related adverse events or lack of efficacy.

The PP analysis was based on the PP population.

Safety population

The safety population consisted of all randomized patients who received at least one dose of any IMP. All safety analyses were based on this population.

Efficacy analyses

Statistical analyses

The MITT analyses were considered primary. The PP analyses were considered supportive.

The variables treatment success, culture for mycology, clinical success, physician's global assessment score and physician's assessment of individual signs and symptoms were summarized by treatment and visit providing frequencies and rates. Additionally, the physician's assessment of individual signs and symptoms was summarized providing standard descriptive statistics. For the total clinical score and physician's global assessment score the changes from baseline were determined and summarized by means of descriptive statistics.

Pairwise differences between Octenidine/prednicarbate cream and its active ingredients octenidine cream and prednicarbate cream with respect to treatment success, negative culture for mycology and clinical success were assessed by confidence intervals of the pairwise differences in success rates with respect to the derived variables, determined by normal approximation for each visit separately. The comparison with respect to the change from baseline in total clinical score was assessed by 95 %-confidence intervals of the differences in means. The comparison with respect to the change from baseline in physician's global assessment score was assessed by the Hodges-Lehmann estimate of location shift including its 95 % -confidence intervals.

Descriptive summaries by investigational site were provided for treatment success, clinical success, culture for mycology, physician's assessment of signs and symptoms and physician's global assessment score.

<u>Safety analyses</u>

Safety was evaluated by tabulations of total amount of IMP used, AEs and vital signs.

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Summary, conclusions:

Efficacy results

Under the conditions of this trial with once daily treatment over a 2-week period in patients with inflammatory candida infections in intertriginous areas on the trunk the topical combination product LAS 41003 (octenidine/prednicarbate cream) showed anti-inflammatory action and anti-mycotic efficacy comparable to the effects seen for the corresponding single agent creams.

Treatment success was noted in approximately half of the patients (51.5 %) treated with octenidine/prednicarbate cream. The percentage of patients demonstrating treatment success was comparable in the prednicarbate cream group (48.5 %) and somewhat less in the octenidine cream group (42.9 %).

The percentage of patients showing clinical success was identical (78.8 % in both) and the percentage of patients with negative culture for mycology was comparable (57.6 % and 54.5 %, respectively) in the combined octenidine/-prednicarbate cream and the prednicarbate cream group. The percentages of patients with clinical success (67.9%) and negative culture for mycology (46.4 %) were slightly lower in the group treated with the octenidine cream.

Clinical success but no negative culture for mycology was seen in 27.3 % of the patients in the octenidine/prednicarbate cream group, in 25 % patients in the octenidine cream group and in 30.3 % of the patients in the prednicarbate cream group. Negative culture for mycology but no clinical success was noted in two patients (6.1 %) in both the octenidine/prednicarbate cream and the prednicarbate cream groups and in one patient (3.6 %) in the octenidine cream group.

The comparisons between treatments showed that there were no significant differences in treatment success, clinical success and negative culture for mycology in favor of the combined treatment since the lower limits of the confidence intervals of all comparisons at each time point were below zero.

Over the trial period all individual clinical signs and symptoms (erythema, papules, pustules and maceration), the total clinical scores and the PGA scores decreased in all three treatment groups. However, mild signs and symptoms were still present in most of the patients at the end of the trial.

There were no significant differences in the total sign scores in favor of the combined treatment. The upper limits of the confidence intervals of all comparisons at each time point were above zero. There were no relevant treatment differences in PGA score.

Safety results:

During the trial a total of two non-serious AEs were experienced by two patients (one patient in the octenidine/prednicarbate group and one in the prednicarbate cream group). Both AEs were assessed as mild and resolved without sequelae. One AE (cystitis) required therapy and was considered unlikely to be related to IMP. The other AE (common cold) was assessed as not related to IMP.

The physical examinations did not show any relevant findings in any of the patients and there were no other relevant observations related to safety in this trial.

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Summary, conclusions (continued):

Conclusion:

The purpose of this trial was to assess the efficacy of a combined octenidine/prednicarbate cream (LAS 41003) in comparison to creams with prednicarbate or octenidine alone after once daily treatment over a 2-week period in patients with inflammatory candida infections in intertriginous areas.

In previous studies the combination of an effective antifungal agent with a potent steroid was demonstrated to be superior to treatment with anti-mycotic agents alone. The steroid component provided rapid symptomatic relief while the slower-acting antifungal agent eradicated the causative organism. In addition, it was assumed that the steroid enhanced the antifungal activity (1).

In the present trial the expected advantage of a combination therapy (antifungal plus steroid) could not be confirmed. LAS 41003 cream and the corresponding single agent creams demonstrated a comparable treatment success represented by a composite of both anti-mycotic and anti-inflammatory efficacy in approximately half of the patients in each treatment group. The steroid component prednicarbate did not lead to faster relief of symptoms and the addition of the antiseptic octenidine did not lead to enhanced antifungal activity. The lack of overall treatment success is explained by the low level of negative mycology cultures and the former finding arising due to an improvement of clinical signs and symptoms being seen in most of the patients.

The presence of inflammatory signs and symptoms and of fungi was similar for patients randomized to either of the single agent creams, although anti-mycotic efficacy is regarded to be associated with octenidine and anti-inflammatory action with steroids. The observed “anti-mycotic” effect of prednicarbate might be attributed to the general improvement of the skin condition and barrier function making the environment less favorable to fungal growth, whereas octenidine would reduce the number of yeast organisms and so lead in consequence to a decreased stimulus to inflammation.

None of the efficacy comparisons between LAS 41003 and the single agents showed significant differences in favor of the combined treatment in the endpoints: treatment success, clinical success, negative culture for mycology, total clinical score or PGA score.

In summary, the clinical outcome of this trial does not support the original proposition that the addition of prednicarbate would make patients more comfortable more quickly than with octenidine alone, and that adding octenidine would cure more patients than with prednicarbate alone, by clearing the yeasts in more patients.

There were two treatment-emergent AEs reported by two patients which were considered to be unlikely or not related to the IMPs and so there were no safety concerns based on the results of this trial.

Date of the report: 23 March 2012