Clinical Study Report

Sponsor:	Almirall Hermal GmbH
Trial No.:	H 552 000-0919 / 290506BS
EudraCT-No.:	2009-016626-14
Title:	A phase IIa, two-center, randomized, double-blind study with parallel groups to evaluate the anti-mycotic and anti-inflammatory efficacy of topical combinational product LAS 41003 versus corresponding mono-substances in patients with inflammatory tinea pedis
Investigational Product/s:	Octenidine/Prednicarbate cream (0.25 % octenidine, 0.25 % prednicarbate) Octenidine cream (0.25 % octenidine) Prednicarbate cream (0.25 % prednicarbate)
Clinical Phase:	IIa
Indication:	Tinea pedis
Objective:	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 tinea pedis
Description:	This phase IIa, two-center, randomized, controlled trial was double-blind with three parallel groups. Altogether 120 male or female patients, aged 18 years or older, with symptomatic moderate to severe tinea pedis were included in a 1:1:1 ratio in three groups (40 patients each) 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. There were two dropouts. One hundred and twenty patients were included in the safety and 119 patients in the intent-to-treat (ITT) analyses. Data from 81 patients were valid for modified ITT (MITT) and per-protocol (PP) analyses. The MITT excluded those patients who were found to have a negative culture for mycology at study start. A rate of 25 % of patients with delayed exclusion due to negative mycological culture was expected. The rate of patients with delayed exclusion in this trial was somewhat higher (32 %). However, the smaller sample size had no impact on the overall outcome of this trial. Fungal status was determined using mycological cultures at screening and on Days 8 and 15. On Day 1 (baseline) and on Days 8 and 15 clinical assessments were performed. At baseline and on Day 15 additionally photodocumentation was performed. Patients treated both feet with prednicarbate/octenidine cream, octenidine cream or prednicarbate cream at home once daily over a 2-week treatment period.
Coordinating Investigator:	[redacted] bioskin GmbH, Burchardstrasse 17, 20095 Hamburg, Germany [redacted]
Clinical Trial 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 (GCP) including the archiving of essential documents.
Trial Period:	February 03 to June 16, 2010
Date of Report:	May 09, 2011

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: Not applicable (n.a.)		
Name of Active Ingredient: Octenidine, prednicarbate		

Title of Study: A phase IIa, two-center, randomized, double-blind study with parallel groups to evaluate the anti-mycotic and anti-inflammatory efficacy of topical combinational product LAS 41003 versus corresponding mono-substances in patients with inflammatory tinea pedis	
Investigator(s): [redacted]	
Study center(s): bioskin GmbH, Hamburg and Berlin, Germany	
Publication (reference): Not applicable to this trial	
Studied period (years): 2010	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 tinea pedis	
Methodology: The patients were instructed to apply the study medication to both feet to the affected area and to approximately 2.5 cm of the surrounding clinically healthy skin. The application had to be performed once daily over a 2-week period. Approximately 2 – 3 mg/cm^2 of the respective study medication to all lesions on the feet were sufficient (up to approximately 1.0 g per application). The study medication had to be rubbed in carefully. Washing of the feet or bathing were to be avoided for at least two hours after application. No treatment had to be performed before the visit at bioskin on Days 8 and 15.	
Number of subjects (planned and analyzed): One hundred and twenty male or female patients were planned and included in three groups of 40 patients each in this clinical trial. Assuming a rate of 25 % of patients with delayed exclusion due to negative mycological cultures, three groups of 30 evaluable cases were expected. In reality the rate of patients with delayed exclusion was somewhat higher (32 %). There were two dropouts (both were patients in the octenidine cream group). One hundred and twenty patients were included in the safety and 119 patients in the intent-to-treat (ITT) analyses. Data from 81 patients were valid for modified ITT and per-protocol (PP) analyses.	
Diagnosis and main criteria for inclusion: Male or female patients with symptomatic moderate to severe tinea pedis, aged 18 years or older	
Test product(s), dose and mode of administration, batch number: Octenidine/Prednicarbate cream (0.25 % octenidine, 0.25 % prednicarbate), batch no. 002KK03 Octenidine cream (0.25 % octenidine), batch no. 002KK03 Prednicarbate cream (0.25 % prednicarbate), batch no. 002KK03 Topical application of approximately 2 - 3 mg/cm^2 (up to approximately 1 g) of the respective formulation to all lesions on the feet	
Duration of treatment: Once daily over a 2-week treatment period	
Reference therapy or controls, dose and mode of administration, batch number: n.a.	
Duration of treatment: n.a.	

2. Synopsis (continued)

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Criteria for evaluation:

Treatment success was the primary endpoint for this explorative study.

Efficacy variables

Physician's assessment of signs and symptoms

Clinical assessments were done at all visits.

The overall severity of each sign and symptom (erythema, scaling, vesicles, pustules, crusting, fissuring and maceration) was assessed by the investigator according to a 4-point scale in the selected a target lesion (0 = absent [normal], 1 = mild [barely abnormal], 2 = moderate [distinctly abnormal], 3 = severe [intense involvement or marked abnormality]).

Physician's global assessment (PGA) score

Clinical assessments were done at all visits.

The physician's global assessment was performed according to a 4-point scale in the selected a target lesion:

0 = clinical cure/clear: normal appearance of the skin. No signs and symptoms associated with tinea pedis 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.

Mycologic assessment by microscopy and culture

The mycologic assessment was performed at screening and on Days 8 and 15. Samples were taken from a selected target lesion.

Derived variables

- Mycological cure:

  mycological cure = negative KOH and negative culture

  no mycological cure = positive KOH and/or positive culture

- Total clinical score was defined as the sum of all clinical score values for signs and symptoms
- Change from baseline in total clinical score was determined by subtracting the baseline value from all post baseline assessments.
- Clinical success:

  clinical success = all clinical sign and symptom scores ≤ 1 and total clinical score ≤ 5

  no clinical success = otherwise

- Treatment success:

  treatment success = mycological cure and clinical success

  no treatment success = otherwise.

The last observation carried forward (LOCF) principle was applied to impute missing assessments of the efficacy parameters (e.g. due to a missed visit or due to treatment discontinuation).

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Criteria for evaluation (continued):

Safety variables

Medical history and physical examination including vital signs (blood pressure and pulse rate) were assessed at screening. A final physical examination including vital signs was performed on the last day of the trial.

Spontaneously noted complaints (adverse events) were recorded with duration, intensity and probability of a correlation with the IMP (investigational medicinal product).

Statistical Methods:

Efficacy populations

Intent-to-treat (ITT)

The full analysis set (FAS) included all randomized patients who received at least one dose of investigational product, and had at least one post baseline assessment. The intention-to-treat analysis was based on the FAS.

Modified intent-to-treat (MITT)

The modified intent-to-treat population consisted of all ITT patients who had positive KOH and positive culture 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 culture for mycology following randomization (patients with delayed exclusion) since patients had been randomized based on a positive KOH microscopy result and the culture results were not available at time point of randomization.

Per-protocol (PP)

The valid-cases set included all MITT patients

- without any major protocol violation including violation of inclusion criteria;
- who received the full trial medication doses, except for treatment discontinuation due to treatment related adverse events or lack of efficacy;
- with available values of the primary variables at all days, i.e. with no imputed values, except for treatment discontinuation due to treatment related adverse events or lack of efficacy.

The per-protocol analysis was based on the valid-cases set.

Safety population

The safety population comprised all patients who received any investigational medicinal product at least once. All safety analyses were based on the safety population.

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Statistical Methods (continued):

Efficacy analyses

Hypotheses

No formal hypotheses were evaluated in this explorative trial. The analyses specified below were interpreted in a non-confirmatory manner, and the data were evaluated descriptively.

Statistical analyses

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

The variables microscopy, culture, mycological cure, clinical success and treatment success as well as physician's global assessment score and physician's assessment of signs and symptoms were summarized by treatment and visit providing frequencies and rates. In addition, the physician's assessment of 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 alone, with respect to microscopy, culture, mycological cure, clinical success and treatment success were assessed by 95 % confidence intervals of the pairwise differences in rates 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 microscopy, mycological cure, physician's global assessment score and physician's assessment of signs and symptoms.

Safety analyses

Safety was evaluated by tabulations of extent of exposure to investigational products, adverse events (AEs) and vital signs.

2. Synopsis (continued)

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Summary, conclusions:

Efficacy results:

Under the conditions in this trial with once daily application of the combination product LAS 41003 (octenidine/prednicarbate cream) and octenidine and prednicarbate creams alone over a 2-week period neither LAS 41003 nor the mono-substances showed a relevant anti-mycological effect in patients with inflammatory tinea pedis, as measured by microscopy (KOH) and culture. In the clinical assessment a slight decrease of signs and symptoms was seen for all three formulations.

At baseline the affected areas of both feet to be treated with octenidine/prednicarbate cream, octenidine cream and prednicarbate cream were comparable regarding the occurrence of species: Trichophyton rubrum was seen in the majority of patients (between 81.5 % and 89.3 %), Trichophyton mentagrophytes in the remaining patients (between 7.1 % and 15.4 %) and Epidermophyton floccosum was observed sporadically. Furthermore, no relevant difference in the size of the mean treated area was seen between the feet lesions to be treated with the three formulations (between 325.4 cm² and 401.9 cm²).

Primary efficacy variable- Treatment success

Treatment success, as determined by mycological cure and clinical success, was noted only on Day 15 in one patient of the prednicarbate cream group, and in none of the patients treated with octenidine/prednicarbate cream or octenidine cream as monotherapy.

Secondary efficacy assessments

Clinical success, as determined by all clinical sign and symptom scores ≤ 1 and total clinical score ≤ 5, was noted for a few patients of each treatment group following 14 days of treatment: Clinical success was noted in two patients (7.7 %) in the octenidine/prednicarbate cream group, in four patients (14.3%) in the octenidine cream and in five patients (18.5 %) in the prednicarbate cream group.

Mycological cure, as defined as negative KOH and negative culture, was found at the end of the trial (Day 15) in a total of only two patients, one in the octenidine/prednicarbate cream group and one in the prednicarbate cream group.

When microscopy and culture results were considered separately, a greater number of patients showed negative results: The microscopy (KOH) results were comparable for all three formulations over the course of the trial: Negative microscopy results were noted in a total of ten patients, in five patients (19.2 %) in the octenidine/prednicarbate cream group and in five patients (17.9 %) in the octenidine cream group. In the prednicarbate cream group three patients (11.1%) showed negative microscopy results at the end of the trial. Similar culture results were found for all three formulations after 14 days of treatment: Negative culture was noted in six patients (23.1 %) in the octenidine/prednicarbate cream group, in five patients (17.9%) in the octenidine cream group and in seven patients (25.9%) in the prednicarbate cream group.

The overall severity of signs and symptoms (erythema, scaling, vesicles, pustules, crusting, fissuring and maceration) showed a slight decrease following two weeks of treatment with octenidine/-prednicarbate cream, octenidine cream and prednicarbate cream.

A comparable slight decrease in the mean total clinical assessment score was noted for the octenidine/prednicarbate cream, octenidine cream and prednicarbate cream groups over the course of the trial. The mean total clinical assessment score of 6.6, 6.1 and 5.8 (baseline) had decreased to 4.8, 4.3 and 4.2, respectively on Day 15.

More than half of the patients of each treatment group showed prominent (PGA score 2) and the other patients notable signs and symptoms (PGA score 3) of tinea pedis at baseline. Over the course of the trial a slight improvement in the physician's global assessment was seen for all three formulations. At the end of the trial almost clear (PGA score 1) was noted in a few patients. However, notable or prominent signs and symptoms were still present in most of the patients, whereas more patients of each treatment group showed notable signs and symptoms. The median physician's global assessment score had decreased from 3.0 at baseline to 2.0 at the end of the trial in all three treatment groups.

2. Synopsis (continued)

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Summary, conclusions:

Safety results:

A total of three non-serious treatment-emergent AEs (sprain, cold, worsening of tinea pedis) and one treatment-emergent SAE (back pain worsening) were reported in four patients.

One non-serious AE was reported in one patient in the group treated with octenidine/prednicarbate cream. Two non-serious AEs and one SAE were reported in three patients in the group treated with octenidine cream.

The patient with the SAE and one patient with a non-serious AE (worsening of tinea pedis) discontinued the trial prematurely, both belonged to the octenidine group. The relationship to IMP (octenidine cream) was considered possible in the patient with the worsening of tinea pedis. The other AEs and the SAE were considered to be unlikely or not related to IMP.

One patient with a non-serious AE (cold) recovered without sequelae. The other AEs and the SAE were ongoing on the last study day, but a follow-up was not deemed necessary for any case.

The final physical examinations at the end of the trial did not show relevant findings in any of the patients. There were no other relevant observations to safety in this trial.

Conclusion:

The aim of this phase IIa, two-center, randomized, double-blind trial was to evaluate the anti-mycotic and anti-inflammatory efficacy of the combination product LAS 41003 (octenidine/prednicarbate cream) in comparison to octenidine and prednicarbate cream alone after once daily treatment over a 2-week period in patients with inflammatory tinea pedis.

Overall, under the present trial conditions no anti-mycological and no convincing anti-inflammatory effect was seen following treatment either with LAS 41003 or the mono-substances in patients with inflammatory tinea pedis.

Treatment success, as determined by mycological cure and clinical success, was noted only on Day 15 in one patient in the prednicarbate cream group, and in none of the patients treated with octenidine/prednicarbate cream or octenidine cream as monotherapy.

Clinical success was noted for a few patients in each of the treatment groups. Mycological cure, as defined as negative KOH and negative culture, was found at the end of the trial (Day 15) in a total of only two patients, one in the octenidine/prednicarbate cream group and one in the prednicarbate cream group.

However, when microscopy and culture results were regarded separately, an increased number of patients showed negative results.

Although there was a slight clinical improvement, comparable in all three groups, reflected in a slight improvement in the overall severity of individual signs and symptoms (erythema, scaling, vesicles, pustules, crusting, fissuring and maceration), the total clinical assessment score and physician's global assessment following treatment with the three formulations, the anti-inflammatory effect was not convincing, particularly in regard to the clinical assessment of erythema.

A total of three non-serious AEs and one SAE were reported in four patients in this trial. The patient with the SAE and one patient with a non-serious AE (worsening of tinea pedis) discontinued the trial prematurely. The relationship to IMP (octenidine cream) was considered possible in the patient with the worsening of tinea pedis. The other AEs including the SAE were considered to be unlikely or not related to IMP. There were no safety concerns based on the results of this trial.

Date of the report: May 09, 2011