Clinical Study Report

Sponsor: **Represented by:**	**Almirall, S.A.** **Almirall Hermal GmbH**
Trial No.:	**H578 000 - 1114 / 311010BS**
EudraCT-No.:	2011-005883-10
Title:	Two-center, randomized, vehicle- and comparator controlled trial, double-blind for the LAS186323 formulations and vehicle, and observer-blind for the active comparators, to compare the safety and efficacy of topical LAS186323 formulations with the vehicle and three marketed active comparators in subjects with stable plaque type psoriasis
Investigational Medicinal Product/s (IMPs):	**IMP 1:** LAS186323 0.5 % ointment **IMP 2:** LAS186323 0.2 % ointment **IMP 3:** Active-ingredient-free vehicle to LAS186323 ointment **Comparators** **IMP 4:** Daivonex® Creme (50 µg/g calcipotriol) **IMP 5:** Daivobet® Salbe (50 µg/g calcipotriol + 0.5 mg/g betamethasone) **IMP 6:** Diprosone® Creme (0.5 mg/g betamethasone)
Clinical Phase:	I
Indication:	Psoriasis
Description:	This phase I trial was performed as a two-center, randomized, vehicle- and comparator-controlled trial and was double-blind for the two LAS186323 ointments and the respective vehicle (IMPs 1 to 3), and observer-blind for the active comparators (IMPs 4 to 6). Treatments were randomly assigned to the test fields. All subjects received all treatments, with intraindividual comparison of the treatments. In total, 22 male subjects aged 18 years or older with mild to moderate stable plaque type psoriasis were included in this trial to evaluate the safety, tolerability and efficacy of two different concentrations of LAS186323 ointment (IMP 1 and 2) in comparison to their active-ingredient-free vehicle (IMP 3) and to three marketed active comparators (IMPs 4 - 6). Data of all 22 subjects were valid for the safety evaluation set (SES), the full analysis set (FAS) and the valid cases set (VCS) analyses. There were no dropouts. Altogether six test fields (each 1.1 cm^2) located on the torso or the extremities were examined per subject. The test fields were treated occlusively with approximately 200 µl of each IMP on 11 consecutive days. A clinical tolerability assessment was performed daily from Day 2 to 12. Global clinical assessments of efficacy were performed on Days 4, 8 and 12, and assessments of individual clinical signs of erythema and induration on Days 1, 4, 8, and 12. Sonography and photographic documentation of test fields were performed on Days 1 (baseline), 4, 8, and 12. A safety follow-up visit (final visit) was scheduled on Day 19 (seven days after end of treatment).
Coordinating Investigator (CI)	[redacted] bioskin GmbH, Bergmannstrasse 5, 10961 Berlin, Germany [redacted]
Clinical Trial Manager (Sponsor):	[redacted] Global Clinical Development Almirall Hermal GmbH, Scholtzstrasse 3, 21465 Reinbek, Germany [redacted]
GCP Compliance:	The clinical trial was conducted in compliance with Good Clinical Practice including the archiving of essential documents.
Trial Period:	September 20 to October 27, 2012
Date of Report:	February 15, 2013

2. Synopsis

Name of Company: Almirall, S.A. represented by 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		
Name of Active Ingredient: LAS186323 (N-aryl substituted aminoaryloic acid derivative)		

Title of Study:
Two-center, randomized, vehicle- and comparator controlled trial, double-blind for the LAS186323 formulations and vehicle, and observer-blind for the active comparators, to compare the safety and efficacy of topical LAS186323 formulations with the vehicle and three marketed active comparators in subjects with stable plaque type psoriasis

Investigator(s):
[redacted]

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

Publication (reference):
Not applicable to this trial

Studied period (years):	Phase of development:
2012	I

Objectives:
Primary objective:
To evaluate the safety and tolerability of two different concentrations of LAS186323 ointment in comparison to vehicle and three marketed active comparators in subjects with plaque psoriasis
Secondary objective:
To explore the antipsoriatic efficacy of two different concentrations of LAS186323 ointment in comparison to their vehicle and to three marketed active comparators in subjects with plaque psoriasis

Methodology:
Altogether six test fields (each 1.1 cm^2) located on the torso or the extremities were examined per subject. The test fields were treated occlusively with approximately 200 µl of each IMP on 11 consecutive days. A clinical tolerability assessment was performed daily from Day 2 to 12. Global clinical assessments of efficacy were performed on Days 4, 8 and 12 and assessments of individual clinical signs of erythema and induration on Days 1, 4, 8, and 12. Sonography and photographic documentation of test fields were performed on Days 1 (baseline), 4, 8, and 12. A safety follow-up visit (final visit) was scheduled on Day 19 (seven days after end of treatment).

Number of subjects (planned and analyzed):
22 male subjects were planned to get at least 20 evaluable cases. All 22 subjects were randomized and included in the SES, FAS and VCS analyses. There were no dropouts.

Diagnosis and main criteria for inclusion:
Male subjects, aged 18 years or older with mild to moderate stable chronic plaque-type psoriasis

Test product(s), dose and mode of administration, batch number:
IMP 1: LAS186323 0.5 % ointment (internal code: LAS186323 / H 578 012), batch no. 236K01
IMP 2: LAS186323 0.2 % ointment (internal code: LAS186323 / H 578 015), batch no. 236K01
IMP 3: Active-ingredient-free vehicle to LAS186323 ointment (internal code: LAS186323 / H 578 008), batch no. 236K01
Occlusive topical application of approximately 200 µl of each IMP per treatment to six test fields (each 1.1 cm^2) once daily

Duration of treatment:
12-day trial period (11 treatments)

2. Synopsis (continued)

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

Comparators

IMP 4: Daivonex® Creme (50 µg/g calcipotriol), batch no. EF3K3248
(internal code Daivonex® Creme: LASW1851,internal code calcipotriol: LASW1853)

IMP 5: Daivobet® Salbe (50 µg/g calcipotriol + 0.5 mg/g betamethasone)
(internal code Daivobet® Salbe: LASW1852, internal code calcipotriol: LASW1853, internal code betamethasone: LASW1854), batch no. EF7K658

IMP 6: Diprosone® Creme (0.5 mg/g betamethasone)
(internal code Diprosone® Creme: LASW1850, internal code betamethasone: LASW1854), batch no. 1YTKFZ0404

Occlusive topical application of approximately 200 µl of each IMP per treatment to six test fields (each 1.1 cm^2) once daily

Duration of treatment:
12-day trial period (11 treatments)

Criteria for evaluation:

Subject characteristics:

- Demographic and background characteristics
- Medical history
- Prior and concomitant therapy

Safety variables:

- Local tolerability (overall clinical assessment)
- Adverse events (AEs)
- Physical examination of the skin
- Vital signs

Efficacy variables:

- Thickness of the ELB (echo lucent band) by 20 MHz sonography as a surrogate for the psoriatic infiltrate thickness
- Assessment of efficacy (global clinical assessment)
- Assessment of individual clinical signs of erythema and induration

Statistical Methods:

Study populations

Intent-To-Treat (ITT)

The FAS included all randomized subjects who received at least one dose of IMP, and had at least one post-baseline assessment. The ITT analysis was based on the FAS.

Per-Protocol (PP)

The VCS included all subjects

- without any major protocol violation including violation of inclusion criteria;
- who had not taken any interfering concomitant medication;
- who received the full IMP doses, except for treatment discontinuation due to reaching the discontinuation criteria;
- with available values of the primary variables at all days, i.e. with no imputed values, except for treatment discontinuation due to reaching the discontinuation criteria.

The PP analysis was based on the VCS.

Safety

The SES included all subjects who received any IMP at least once. All safety analyses were based on the SES.

2. Synopsis (continued)

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Statistical Methods (continued)::

Safety analyses

All safety analyses were based on the SES.

Safety was evaluated by tabulations of extent of exposure to IMP, clinical assessment of tolerability, AEs, physical examination of the skin and vital signs.

Clinical assessment of tolerability

Clinical assessment of tolerability was evaluated descriptively. The scores are presented by treatment for each time point using frequency tables and descriptive statistics (N, mean, standard deviation, median, min, max). Additionally, the total clinical assessment score was summarized descriptively by treatment.

Efficacy analyses

Statistical analyses

The efficacy analyses were performed on the FAS and VCS.

Primary efficacy analyses

The thickness of the ELB by 20 MHz sonography as a surrogate for the psoriatic infiltrate thickness was evaluated descriptively. Change in the thickness of the ELB was determined as the difference of each post-baseline assessment to the baseline assessment. Additionally, the area under the time curve (AUC) of change in the thickness of the ELB was determined using the linear trapezoidal rule.

The absolute values of the thickness of the ELB and their changes from baseline were summarized by treatment and time point using descriptive statistics (N, mean, standard deviation, median, minimum, maximum). The AUC was summarized accordingly by treatment.

Explorative inferential evaluation of the superiority of IMP 1 and IMP 2 versus IMP 3, with respect to the change from baseline in thickness of the ELB on Day 12 (end of treatment [EoT]) was performed. The treatment effects were determined as the difference of either IMP 1 or IMP 2 to IMP 3, and are presented as descriptive statistics including the 95 %-confidence interval. Additionally, the p-value is provided using the two-sided paired t-test at a significance level of 0.05.

Pairwise comparisons of the comparators IMP 4, IMP 5 and IMP 6 to IMP 1 and IMP 2, respectively, were performed accordingly, with respect to the change from baseline in thickness of the ELB on Day 12 (EoT) and the AUC of change in the thickness of the ELB.

Secondary efficacy analyses

The clinical efficacy assessment was evaluated descriptively. The scores are presented by treatment for each time point using frequency tables and descriptive statistics (N, mean, standard deviation, median, min, max). Additionally, the total clinical assessment score, determined for each subject and treatment as the sum over the treatment period was summarized descriptively by treatment.

Each clinical efficacy assessment of the individual signs of erythema and induration were evaluated descriptively. The scores are presented by treatment for each time point using frequency tables and descriptive statistics (N, mean, standard deviation, median, min, max). The change from baseline in each clinical assessment score was determined and is presented descriptively by treatment and visit. Additionally, the total change in clinical assessment score, determined for each subject and treatment as the sum of the changes from baseline over the treatment period, was summarized descriptively by treatment.

2. Synopsis (continued)

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Summary, conclusions:

Tolerability and safety results (primary objective):

Under the present trial conditions with once daily occlusive application over a 12-day treatment period (11 treatments), both concentrations of LAS186323 ointment (0.5 and 0.2 %) demonstrated very good dermal tolerability and no other relevant observations to safety were reported.

The clinical tolerability assessment showed also very good dermal tolerability for the active ingredient-free vehicle as well as for the comparators Daivobet® Salbe and Diprosone® Creme. The mean total clinical tolerability assessment score was 0.0 for both LAS186323 ointments, the vehicle and Daivobet® Salbe and Diprosone® Creme (SD = ± 0.0 for each, except for the vehicle where SD = ± 0.2). The comparator Daivonex® Creme was also very well tolerated by nearly all subjects (mean total = 0.2 ± 0.7), however there was one subject showing poor clinical tolerability on Day 12 which was considered as an AE (application site dermatitis).

The evaluation of AEs showed no AEs with relationship to any of the LAS186323 ointments or the vehicle. Two mild non-serious AEs were considered to be related to the comparators (Daivonex® Creme: application site dermatitis; Diprosone® Creme: application site pruritus). Furthermore, there was one severe, serious AE (brain stem infarction) and one mild non-serious AE (nasopharyngitis) in this trial with no relationship to IMP. None of these AEs including the SAE led to a premature study discontinuation and all AEs recovered.

The final physical examinations at the end of the trial including assessment of vital signs did not show relevant findings in any of the subjects.

Efficacy results (secondary objective):

An antipsoriatic effect could not been shown under the conditions in this trial which was confirmed by sonography and clinical assessment.

The sonographic measurements showed no reduction in the mean thickness of the ELB for the two LAS186323 ointments, reflecting no decrease of the psoriatic infiltrate. For the 0.5 % concentration the mean thickness of the ELB had even slightly increased over the trial period (mean change from baseline to Day 12 = 67.4 µm ± 176.34; % mean change = 14 %). Only minor changes were seen in mean thickness of the ELB following treatment with LAS186323 ointment 0.2 % (mean change from baseline = -3.6 µm ± 139.84; % mean change = -1 %). The calculated mean areas under the curve (AUC) were positive (0.5%: 671 ± 1356 a.u.; 0.2 %: 345 ± 1470 a.u.), which also indicated no reduction of infiltrate thickness.

No statistically significant differences were found between the two LAS186323 ointments and their corresponding vehicle with respect to change from baseline to Day 12/EoT in thickness of the ELB. Treatment with the vehicle led to a slight increase in the mean thickness of the ELB (mean change from baseline to Day 12 = 47.5 ± 195.77 µm; % mean change of 10 %). The mean AUC was 552 ± 1320 a.u.

By contrast, clear improvement of psoriatic lesions represented by a clear reduction of thickness of the ELB was demonstrated for the three comparators Daivonex® Creme, Daivobet® Salbe and Diprosone® Creme (mean changes from baseline: -242.6 ± 215.87, -363.2 ±155.71, -377.8 ± 202.60 µm; % mean changes = -52, -77 and -80 %, respectively). The mean AUCs were -1528 ± 1217 a.u., -2731 ± 1152 a.u. and -2722 ± 1540 a.u., respectively.

All statistical comparisons between the LAS186323 ointments and each comparator were significant in favor of the comparator showing greater changes from baseline in thickness of the ELB and great negative mean AUCs of change from baseline in thickness of the ELB ($p<0.001$, each).

The results of the global clinical assessment of efficacy as well as the individual assessments of erythema and induration are consistent with the results of the sonographic measurement and show no clinically relevant reduction of psoriatic lesions following treatment with the LAS186323 ointments and the vehicle but a clear improvement following treatment with the comparators.

2. Synopsis (continued)

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Summary, conclusions:

Conclusion:

The primary aim of this trial was to evaluate the safety and tolerability of two different concentrations of LAS186323 ointment (0.5 and 0.2 %) in comparison to their vehicle and to three marketed active comparators in subjects with plaque psoriasis. Secondly, the antipsoriatic efficacy of these IMPs was assessed.

Both concentrations of LAS186323 ointment were very well tolerated and safe under the conditions in this trial.

No adverse observations in relation to safety were seen for the two LAS186323 ointments either in the clinical tolerability assessment or in the final physical examination (including vital signs) at the end of treatment as well as at the safety-follow up visit seven days after the end of treatment. No causal relationship to any of the two LAS186323 ointments was assessed in the evaluation of AEs when applied occlusively once daily over a 12-day treatment period (11 treatments).

The clinical tolerability assessment showed also very good dermal tolerability for the active ingredient-free vehicle as well as for the comparators Daivobet® Salbe and Diprosone® Creme. The comparator Daivonex® Creme was also very well tolerated by nearly all subjects, however there was one subject showing poor clinical tolerability on Day 12 which was considered as an AE.

In total, four treatment-emergent AEs (TEAEs) were noted in two subjects: two mild non-serious AEs were considered to be related to the comparators (Daivonex® Creme: application site dermatitis; Diprosone® Creme: application site pruritus). One subject additionally experienced a severe SAE (brain stem infarction) and another subject experienced a mild cold. Both AEs were considered not related to any IMP. None of these AEs including the SAE led to a premature study discontinuation and all AEs recovered.

No reduction of infiltrate thickness could be shown for the two LAS186323 ointments as well as for their vehicle since the mean thickness of the ELB did not decrease over the trial period and the calculation of the mean AUC of change from baseline in thickness of the ELB only revealed positive values. A clinically significant decrease in infiltrate thickness, reflected by clear mean changes from baseline of the ELB and great negative mean AUCs was seen for all three comparators, whereas the greatest reduction was demonstrated for Diprosone® Creme. The sonographic results of the three comparators seen in this trial are in accord with the literature data (5 - 8).

The results of the global clinical assessment of efficacy as well as the individual assessments of erythema and induration are consistent with the results of the sonographic measurement showing no clinically relevant reduction of psoriatic lesions for the LAS186323 ointments and the vehicle but a clear improvement for the comparators.

Overall, there were no safety concerns based on the results of this trial. However, an antipsoriatic effect of LAS186323 could not be demonstrated either by sonographic measurement or clinical assessment.

Date of the report: February 15, 2013