1. TITLE PAGE

CONFIDENTIAL

CLINICAL STUDY REPORT

Clinical Study Report Code: M/37779/23

Name of the investigational medicinal product: LAS37779, Topical PDE-IV inhibitor
Indication studied: Psoriasis
Phase of the study: IIa

"A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, VEHICLE AND ACTIVE CONTROLLED CLINICAL TRIAL, TO ASSESS THE EFFICACY AND SAFETY OF LAS37779 CREAM FOR THE TREATMENT OF CHRONIC PLAQUE PSORIASIS"

(Protocol No. M/37779/23**; Eudract No.** 2007-001793-87**)**

Final Statistical Report Version dated: 10 March 2008
Date of initiation of the study: 03 August 2007
Date of completion of the study: 27 December 2007
Date of completion of the Report: 30 April 2009

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The study was performed in accordance with Good Clinical Practices (GCP) including the archiving of essential documents

2. SYNOPSIS

Name of Sponsor / Company: Laboratorios Almirall, S.A **Name of Finished Product:** N.A. **Name of Active Ingredients:** LAS37779	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Title of Study: A MULTICENTRE, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP, VEHICLE AND ACTIVE CONTROLLED CLINICAL TRIAL, TO ASSESS THE EFFICACY AND SAFETY OF LAS37779 CREAM FOR THE TREATMENT OF CHRONIC PLAQUE PSORIASIS.

Investigators:
This study was conducted by 12 investigators in two countries (see Appendix 16.1.4)
Germany: [redacted]
Romania: [redacted]
Co-ordinating Investigator: [redacted]
Centre: 183
City: Frankfurt
Country: Germany

Study centre (s):
The study was conducted in a total of 12 sites, 8 in Germany, 4 in Romania (see Appendix 16.1.4).
Germany: Centre 871 in Wuppertal, Centre 872 in Dresden, Centre 179 in Berlin, Centre 874 in Hamburg, Centre 875 in Osnabruck, Centre 183 in Frankfurt, Centre 876 in Berlin, Centre 4305 in Schwerin
Romania: 2 Centres 877 in Bucharest (2 centres with the same number), Centre 878 in Bucharest, Centre 879 in Dolj.

Publication (reference):
None

Studied period: Date study initiated (first screening): 03 August 2007 Date study finalized (last patient last visit): 27 December 2007	**Phase of development:** IIa

Objectives:
Primary Objectives:
- To assess the efficacy, safety, and tolerability of LAS37779 1% cream applied twice daily for 8 weeks, compared to 8 weeks of twice daily applications of LAS37779 vehicle cream.

Secondary Objectives:
- To assess the relative efficacy, safety, and tolerability of LAS37779 1% cream applied twice daily for 8 weeks compared to Calcipotriol 0.005% cream applied twice daily.
- To investigate the systemic drug levels of LAS37779 and its main metabolites after single and multiple cutaneous applications of LAS37779 1% cream in psoriasis patients.
- To evaluate the cosmetic acceptability of study creams in patients.

Methodology:
This was an 8-week treatment, prospective, multicenter, randomized, double-blind, parallel-group, vehicle and active-comparator controlled study of repeated cutaneous applications of LAS37779 cream in patients with chronic plaque psoriasis.

Drug administration:

Treatments administered were topical creams: LAS37779 cream at 1%, LAS37779 vehicle cream and calcipotriol 0.005% cream (Daivonex®) (randomization ratio 1:1:1). Treatments were administered twice daily for 8 consecutive weeks in all affected areas excluding the head, neck and face.

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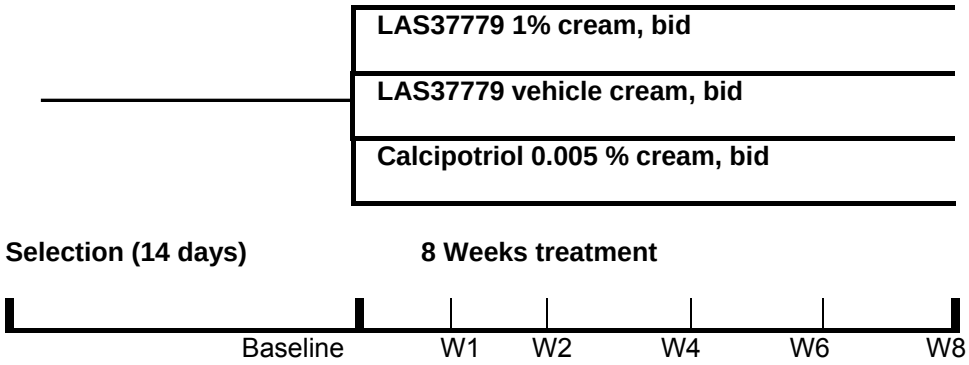
After randomization (Baseline Visit), patients attended weekly study visit during the first two weeks and then every two weeks study visits until completion of the 8-weeks treatment period.

A study scheme is presented below:



Number of subjects (planned and analyzed):
The total number of patients planned to be randomized was 120 to ensure a total of 96 evaluable patients so 32 patients per treatment arm.

Treatment was allocated using a 1:1:1 ratio for LAS37779 1% cream, LAS37779 vehicle cream or Calcipotriol 0.005% cream. The final total number of randomized patients was 125 patients. Overall, 113 patients (90.4%) completed the study period, whereas 12 patients (9.6%) were withdrawn prematurely. There were no marked differences between treatment groups with regard to the number of randomized patients, as well as with the number of patients who completed or withdrew from the study. 125 patients (100%) received study medication and were included in the Safety population.

The 125 randomized patients (100%) were included in the Intent-to-Treat (ITT) population, and 110 patients (88%) were analyzed in the Per Protocol (PP) population. 15 patients (12%) were excluded from this PP analysis following major protocol deviations during the study period. There were no relevant differences between study groups with regard to the number of patients in each analysis population.

	LAS37779 1% cream	Calcipotriol 0.005% cream	LAS37779 vehicle cream	Total
Randomized	40 (100%)	44 (100%)	41 (100%)	125 (100%)
Withdrawn	4 (10.00%)	3 (6.82%)	5 (12.20%)	12 (9.60%)
Completed	36 (90.0%)	41 (93.18%)	36 (87.80%)	113 (90.40%)
ITT population	40 (100%)	44 (100%)	41 (100%)	125 (100%)
PP population	35 (87.50%)	40 (90.91%)	35 (85.37%)	110 (88.0%)
Safety population	40 (100%)	44 (100%)	41 (100%)	125 (100%)

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Diagnosis and main criteria for inclusion:
Patients eligible to be enrolled in this study

1. Were male or female, 18 to 70 years of age;
2. If female of childbearing potential, used of a highly effective method of birth control defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomy of the partner. In addition these female patients had to have a negative pregnancy test at screening and agreed to submit to a pregnancy test at the end of study.
3. Had clinical diagnosis of chronic plaque psoriasis, characterized at screening visit by:
   - An Investigator's Global Assessment of Disease Severity (IGA static) score of 2 (=mild) or 3 (=moderate).
   - Two target lesions, one located in the elbow or knee and the other on trunk or limbs of similar size (minimum size of 2 cm in diameter) and severity with score of at least 2 (=moderate) for induration and 2 (=moderate) for erythema.
   - At least 2% but no more than 20% of body surface area (BSA) affected by the disease
   - Had lesions in at least two anatomical regions (trunk, legs or arms)
4. Were free of any systemic and dermatologic disorders, which, in the opinion of the investigator, could interfere with the study results or increase the risk of adverse events;
5. Might read, understand and provide signed informed consent;
6. Were willing to follow the study procedures for treatment application and dosing regimen and complete the study

Patient was excluded, mainly, if he (she):

1. Had inverse or palmoplantar psoriasis, acute guttate, erythrodermic, exfoliative or pustular psoriasis, atopic dermatitis, seborrheic dermatitis; or any inflammatory skin disease other than the primary diagnosis of chronic plaque psoriasis;
2. Had markedly improving or worsening psoriasis during the wash-out period (e.g. ≥ 1 point in IGA static) or before study entry.
3. Had an Investigator's Global Assessment of Disease Severity (IGA static) score of 4 (=severe) or 5 (=very severe) and/or were eligible for systemic or ultraviolet light therapy at the investigator's criteria;
4. Had lesions with very severe (= 4) scaling
5. Were known to be non-responders to topical treatments;
6. Were known to be immuno-compromised, to have an auto-immune disorder, or to have a history of non-cured malignancy;
7. Had active Hepatitis B or C, or Acquired Immunodeficiency Syndrome (AIDS);
8. Had any unstable concomitant disease or any significant disease, or any gross physical impairment, which might, in the opinion of the investigator, interfere with the performance of the study, or with the interpretation of study outcomes, or place the subject at undue risk;
9. Had a clinically significant laboratory test abnormality at the Screening Visit.

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Test product, dose and mode of administration, batch number, expiry date:
LAS37779 1% cream
Administration route: Topical
Dosage form: 30 g cream tubes containing LAS37779 at 1%
Dose and regimen: A thin layer of approx. 2 mg/cm^2 applied to all affected areas (except head, neck and face) twice a day
Batch numbers: 063F0103/064F0104
Expiry date: April 2008

Duration of treatment:
8 weeks of treatment.

Reference therapy, dose and mode of administration, batch number, expiry date:
Calcipotriol (Daivonex®)
Administration route: Topical
Dosage form: Vehicle cream
Dose and regimen: A thin layer of approx. 2 mg/cm^2 applied to all affected areas twice daily
Batch numbers and expiry dates:
00001579: expiry date November 2008
00001580: expiry date July 2008
00001620: expiry date November 2008
00001621: expiry date April 2009
00001637: expiry date June 2009
00001638: expiry date November 2008
00001639: expiry date May 2009
00001640: expiry date April 2009
00001642: expiry date June 2009
00001643: expiry date April 2009
00001644: expiry date May 2009

Vehicle, dose and mode of administration, batch number, expiry date:
LAS37779 vehicle
Administration route: Topical
Dosage form: Vehicle Cream
Dose and regimen: A thin layer of approx. 2 mg/cm^2 applied to all affected areas twice daily
Batch number: 058F0095/060F0097
Expiry date: April 2008

Criteria for evaluation:
Efficacy:

Primary efficacy end-point:
Change from baseline in the average Total Sign Score (TSS) of two target lesions to the end of treatment (Visit 6 - Day 56).

Secondary end-points:
Efficacy
Induration, erythema and scaling scores of two target lesions, Investigator's Global Assessment of Overall Disease Severity (IGA), PASI score, body surface area (BSA) affected, Investigator's Global Improvement Score (IGIS), Visual Analogue scale (VAS) pruritus evaluation, Pain intensity scale evaluation.

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Safety and tolerability

Adverse events (AEs), laboratory evaluations, vital signs, ECG tracings, Investigator's Global Assessment of Tolerability and number of withdrawals.

Plasma levels of LAS37779 and its metabolites:

Plasma concentrations of LAS37779 and its main metabolites were measured on a subset of 30 subjects enrolled at three selected investigational sites only (site 4305, site 874 and site 183), located in Germany. Plasma levels and pharmacokinetic (PK) parameters were determined in a subset of (30) patients after single (Day 1 of treatment) and repeated application (week 8 of treatment); C_{max}, t_{max}, AUC(0-t) and AUC(0-12) were determined.

At visits 2, 3, 4, 5 and 6 (weeks 1, 2, 4, 6 and 8 of treatment, respectively), plasma drug levels were determined before IMP morning application to determine $C_{pre\text{-}dose}$.

The drug compliance consisted of assessing the plasma concentrations of LAS37779 and its metabolites in order to assess the compliance of the patients.

Cosmetic acceptability

Cosmetic acceptability of study cream in patients.

Statistical methods:

Statistical analyses of demographic, baseline characteristics, efficacy, safety and tolerability data were performed by Trial Form Support (TFS). The calculation of pharmacokinetic parameters, as well as descriptive statistics and graphs for those were provided by the Pharmacokinetic and Drug Metabolism Department of Laboratorios Almirall, S.A.

Primary efficacy endpoint: The comparison between treatments of the change from baseline in the average Total Sign Score of two target lesions after 56 days (8 weeks) of treatment was carried out using an Analysis of covariance (ANCOVA) model adjusting for baseline and centre. All analyses of the primary efficacy variable were performed on the Intention to Treat (ITT) population. The primary efficacy variable was also analyzed on the Per Protocol (PP) population.

Secondary efficacy endpoints:

- Change from baseline in the average TSS of two target lesions to Days 7, 14, 28 and 42 of treatment.
- Change from baseline in the TSS of the Target Lesion of elbow or knee to Days 7, 14, 28, 42 and 56 of treatment.
- Change from baseline in the TSS of the Target Lesion of trunk or limbs to Days 7, 14, 28, 42 and 56 of treatment.
- Change from baseline in the score for each of the individual signs (erythema, induration and scaling) of each target lesion to Days 7, 14, 28, 42 and 56 of treatment.
- Change from baseline in the score for each of the individual signs (erythema, induration and scaling) of the average of the two Target Lesions to Days 7, 14, 28, 42 and 56 of treatment.
- Change from baseline in PASI to Days 7, 14, 28, 42 and 56 of treatment.
- Change from baseline in the percentage of BSA affected to Days 7, 14, 28, 42 and 56 of treatment.
- Change from baseline in Pruritus (VAS scale) to Days 7, 14, 28, 42 and 56 of treatment.
- Change from baseline in pain intensity to Days 7, 14, 28, 42 and 56 of treatment.
- Number (%) of patients with "clear" or "almost clear" and at least 2-point decrease from baseline in the Investigator's Global Assessment of Disease Severity at Days 7, 14, 28, 42 and 56 of treatment.
- Number (%) of patients with ≥ 50% and ≥ 75% decrease from baseline of PASI score (PASI50 and PASI75) at Days 7, 14, 28, 42 and 56 of treatment.
- Number (%) of patients with al least "marked improvement" in the Investigator's Global Improvement Score (IGIS) at Days 7, 14, 28, 42 and 56 of treatment.

All analyses of secondary endpoints were performed on the ITT and PP populations.

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Changes from baseline in all endpoints were calculated and analyzed as both absolute and relative changes. All continuous secondary endpoints as either change from baseline or absolute values, were analyzed using an Analysis of covariance model as appropriate.

Missing values of the primary and secondary efficacy variable were treated using the Last Observation Carried Forward (LOCF) methodology. In all statistical tests, the significance level was set at 0.05 two-tailed. For exploratory purposes, some efficacy variables were analyzed descriptively using the Available Data Only (ADO).

Safety outcomes: The safety outcomes consisted on: collection of adverse events (AEs), physical examination, vital signs measurements, clinical laboratory evaluation, ECG tracing and Investigatior's global Assessment of Tolerability. All analyses of safety outcomes were performed on the Safety population. Appropriate descriptive analyses were performed for these outcomes. Investigator´s Global Assessment of Tolerability of each treatment was analyzed by means of a contingency table and using the Fisher exact test.

Pharmacokinetic parameters: All pharmacokinetic analyses were performed on the subset of patients with pharmacokinetic data. Pharmacokinetics parameters were analyzed using descriptive statistics.

Other variables: All number of withdrawals and reasons for withdrawal, number (%) of patients that used emollient, number (%) of days using emollient and other baseline characteristics were summarised on the Safety population.

Cosmetic acceptability questionnaire: were summarised on the Safety population. This parameter was analyzed in a descriptive way.

SUMMARY – CONCLUSIONS

Demographic Data:

A total of 125 patients suffering from chronic plaque psoriasis were randomized in 12 centres in Europe from August 3rd, 2007 (first screening visit) to December 27th, 2007 (last patient last visit).
Most of the patients included in the ITT population were Caucasian (98.4%) and a higher proportion was males (61.6%) compared to females (38.4%).

The mean age of the patients was 48.3 ± 12.7 years i.e. 47.5 ± 12.5 years in the LAS37779 1% group, 48.5 ± 14.0 years in the Calcipotriol 0.005% group and 48.8 ± 11.6 years in the vehicle group.

The ITT and Safety populations have been conducted on the totality of the randomised patients (125): 40 patients (100%) in the LAS37779 1% group, 44 patients (100%) in the Calcipotriol 0.005% group and 41 (100%) in the vehicle group.

The PP population has been conducted on 110 patients (88.0%): 35 patients (87.5%) in the LAS37779 1% group, 40 patients (90.9%) in the Calcipotriol 0.005% group and 35 patients (85.3%) in the vehicle group.

Among the randomized patients, 12 (9.6%) were withdrawn from the study i.e. four patients (10.0%) in the LAS37779 1% group, three patients (6.8%) in the Calcipotriol 0.005% group and five patients (12.2%) in the vehicle group.

The most frequent reason for withdrawal was patient's personal request in three patients (7.5%) in the LAS37779 1% group and one patient (2.4%) in the vehicle group, while adverse event were only reported as a reason for withdrawal in one patient (0.8%) in the Calcipotriol 0.005% group.

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Psoriasis plaques were located mainly on patients' arms (125 patients, 100.0%), legs (122 patients, 97.6%), trunk (89 patients, 71.2%), and head and neck (73 patients, 58.4%) for all groups.
The mean last exacerbation of psoriasis occurred 14.0 ± 34.6 months before patients' recruitment: 15.6 ± 51.7 months in the LAS37779 1% group, 13.1 ± 24.0 months in the Calcipotriol 0.005% group and 13.4 ± 22.5 months in the vehicle group.

Mean time window between patients' last treatment for psoriasis and patients' recruitment was 7.6 ± 34.6 months: 11.9 ± 51.7 months in the LAS37779 1% group, 7.8 ± 24.0 months in the Calcipotriol 0.005% group and 3.3 ± 22.5 months in the vehicle group.

During the study period, emollients were used by 17 patients (42.5%) in the LAS37779 1% group, 19 patients (43.2%) in the Calcipotriol 0.005% group and by 23 patients (56.1%) in the vehicle group. Emollients were used during 19 ± 17.0 days in the LAS37779 1% group, 21.1 ± 19.6 days in the Calcipotriol 0.005% group and 26.7 ± 19.4 days in the vehicle group.

The baseline characteristics of the safety population showed that mean TSS values for site 1 (elbow or knee) and for site 2 (trunk or limbs) were similar for all patients: 6.9 ± 1.3 and 6.8 ± 1.3, respectively. The mean total PASI score was 9.3 ± 3.8 with 8.6 ± 3.4 in the LAS37779 1% group, 9.3 ± 4.1 in the Calcipotriol 0.005% group and 10.1 ± 3.9 in the vehicle group.

In all groups, the compliance to treatment was good (i.e. at least 80%).

Efficacy results:

Analysis of primary efficacy endpoint:
Mean change from baseline to the end of treatment in the TSS of the two target lesions in the ITT population showed a global decrease in the three groups of treatments, with mean changes of -2.0 ± 1.8, -3.5 ± 1.6 and -1.4 ± 2.0 in the LAS37779 1% group, Calcipotriol 0.005% group and vehicle group, respectively.

The mean relative change from Baseline to the end of treatment (visit 6) was -31.1 ± 27.5%, -52.3 ± 24.6% and -19.0 ± 28.6% for the LAS37779 1% group, Calcipotriol 0.005% group and vehicle group, respectively.

Despite the slight improvement reported in patients treated with LAS37779 1% compared to patients treated with its vehicle (Delta of 0,6 pts), the ITT analysis of the primary efficacy criteria "Change in the average TSS of two target lesions from baseline to the end of treatment" failed to demonstrate significant difference between the two groups.

Additionally, the ITT analysis of the primary endpoint "Change in the average TSS of two target lesions from baseline to the end of treatment" when comparing LAS37779 1% with Calcipotriol 0.005% demonstrated a statistically significant difference in favour of Calcipotriol 0.005% ($p = 0.0002$).
In both cases, similar results were observed in the PP population.

Analyses of other secondary efficacy criteria (TSS sub-scores erythema, induration and scaling, PASI, BSA affected, pruritus, pain intensity, IGA, GIS) did not show any significant difference between LAS37779 1% and its vehicle, and confirm the numerical superiority of calcipotriol 0.005% over LAS37779 1%.

Pharmacokinetic Results:
Pharmacokinetic results will be presented separately in a Pharmacokinetic report completed by Almirall Pharmacokinetic and Drug Metabolism Department.

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Safety Results:
Of the 125 randomized patients in the study, nine (7.2%) experienced at least one local Treatment Emergent Adverse Event (TEAE) (16 episodes): four episodes experienced by three patients (7.5%) in the LAS37779 1% group, four episodes experienced by two patients (4.5%) in the Calcipotriol 0.005% group and eight episodes experienced by four patients (9.8%) in the vehicle group.

All these local TEAE belonged to the “skin and subcutaneous tissue disorders” and the most commonly reported were: skin burning sensation and pruritus. These TEAEs were study drug-related and were of mild/moderate intensity except for three severe episodes of pruritus (one with Calcipotriol 0.005% and two with vehicle).

A total of 50 patients (40.0%) experienced at least one systemic TEAE (93 episodes): 28 episodes experienced by 16 patients (40.0%) in the LAS37779 1% group, 34 episodes experienced by 18 patients (40.9%) in the Calcipotriol 0.005% group and 31 episodes experienced by 16 patients (39.0%) in the vehicle group. The most commonly reported systemic TEAEs were nasopharyngitis, influenza, rhinitis, erythema, arthralgia and headache. All the systemic TEAEs were of mild/moderate intensity except for four severe episodes (one episode of infection and another one of angioderma in the vehicle group and two episodes of migraine in the Calcipotriol 0.005% group).

One male patient in the Calcipotriol 0.005% group had a serious and severe polyarthritis with no relationship to the study drug. The patient was withdrawn from the study.

Analysis of laboratory values showed that values remained in normal range in most of patients, in all treatment groups and for all parameters.

When considering the global assessment for ECGs at visit 6 (Day 56), a total of seven patients (5.9%) had abnormal ECGs with clinical relevance, as determined by the investigator (three patients in the LAS37779 1% group, none in the Calcipotriol 0.005% group and four patients in the vehicle group).

In conclusion, with the relative similar distribution of drug related local and systemic TEAEs in the three treatment groups (active groups and vehicle), it can be considered that LAS37779 1% has a safe profile when used twice daily for up to 8 weeks.

CONCLUSIONS:

The study failed to demonstrate significant difference between LAS37779 1% and its vehicle when assessing the primary efficacy variable. Additional analysis of secondary variables was coherent with the result of the primary efficacy variable showing only limited/slight difference of LAS37779 versus its placebo.

Additionally, due to the quite important difference between the active groups in the primary efficacy criteria, ITT and PP analysis of the primary endpoint “Change in the average TSS of two target lesions from baseline to the end of treatment” when comparing LAS37779 1% with Calcipotriol 0.005% managed to reach statistically significant difference in favour of Calcipotriol 0.005%.

On the basis of the number of local and systemic TEAEs reported and of their characteristics in terms of intensity and correlation with study drug, LAS37779 1% had a satisfactory safety profile.

DATE OF REPORT:
30 April 2009