2. Synopsis

Name of sponsor/company: Almirall Hermal GmbH	Individual study table referring to part V of the dossier Volume: Page:	*(For national authority use only)*
Name of finished product: Not applicable (n.a.)		
Name of active ingredient: Bexarotene (BX) and betamethasone dipropionate (BDP)		

Title of clinical trial:

A phase IIa, 28-day treatment, multi-center, randomized, comparator-controlled, observer-blind trial with intra-individual left/right comparison to investigate the anti-psoriatic efficacy and the safety of an LAS41004 formulation in comparison to an active reference in patients with mild to moderate plaque psoriasis

Investigator(s):

- Center 01: [redacted]
- Center 02: [redacted]
- Center 03: [redacted]

Trial center(s):

3 trial centers in Germany:

- Center 01: bioskin GmbH Hamburg
- Center 02: Dermatological Practice, Blankenfelde-Mahlow
- Center 03: Dermatological Practice, Berlin

Publication (reference):

n.a.

Studied period:	Phase of development:
Date study initiated (first patient first screening): 13-Jun-2014 Date study completed (last patient last visit): 13-Oct-2014	IIa

Objectives:

The objective of this trial was to assess the anti-psoriatic efficacy and safety of the fixed combination LAS41004 in a topical formulation by reference to Daivobet® ointment (calcipotriol plus BDP).

Methodology:

Altogether 2 comparable lesional areas (20 – 300 cm^2, each) were examined per patient; one psoriatic lesion located on the right side and the other one on the left side, whereby both lesions were located in the same anatomical region and were within reach for self-application. The lesions were treated with approximately 2 – 6 mg/cm^2 of IMPs 1 and 2, each, once daily without occlusion on 28 consecutive days. Treatment was performed at the clinical center from Mondays to Fridays under supervision of a study nurse and by the patients at home during the weekend. Prior to treatments clinical assessments were performed: Clinical assessment of erythema, scaling and infiltration for individual evaluation and subsequent calculation of the TSS were performed for both psoriatic lesions at screening and on Days 1, 4, 8, 15, 22 and 29. PGA was performed on Days 1, 4, 8, 15, 22 and 29. A PGTA was performed on Days 4, 8, 15, 22 and 29. On Day 29 the patients were asked their subjective preference on the efficacy and tolerability of the IMPs as PRO. From screening throughout the treatment phase daily recording of AEs/ SAEs, including possible signs of irritation as assessed by clinical assessment of local tolerability and by information on itching and burning from patient was done.

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Methodology (continued): Furthermore, AEs were recorded during a 7-day FU period. Photographs of the 2 treatment areas were taken at baseline (Day 1) and on Day 29. The patients had to perform a FU (visit or telephone call) on Day 36, 7 days after EoT (Day 29). In case of possible AEs/SAEs identified after EoT a further FU was performed up to 30 days after EoT.
Number of patients (planned and analyzed): 40 patients with mild to moderate stable plaque-type psoriasis were planned, randomized and included in the analyses of the FAS and SES. 36 patients were included in the VCS. 4 patients were excluded from the VCS due to major protocol deviations concerning the inclusion/exclusion criteria.
Diagnosis and main criteria for inclusion: Male or female patients aged 18 years or older with mild to moderate stable chronic plaque-type psoriasis, at least 2 symmetrical lesions (plaques for investigation with a TSS $\geq$ 6)
Test product(s), dose and mode of administration, batch number: **IMP 1:** LAS41004 formulation, batch no.: 402KK02, production batch code: 10055320 Topical application of approximately 2 – 6 mg/cm^2 of IMP 1 to an area of 20 – 300 cm^2 once daily. Assuming a daily dosage of 6 mg/cm^2 and an area of 300 cm² (1.8 g/300cm²), a dosage of 2 g/day should not have been exceeded.
Duration of treatment: 28 consecutive days
Reference therapy or controls, dose and mode of administration, batch number: **IMP 2 (comparator/reference listed drug):** Daivobet® ointment, batch no.: 402KK02, production batch code: K0553/913 (calcipotriol 0.05 mg/g plus betamethasone dipropionate 0.5 mg/g [BDP 0.643 mg/g]) Topical application of approximately 2 – 6 mg/cm^2 of IMP 2 to an area of 20 – 300 cm^2 once daily.
Duration of treatment: 28 consecutive days
Criteria for evaluation: **Efficacy variables:** • Evaluation of individual signs (erythema, scaling and infiltration) and calculation of TSS (primary efficacy variable). • PGA. • PRO (subjective preference for efficacy). **Safety variables:** • Relevant medical history. • Physical examination. • Blood pressure and heart rate. • AEs. *Laboratory variable:* • Serum pregnancy test. *Tolerability variables:* • PGTA. • PRO (subjective preference for tolerability). **Cosmetic trait variables:** PRO (subjective preference for cosmetic traits).

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Statistical methods:

Efficacy populations

Intent-to-Treat (ITT)

The full analysis set (FAS) included all randomized patients who received at least one dose of IMP, and had at least one post-baseline assessment of the primary variable. The ITT analysis was based on the FAS.

Per-protocol (PP)

The valid cases set (VCS) included all patients of the FAS, but excluded patients:

- Who did not receive at least 80 % or who received more than 120 % of the planned doses.
- Who took any interfering concomitant medication.

Prior to breaking the blind, other additional criteria might have been added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that resulted in noteworthy study protocol violations.

The PP analysis was based on the VCS.

Safety population

The safety evaluation set (SES) included all patients who received any trial medication at least once; all safety analyses were based on the SES.

Efficacy analyses

Since this was an exploratory trial, all the analyses specified in the following sections were interpreted as non-confirmatory results.

Statistical analyses

Efficacy analyses were based primarily on the FAS. Analyses based on the VCS are provided to assess the sensitivity of the outcomes.

Primary Analysis

The treatment effect was determined within the framework of an analysis of covariance (ANCOVA) model of the TSS on Day 29 with center, application site (`APPLSITE`), baseline TSS (`BaseTSS`) and treatment as fixed effects and subject as random effect.

The difference in treatment effect is given using contrasts within the ANCOVA model by the statistical analysis system (SAS) statement.

The least squares means (LSMeans) of the difference in baseline corrected TSS were tabulated, together with the standard error (SE), two-sided 95 %-confidence interval and p-value. Additionally, p-values of the Type III tests of fixed effects of the model are provided.

Secondary analyses

- Changes from baseline in the TSS on Days 4, 8, 15, and 22 were evaluated for each treated plaque in a similar way to the primary analysis to assess the onset of treatment effect.
- Summary statistics are given for the primary variable TSS and its changes from baseline by treatment and visit for each center.

All the following secondary endpoints were summarized descriptively by treatment:

- Each of the individual signs (erythema, scaling and infiltration) of each treated plaque on Days 1, 4, 8, 15, 22 and 29 including changes in comparison to baseline.
- PGA score of each treated plaque on Days 1, 4, 8, 15, 22 and 29 including the changes in comparison to baseline.

For all individual signs and PGA, frequency counts are presented by treatment and visit, in addition to summary statistics of the scores. Differences in treatment effects were determined following the lines of the primary analysis.

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Statistical methods (continued):

Patients' subjective preference for efficacy of the IMPs is presented by frequency counts. Additionally cumulative frequency counts with decreasing efficacy are presented.

Safety analyses

No formal inferential tests were performed on safety data. The safety analyses were performed on the SES.

Safety was evaluated by tabulations of AEs, vital signs and serum pregnancy tests. Additionally, PGA of tolerability and patient's assessment of tolerability were evaluated.

Adverse events

All AEs occurring during the trial were recorded and classified on the basis of medical dictionary for regulatory activities (MedDRA) terminology, in which a lower level term was assigned to each AE. A listing of each verbatim term and its assigned lower level term is provided.

Treatment-emergent adverse events (TEAEs) were those AEs with an onset on or after the time of the first IMP application. All reported TEAEs were summarized by the number of patients reporting TEAEs stratified by primary system organ class (SOC), preferred term (PT), together with cross-tabulations by seriousness, severity, and relationship to IMP. When summarizing TEAEs by severity or relationship to IMP, each patient was counted only once within an SOC or a PT by using the event with the greatest severity or judged to have the closest causal relationship, respectively, within each category. Summaries are provided by the relation to a specific treatment test field or as not related to a specific test field.

Listings of SAE and patients who prematurely discontinued treatment due to AEs were to be given.

Laboratory analyses

A frequency count of the outcomes of the serum pregnancy test is given by visit.

Other safety analyses

Vital signs (blood pressure and heart rate) and their changes from baseline to Day 29/early discontinuation are presented by summary statistics. Listings are provided for clinical relevance of values outside the acceptable limit on Day 29, given by the investigator. Findings in the physical examination were listed.

PGA of tolerability and patient's assessment of tolerability are presented by treatment using frequency counts. Cumulative frequency counts are provided for patient's outcomes.

Cosmetic traits analyses

Frequency counts of assessments 3 to 10 within the PRO questionnaire are given by treatment.

Summary, conclusions:

Efficacy, tolerability and other results

LAS41004 formulation showed a clear effect in the treatment of mild to moderate plaque-type psoriasis in the clinical assessment after once daily open application over a 28-day treatment period; however, the reference treatment with Daivobet® ointment demonstrated a stronger anti-psoriatic effect.

The primary ANCOVA analysis showed positive estimates of the difference between LAS41004 formulation and Daivobet® ointment in the change from baseline in total sign score (TSS) at each assessment time point (0.6, 1.0, 1.3, 1.5 and 1.2) with p-values of < 0.05 on Days 4, 8, 15, 22 and 29, respectively, indicating statistically significant lower changes from baseline for the treatment with LAS41004 formulation compared to Daivobet® ointment.

The LAS41004 formulation showed a continuous but lower decrease when compared to Daivobet® ointment in mean TSS (mean change from baseline to Day 29/EoT = -4.2 vs.
-5.5, primary endpoint) as well as for each mean individual score—erythema (-1.1 vs. -1.3, scaling (-1.7 vs. -2.2) and infiltration (-1.5 vs. -2.0).

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Summary, conclusions (continued):

Efficacy, tolerability and other results

Overall, moderate erythema, scaling and infiltrate (score 2) had improved following both treatments: In the test areas treated with LAS41004 formulation slight erythema (score 1) and slight infiltrate (score 1) and absent scaling (score 0) were noted in 50 % of the patients; erythema was absent in 15 % and infiltration in 27.5 % of the patients at EoT. A greater improvement was noted in the test areas treated with Daivobet® ointment with more patients showing slight erythema (67.5 %) and more patients with no infiltrate (60 %) and no scaling (77.5 %) at EoT.

The results of the physician's global assessment (PGA) are consistent with the results of the individual signs and the TSS demonstrating an improvement following both treatments: In the test areas treated with LAS41004 formulation mild PGA score (score 2) was assessed in 50 % of the patients, almost clear PGA score (score 1) in 27.5 % and clear PGA score (score 0) in 10.0 % of the patients at EoT. A greater improvement was seen in the test areas treated with Daivobet® ointment with more patients showing almost clear PGA score (55.0 %) or clear PGA score (15.0 %) at EoT.

The patient's reported outcome (PRO) on subjective preference for efficacy results agree with the findings of the clinical efficacy assessment showing that the overall efficacy was rated as very good to good in more than half of the patients (61 %) for LAS41004 formulation and in nearly all patients (98 %) for Daivobet® ointment.

The questionnaire results on consumer traits showed that most of patients rated the handling (practicality of removal and application) and the easiness of application and distribution/spreading as good to very good for both formulations. The majority of patients reported that the skin felt pleasant and caused no itching after treatment with both formulations in the lesional treatment areas. Burning was reported in none of the patients. The disappearing after application on the skin was rated somewhat worse for LAS41004 formulation than for Daivobet® ointment showing more patients rating moderate for this trait. Most of the patients would like using LAS41004 formulation and would recommend using this formulation to a friend/family, but even more patients would prefer and recommend Daivobet® ointment.

In general, the results of the individual centers parallel the findings of the pooled data with respect to the mean TSS reflecting an improvement of psoriatic lesions in both treated test areas, whereby a greater improvement was seen for Daivobet® ointment when compared to the LAS41004 formulation.

Overall, the results of the physician's global tolerability assessment (PGTA) and the PRO on subjective preference for tolerability demonstrated a very good dermal tolerability for LAS41004 formulation and Daivobet® ointment in most of patients.

Safety results

In total, 6 non-serious TEAEs of mild to moderate intensity were reported in 4 patients. 1 TEAE (sensation of burning, PT = application site pain) was considered to be related to treatment with LAS41004 formulation. All other 5 TEAEs (circulatory disturbance, common cold, panic attack, acute rhinosinusitis and worsening of psoriasis on right hand back) were not corresponding to specific test areas and not related to IMP.

The physical examinations did not show any relevant findings in any of the patients except for 1 patient who showed worsening of psoriasis on right hand back outside the test area which was considered as AE and had to be treated with a concomitant medication.

None of the 6 TEAEs had led to premature trial discontinuation and all TEAEs had recovered at the end of the trial.

Overall, both treatments LAS41004 formulation and Daivobet® ointment demonstrated a very good dermal tolerability and there were no other relevant observations related to safety in this trial.

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Summary, conclusions (continued):

Conclusion

The aim of this phase II, multi-center, randomized, comparator-controlled and observer-blind trial was to assess the anti-psoriatic efficacy and safety of LAS41004 formulation (BX 1.0 % plus BDP 0.064 %) in an intra-individual left/right comparison to the active comparator Daivobet® ointment in patients with mild to moderate plaque-type psoriasis.

Overall, under the conditions of this trial LAS41004 formulation showed an anti-psoriatic efficacy and demonstrated to be safe when applied open once daily over a 28-day treatment period; however a greater anti-psoriatic effect was seen for Daivobet® ointment while the dermal tolerability was comparable.

This was confirmed by clinical and subjective assessments: A continuous but lower decrease was seen in mean TSS, mean individual sign scores (erythema, scaling and infiltration) as well as in mean PGA score for LAS41004. The results of the PRO on patient's subjective preference for efficacy agree with these findings reflecting a somewhat less improvement for LAS41004 formulation compared Daivobet® ointment.

The tolerability results of the PGTA and the PRO on patient's subjective preference for tolerability showed a very good and comparable dermal tolerability for LAS41004 formulation and Daivobet® ointment.

In total, 6 non-serious TEAEs were reported in 4 patients of which 1 TEAE (sensation of burning, PT = application site pain) was considered to be related to treatment with LAS41004 formulation. Overall, there were no safety concerns on basis of the results in this trial.

The questionnaire results on consumer traits showed almost comparable results for the two formulations with respect to handling, application, distribution and feeling. Most of the patients would like using LAS41004 formulation and would recommend using this formulation to a friend/family, but even more patients would prefer and recommend Daivobet® ointment.

The slight preference of Daivobet® ointment corresponds with the other outcomes in this trial showing that the fixed dose combination of BX 1.0 % and BDP 0.064 %—LAS41004 formulation—was effective and safe in the treatment of mild to moderate plaque-type psoriasis but the combination of calcipotriol and BDP (Daivobet® ointment) demonstrated a somewhat stronger anti-psoriatic effect in this trial.

Date of the report: 11-May-2015