2 Synopsis

Name of Sponsor/Company: Almirall Hermal GmbH **Name of Finished Product:** LAS 41004 **Name of Active Ingredient:** Betamethasone dipropionate Tazarotene	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)

Title of study:

An Investigator-blind, Controlled Study to Assess the Efficacy of Five Distinct Combinations of LAS 41004 in Different Concentrations Compared to Placebo and to Two Active Controls in a Psoriasis-Plaque-Test

Investigators and related study site:

[redacted]
Gemeinschaftspraxis [redacted]
[redacted]
[redacted] Mahlow
[redacted]

Publication (reference): Not applicable

Studied period (month): 2,5 **Date of first enrolment** 28 Jun 2010 **Date of last completed** 06 Sep 2010	**Phase of development:** Phase II

Objectives:

The primary objective was to gain evidence of the efficacy of five distinct combinations of betamethasone dipropionate (BDP) and tazarotene (TZ) in different concentrations compared to placebo, Zorac®- gel and Daivobet®- ointment in the treatment of Plaque-Type Psoriasis assessed by the AUC of the width of the echo-lucent band (ELB) located at the dermo-epidermal junction as measured by ultrasound at visit 1, 4, 8 and 11.

A secondary objective was to evaluate the efficacy assessed by means of the following signs: scaling, erythema and induration of the test areas. In addition, a total score (sum score of these three signs) was evaluated. All scores were analyzed by displaying the evolution over time during the study and by the percentage of change at visit 11 compared to baseline.

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Methodology:

This was a single centre, investigator-blind, randomized, controlled, intra-individual comparator study to evaluate the efficacy, safety and tolerability of five distinct combinations of LAS 41004 in comparison to known active comparators (Daivobet® as an ointment formulation and Zorac® 0.1% as a gel formulation) as positive controls and placebo as a negative control. Treatment took place over 10 days in a time frame of 14 days (2 weeks), plus one subsequent day without treatment at the end of the study for final evaluations.

Enrolment ceased when the target number of 22 patients was reached. No extension was planned.

Number of patients:	**planned:** 22 **screened:** 22	**randomized:** 22 **completed:** 22	**analysed efficacy:** 22 **analysed safety:** 22

Diagnosis and main criteria for inclusion:

Psoriasis vulgaris (Plaque-Type Psoriasis)

- Male or female patients between 18 and 75 years of age with a diagnosis of stable plaque-type psoriasis (psoriasis vulgaris) for at least 6 months
- Psoriasis plaques that were suitable to be defined as target area lesions by the following criteria:
  - Psoriasis plaques must be located at trunk and/or extremities. Plaques that were located on the head (incl. scalp), palms, sole of the feet, intertriginous or genitoanal areas were not suitable as target areas
  - Comparable psoriasis plaques with at least “2” in each score (Range 0-4) for the three distinct symptoms scaling; erythema; and induration
  - No more than 3 points difference in total score (= sum of scores for scaling, erythema and induration; Range 0-12) of the chosen comparable psoriasis plaques
  - Enough psoriatic surface area to define 8 clearly distinguishable (minimum distance between test areas: 1cm) test areas of at least 1 cm² plaque size
- Patient was willing and able to comply with the requirements of the clinical study protocol. In particular, patient must adhered to concomitant therapy prohibitions of the test areas and must agreed to avoid intense UV exposure of the test areas during the study
- Written informed consent to participate in the study, prior to any study related procedures, indicating an understanding of the purpose of the study
- A patient of childbearing potential agreed to use one of the following contraceptive

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methods for the duration of the study and the following 4 weeks after the end of study :

- Strict abstinence (exception: male partner with a vasectomy for at least 3 months prior to study entry was allowed)
- Combined oral, implanted or injectable contraceptives on a stable dose for at least 3 months prior to study entrance
- Intrauterine device (IUD) inserted for at least 1 month prior to study entrance

Test product dose and mode of administration, batch number:

0.10% TZ + 0.10% BDP	Once-daily application	Topical application in a thin layer	#016K01
0.05% TZ + 0.10% BDP	Once-daily application	Topical application in a thin layer	#016K01
0.10% TZ + 0.05% BDP	Once-daily application	Topical application in a thin layer	#016K01
0.05% TZ + 0.05% BDP	Once-daily application	Topical application in a thin layer	#016K01
0.025% TZ + 0.05% BDP	Once-daily application	Topical application in a thin layer	#016K01

Duration of treatment: 10 days

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

Zorac -gel (0.1%)	Once-daily application	Topical application in a thin layer	#625K68
Daivobet -ointment	Once-daily application	Topical application in a thin layer	#EDSK265
Placebo-ointment	Once-daily application	Topical application in a thin layer	#016K01

Criteria for evaluation:

All randomized patients were summarized in the description of the study population. Efficacy analyses were performed on the full analysis set (FAS). In this study 22 patients were randomized. All 22 enrolled patients were included in safety analyses.

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Efficacy:

The analysis of the efficacy parameters was performed on the FAS without imputation of missing data. To evaluate the robustness of the results, a last observation carry-forward (LOCF) analysis was performed additionally. Efficacy was assessed by:

- Area under the curve (AUC) of the width of the echo-lucent band (ELB) located at the dermo-epidermal junction (representing the combination of acanthotic epidermal thickening and inflammation in psoriasis) as measured by ultrasound at visit 1, 4, 8 and 11
- Width of the ELB located at the dermo-epidermal junction at visits 1, 4, 8 and 11
- Percentage change in width of the ELB located at the dermo-epidermal junction (representing the combination of acanthotic epidermal thickening and inflammation in psoriasis) as measured by ultrasonography at visit 11 compared to baseline
- Percentage change of total score (= sum of scores of scaling, erythema and induration) at visit 11 compared to baseline
- Percentage change of scaling score at visit 11 compared to baseline
- Percentage change of erythema score at visit 11 compared to baseline
- Percentage change of induration score at visit 11 compared to baseline
- Total score (= sum of scores of scaling, erythema and induration) over time (visits 1, 4, 8, 11)
    - Scaling score over time (visits 1, 4, 8, 11)
    - Erythema score over time (visits 1, 4, 8, 11)
    - Induration score over time (visits 1, 4, 8, 11)

Safety:

The safety analysis was based on the safety population. Safety was assessed by:

- Physicians' assessment of tolerability at visits 4, 8 and 11
- Telangiectasia score at visits 2 to 10
- Erythema score at visits 2 to 10
- AEs and SAEs

Statistical methods:

The Statistical Analysis Plan (SAP) defined the statistical analyses for all study evaluations.

All efficacy parameters were analyzed descriptively according to the level of data using

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mean, standard deviation, median and range and frequencies and percentages respectively. No hypothesis testing was performed.

Distribution of continuous variables was visualized graphically by side-by-side box-and whiskers plots organized in treatment groups. Additionally, repeated continuous measurements were presented graphically by plotting the time course of means for symmetric distribution resp. medians for non-symmetric distributions by treatment group. Categorical variables were visualized using component chart plots showing the proportion of observed score classification separately for each treatment group.

Safety Analysis

The analysis of the safety data was based on the safety analysis set (SAS).

All safety data were listed, sorted by patient number and broken down by treatment, if possible. Summary tables were grouped by treatment, if possible. Summary tables of AEs were additionally grouped by intensity, relationship to study medication and summarized by group and subgroup respectively.

According to the level of measurement variables were summarized by mean, median, standard deviation, range and frequencies and percentages respectively.

Interim analyses were not planned due to the short treatment period and the small number of patients.

Post-hoc subgroup analysis

In order to gather more information about the characteristics of the tested medications a post-hoc subgroup analysis was performed. In this analysis, the performance of the study drugs at the lower legs and the performance at other locations (the arms, the trunk and the upper legs) were evaluated separately (section 9.8).

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Summary - Conclusions:

Efficacy Results:

In this study the AUC of width of the ELB, the width of the ELB, scaling score, erythema score, induration score and total score (sum of scaling, erythemea and induration score) were used as efficacy parameters in a psoriasis plaque test.

The highest mean and median AUC values occurred in the Zorac and the the Vaseline group. The lowest AUC values were observed in the Daivobet and 0.05%TZ/0.05%BDP group followed by the 0.025%TZ/0.05%BDP group. The mean AUC was slightly lower in the Daivobet group whereas the median AUC was at lowest in the 0.05%TZ/0.05%BDP group.

The width of ELB in the Zorac and the Vaseline group was higher than in the other treatment groups from visit 4 on. The width of the ELB of Daivobet and combinations of TZ and BDP did not differ at visit 4. At visit 8 slight lower values of the ELB were observed in the Daivobet, 0.025%TZ/0.05% BDP and 0.05%TZ/0.05BDP group compared to the other TZ-BDP combinations. At visit 11, the median width of the ELB was comparable in Daivobet and all TZ-BDP combinations. Absolute mean percentage change of the width of ELB between visit 11 and baseline was lowest in the Zorac group and in the Vaseline group as negative control. The highest absolute mean percentage change occurred in the the Daivobet group, followed by 0.025%TZ/0.05%BDP group and 0.05%TZ/0.05%BDP group.

The most favorable scaling profile at visit 11 was observed in 0.025%TZ/0.05%BDP group followed by 0.1%TZ/0.1%BDP and Daivobet group whereas the lowest rates of test areas without scaling occurred in the Zorac and Vaseline group.

The most favorable erythema profile at visit 11 was observed in the Daivobet group, followed by 0.05%TZ/0.05%BDP whereas the lowest rates of test areas without erythema occurred in the Zorac and Vaseline group.

The most favorable induration profile at visit 11 was observed in the 0.1%TZ/0.05%BDP group followed by Daivobet group whereas the lowest rates of test areas without induration occurred in the Zorac and Vaseline group.

The lowest mean total score value at visit 11 was observed for Daivobet followed by 0.025%TZ/0.05%BDP. Zorac and Vaseline showed the highest mean total score.

Safety Results:

All 22 patients were included in the safety population. The topical treatment of eight pre-defined test areas was performed once daily over 10 days in a time frame of 14 days.

During the study no adverse events (AE), deaths, serious adverse events (SAE) or other

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significant AEs occurred.

All combinations of TZ and BDP under study showed a favorable safety profile throughout the study which was comparable with the active control Daivobet.

Results of post-hoc sub-analysis:

Efficacy results:

In all treatment groups, the mean as well as median AUC was higher for test areas located at the lower leg than for test areas at other locations. Nevertheless, in both subgroups, the highest mean AUC of ELB was observed in Zorac and in the Vaseline group. For test areas located at the lower leg, the lowest mean AUC of ELB occurred in the 0.025%TZ/0.05%BDP and 0.05%TZ/0.05%BDP groups followed by the Daivobet group, whereas for other test areas the lowest mean AUC of ELB was observed in the Daivobet group followed by the 0.05%TZ/0.05%BDP group.

In both subgroups, Zorac and the Vaseline group showed the highest mean and median width of ELB from visit 4 until visit 11. At visit 11, the lowest mean and median width of ELB was observed in Daivobet, 0.025%TZ/0.05%BDP and 0.05%TZ/0.05%BDP group in both subgroups. In all treatment groups, the absolute mean percentage change was considerably higher in test areas at other locations than in test areas at the lower leg. In both subgroups, the highest absolute mean percentage change occurred in the Daivobet, 0.025%TZ/0.05%BDP and 0.05%TZ/0.05%BDP groups.

The scaling score was comparable between both subgroups in all treatment groups at visit 1. At visit 11, all lesions in all TZ/BDP combinations and in the Daivobet group at other locations showed no scaling, whereas the rate of test areas at the lower leg without scaling was highest in the 0.025%TZ/0.05% BDP group, followed by the 0.1%TZ/0.1% BDP and Daivobet groups. In both subgroups, the rate of test areas without scaling was lowest for Zorac and the Vaseline group.

The rate of test areas without erythema was equal or higher in test areas at other locations than in test areas at the lower leg at visit 11. In test areas at the lower leg, the highest rate of test areas without erythema was observed in the 0.05%TZ/0.05%BDP group followed by the Daivobet group, whereas in test areas at other locations the highest rate occurred in the Daivobet group followed by the 0.05%TZ/0.05%BDP and 0.05%TZ/0.1%BDP groups.

At visit 11, the rate of test areas at other locations without induration was at least 91% in all TZ/BDP combinations and the Daivobet group, whereas this rate ranged between 55% and 64% in test areas at the lower leg in all TZ/BDP combinations and the Daivobet group. In both subgroups, the lowest rate of test areas without induration was observed in Zorac and the Vaseline group.

The mean total score was considerably lower in test areas at other locations than in test

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areas at the lower leg in all treatment groups at visit 11. In both subgroups, the highest mean total score occurred in Zorac and the Vaseline group. The lowest mean total score in test areas at the lower leg were observed in the Daivobet and 0.025%TZ/0.05%BDP groups and in test areas at other locations in the Daivobet and 0.1%TZ/0.05BDP groups.

Results of physicians' assessment of tolerability

All test areas at the lower leg were classified as very or good at all visits except for Zorac and the Vaseline group. Test areas at other locations were also mainly classified as very good or good. Single lesions in this subgroup were classified as fair or poor for Zorac, the Vaseline group, the 0.05%TZ/0.05%BDP, 0.1%TZ/0.05%BDP and 0.1%TZ/0.1%BDP groups. Only test areas at other locations were classified as good or very good at all visits for the Daivobet, 0.025%TZ/0.05%BDP and 0.05%TZ/0.1%BDP groups.

Conclusion:

Overall, the present study indicates that the five distinct combinations containing tazarotene and betamethasone diproprionate are more efficient in the treatment of Plaque-Type psoriasis than Zorac -gel and Vaseline.

Although the results in the combination groups and in the Daivobet -ointment group were mostly similar, slightly better values could be seen in the Daivobet -ointment group indicating a higher efficacy of Daivobet -ointment in the improvement of psoriasis plaques compared to the five TZ/BDP-combinations. Differences between the single TZ/BDP-combination groups were small as well. Interestingly, the combination group with the lowest amount of tazarotene and betamethasone diproprionate (0.025%TZ/0.05%BDP) showed the best results in mean percentage change between visit 1 and 11 in most of the categories.

All tested combinations of TZ and BDP study showed a favorable safety profile throughout the study.

Conclusion post-hoc sub-analysis

The subgroup analysis showed that psoriasis plaques at the lower legs responded worse to the applied medications than psoriasis plaques at other body locations.
The data indicate that the five distinct combinations containing tazarotene and betamethasone diproprionate and Daivobet -ointment are more efficient in the treatment of plaque-type psoriasis than Zorac -gel and Vaseline at the lower legs as well as at other body locations.

Date of report:

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