2 Synopsis

Name of Sponsor/Company: Almirall Hermal GmbH **Name of Finished Product:** LAS 41004 **Name of Active Ingredient:** Betamethasone dipropionate Bexarotene	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 and Safety of Different Formulations of LAS 41004 Compared to Placebo and to Active Control in a Psoriasis Plaque Test

Investigators and related study site:

[redacted]
Gemeinschaftspraxis Mahlow
[redacted]

Publication (reference): Not applicable

Studied period: 10 weeks **Date first subject enrolment** 10.01.2011 **Date last subject completed** 21.03.2011	**Phase of development:** Phase II

Objectives:

The primary objective of the study was to gain an indication of efficacy for three distinct combinations of betamethasone dipropionate and bexarotene in different concentrations compared to Vaseline® (bland ointment) and Daivobet® ointment in the treatment of plaque-type psoriasis. The primary objective was accomplished by comparison of the treatment areas over time as assessed by:

- Area under the curve of the width of the echo-lucent band located at the dermo-epidermal junction, measured as the primary endpoint by ultrasound at Visits 1 (defined as Baseline), Visits 4, 8 and 11.

Further secondary endpoints were:

- Percentage change of a score for scaling, for erythema and for induration as well as a total score (sum of the scores of these three individual signs) and the change of the scores over time

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

- Absolute and the percentage change of the width of the echo-lucent band over time
- Outcome of a physicians' assessment of tolerability for each formulation. In addition to this, safety and tolerability was assessed by evaluation of adverse events and serious adverse events.

Methodology:

This was a single centre, investigator-blind, randomized, controlled, intra-individual comparator study to evaluate the efficacy, safety and tolerability of three formulations combining different concentrations of bexarotene and betamethasone in comparison to a known active comparator (Daivobet® as an ointment formulation) as a positive control and Vaseline® as a negative control. Treatment took place over 10 days in a time frame up to 14 days (Visit 1 - 10). After the treatment phase an additional visit without treatment was performed (Visit 11) for final evaluations. The study was expected to recruit up to 22 subjects. A total of 21 subjects were screened and randomized and had completed the study. No extension was planned.

Number of subjects:	**planned:** 22 **screened:** 21	**randomized:** 21 **completed:** 21	**analyzed efficacy:** 21 **analyzed safety:** 21

Diagnosis and main criteria for inclusion:

Psoriasis vulgaris (Plaque -Type Psoriasis)

- Male or female subjects between 18 and 75 years of age with a diagnosis of stable plaque -type psoriasis (psoriasis vulgaris) for at least 6 months
- Psoriatic plaques that were suitable to be defined as target area lesions by the following criteria:
  - Psoriatic plaques must be located on 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 psoriatic plaques with at least "2" in each score (range 0-4) for the three distinct signs: scaling, erythema and induration
  - No more than three points difference in total score (= sum of scores for scaling, erythema and induration; range 0-12) of the chosen comparable psoriatic plaques
  - Enough surface area of the psoriatic plaque to define five clearly distinguishable (minimum distance between test areas: 1cm) test areas of at

Name of Sponsor/Company:
Almirall Hermal GmbH
Name of Finished Product:
LAS 41004

Name of Active Ingredient:
Betamethasone dipropionate
Bexarotene

Individual Study Table Referring to Part of the Dossier

Volume:

Page:

(For National Authority Use Only)

least 1 cm² size

- Subject was willing and able to comply with the requirements of the clinical study protocol. In particular, subject must agree not to use prohibited concomitant therapy in the test areas and 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 subject of childbearing potential agreed to use one of the following contraceptive methods for the duration of the study and for the 4 weeks after study drug discontinuation:
  - 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 inserted for at least 1 month prior to study entrance

Test product dose and mode of administration, batch number:

BX: Bexarotene, BDP: Betamethasone dipropionate

1.0% BX + 0.10% BDP	Once daily application	Topical application in a thin layer	Batch No.: 037K01
0.5% BX + 0.05% BDP	Once daily application	Topical application in a thin layer	Batch No.: 037K01
0.25% BX + 0.05% BDP	Once daily application	Topical application in a thin layer	Batch No.: 037K01

Duration of treatment: 10 days

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

Daivobet® ointment (0.005% calcipotriol, 0.05% betamethasone)	Once daily application	Topical application in a thin layer	Batch No.: EE1K311
Merkur® Vaseline (Merkur 791) (Petrolatum, highly refined mixtures of hydrocarbons)	Once daily application	Topical application in a thin layer	Batch No.: 037K01

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

Criteria for evaluation:

All randomized subjects were summarized in the description of the study population. Efficacy analyses were performed on the full analysis set. In this study 21 subjects were randomized. All 21 enrolled subjects were included in the safety analyses. In each subject, five separate areas with comparable disease severity were treated with the five test products in an intraindividual design.

Efficacy:

The analysis of the efficacy parameters was performed on the full analysis set without imputation of missing data. To evaluate the robustness of the results, a next observation carried backward analysis was performed additionally. Efficacy was assessed by:

Primary endpoint:

- Area under the curve of the width of the echo-lucent band located at the dermo-epidermal junction (representing the combination of acanthotic epidermal thickening and inflammation in psoriasis) as measured by ultrasound at Visits 1 (defined as Baseline), 4, 8 and 11

Secondary endpoints:

- Width of the echo-lucent band located at the dermo-epidermal junction at Baseline, Visits 4, 8 and 11
- Percentage change in width of the echo-lucent band located at the dermo-epidermal junction as measured by ultrasound 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 (Baseline, Visits 4, 8, 11)
- Scaling score over time (Baseline, Visits 4, 8, 11)
- Erythema score over time (Baseline, Visits 4, 8, 11)
- Induration score over time (Baseline, Visits 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

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

- Telangiectasia score at Visits 2 to 10
- Irritation score at Visits 2 to 10
- Adverse events and serious adverse events

Statistical methods:

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

Efficacy Analysis

All efficacy parameters were analyzed descriptively according to the level of data using number, mean, standard deviation, median and range and frequencies and percentages respectively. No hypothesis testing was performed.

The distribution of continuous variables was visualized graphically by side-by-side box- and whiskers plots organized in respect of the treatment applied. In addition, repeated continuous measurements were presented graphically by plotting the time course of means for symmetric distribution or medians for non-symmetric distributions by treatment. Categorical variables were visualized using component chart plots showing the proportion of observed score classification separately for each formulation.

Safety Analysis

The analysis of the safety data was based on the safety analysis set.

All safety data were listed, sorted by subject number and broken down by treatment, when possible. Summary tables were grouped by treatment, when possible. Summary tables of adverse events were additionally grouped by intensity, relationship to study medication and summarized by system organ class and preferred term, 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 because there was no information that would be sought that could be provided by such an analysis.

A subgroup analysis was performed in order to assess the potential differences in efficacy and safety for each formulation in relation to their location (i.e. lower leg versus other locations)**.** This analysis was performed for all primary and secondary endpoints as well as for the physicians' assessment of tolerability.

Name of Sponsor/Company:
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Name of Finished Product:
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Betamethasone dipropionate
Bexarotene

Individual Study Table Referring to Part of the Dossier

Volume:

Page:

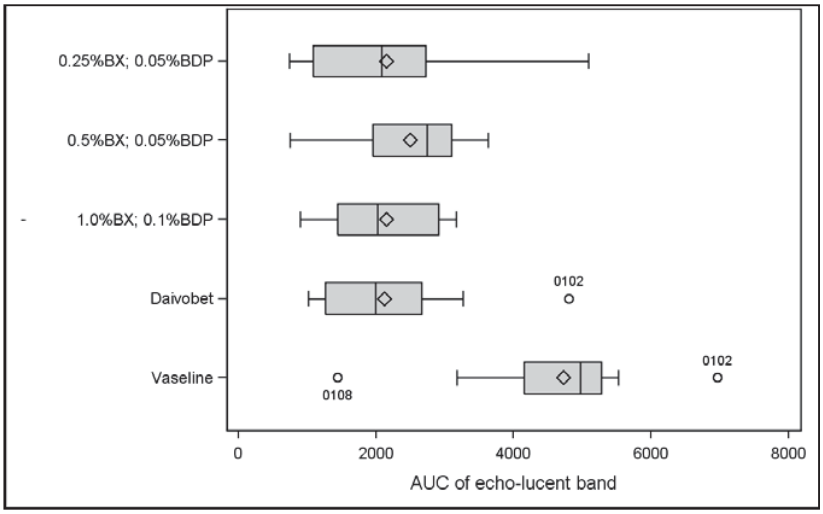
(For National Authority Use Only)

Summary - Conclusions:

Efficacy Results:

In this study the area under the curve of width of the echo-lucent band, the width of the echo-lucent band, scaling score, erythema score, induration score and total score (sum of the scaling, erythema and induration scores) were used as efficacy parameters in a Psoriasis Plaque Test.

The highest mean and median area under the curve values occurred with Vaseline®. The lowest mean area under the curve values were observed with Daivobet® ointment followed by 0.25% bexarotene/0.05% betamethasone dipropionate and 1.0% bexarotene/0.1% betamethasone dipropionate groups, whereas the median area under the curve was lowest with Daivobet® ointment followed by 1.0% bexarotene/0.1% betamethasone dipropionate and 0.25% bexarotene/0.05% betamethasone dipropionate (the results are presented in the Figure below).



The width of the echo-lucent band with Vaseline® was clearly higher than with other treatment from Visit 4 on. At Visit 4, the median width of the echo-lucent band was only slightly higher with 0.25% bexarotene/0.05% betamethasone dipropionate and 1.0 bexarotene/0.1% betamethasone dipropionate compared to Daivobet® ointment. At Visit 8, the median width of the echo-lucent band was comparable between Daivobet® ointment and all bexarotene/betamethasone dipropionate combinations. At Visit 11, the lowest median width of the echo-lucent band was observed with 0.25% bexarotene/0.05% betamethasone dipropionate. The absolute mean and median percentage changes of the width of the echo-lucent band between Visit 11 and Baseline was lowest with Vaseline®. The highest absolute median percentage change occurred with Daivobet® ointment and 0.25% bexarotene/0.05% betamethasone dipropionate whereas the highest absolute

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

mean percentage change occurred with 0.25% bexarotene/0.05% betamethasone dipropionate followed by 1.0% bexarotene/0.1% betamethasone dipropionate and Daivobet® ointment.

The scaling profile at Visit 11 was comparable between all bexarotene/betamethasone dipropionate treatments and Daivobet® ointment. Nevertheless, Daivobet® ointment and all bexarotene/betamethasone dipropionate treatments showed clearly lower scaling scores from Visit 4 on compared to Vaseline®.

The most favorable erythema profile at Visit 11 was observed with 0.25% bexarotene/0.05% betamethasone dipropionate followed by 1.0% bexarotene/0.1% betamethasone dipropionate and 0.5% bexarotene/0.05% betamethasone dipropionate, whereas the percentages of test areas without erythema were clearly lowest with Vaseline®.

The most favorable induration profile at Visit 11 was observed in Daivobet® ointment, followed by 0.25% bexarotene/0.05% betamethasone dipropionate and 1.0% bexarotene/0.1% betamethasone dipropionate, whereas the percentages of test areas without induration were clearly lowest with Vaseline®.

The lowest mean total score values at Visit 11 was observed for Daivobet® ointment, 0.25%bexarotene/0.05% betamethasone dipropionate and 1.0% bexarotene/0.1% betamethasone dipropionate. Vaseline® showed the highest mean total score.

Safety Results:

All 21 subjects were included in the safety analysis set. The topical treatment of five pre-defined test areas was performed once daily over 10 days in a time frame of 14 days.

During the study, a total of two adverse events were observed. Both adverse events were judged as not related to the investigational medicinal products or the study procedure. No deaths, serious adverse events or other significant adverse events occurred.

The physicians' assessment of tolerability at Visit 11 was very good or good in all test areas treated with 0.25% bexarotene/0.05% betamethasone dipropionate, 0.5% bexarotene/0.05% betamethasone dipropionate and Daivobet® ointment, whereas with 1.0% bexarotene/0.1% betamethasone dipropionate and Vaseline® one test area respectively was classified as fair.

In all treatment groups, the physicians' assessment of tolerability was better in other locations than in test areas located on the lower leg.

All combinations of bexarotene and betamethasone dipropionate under study showed a favorable safety profile throughout the study which was comparable with the active control

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

Daivobet® ointment.

Results Subgroup analysis:

Physicians' assessment of tolerability

The tolerability of bexarotene/betamethasone dipropionate combinations and Daivobet® ointment was classified as very good in all test areas in other locations, whereas in single test areas treated with Vaseline® the tolerability was only classified as good at Visit 8 and Visit 11. The tolerability in test areas located on the lower leg was classified as very good or good in 0.25% bexarotene/0.05% betamethasone dipropionate, 0.5% bexarotene/0.05% betamethasone dipropionate and Daivobet® ointment, whereas in single test areas treated with 1.0% bexarotene/0.1% betamethasone dipropionate and Vaseline® the tolerability was assessed as fair.

Conclusion:

Overall, the present study indicates that all combinations of bexarotene and betamethasone dipropionate, as well as Daivobet® ointment, clearly led to more pronounced reduction of the width of the echo-lucent band – representing an improvement of epidermal thickening and inflammation within the psoriatic plaques – than the negative control Vaseline®. This difference could be seen as early as Visit 4 and persisted until the end of the study, leading to clearly higher values of the AUC of width of ELB in the Vaseline® control group than in all the other treatment groups. These results were confirmed by evaluation of the severity of the three psoriasis plaque-related signs, scaling, erythema and induration.

Although the results with Daivobet® ointment and with the bexarotene/betamethasone dipropionate combinations were mostly similar, slightly worse values in some categories (area under the curve and percentage change of width of echo-lucent band, mean percentage change of induration score and percentage change of total score) could be seen in the 0.5% bexarotene/0.05% betamethasone dipropionate group, indicating a trend to a slightly lower efficacy of 0.5% bexarotene/0.05% betamethasone dipropionate in the improvement of psoriatic plaques compared to Daivobet® ointment, 0.25% bexarotene/0.05% betamethasone dipropionate or 1.0% bexarotene/0.1% betamethasone dipropionate.

A subgroup analysis evaluated the performance of the study drugs on the lower legs versus other locations (arms, trunk and upper legs). It could be shown that in most cases psoriatic plaques on the lower legs responded worse to the formulations applied than psoriatic plaques at other body locations. However, 0.5% bexarotene/0.05% betamethasone dipropionate constitutes an exception to this statement by showing better treatment results in the region of the lower leg than at other locations in several categories

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

(median area under the curve of width of echo-lucent band, mean and median percentage change of width of echo-lucent band, median percentage change of redness score, mean percentage change of induration score).

Furthermore, based on the results of the present study a slight tendency to a higher efficacy of 0.25% bexarotene/0.05% betamethasone dipropionate compared to the other combination therapies at other locations than the lower legs can be suspected.

All tested combinations of bexarotene and betamethasone dipropionate showed a favorable safety profile throughout the study.

Date of report:

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