2 Synopsis

Name of Sponsor/Company: Almirall Hermal GmbH	Volume: Page:	(For National Authority Use Only)
Name of Finished Product: LAS 41004		
Name of Active Ingredient: Betamethasone dipropionate Bexarotene		

Title of study:

An Investigator-blind, Controlled Exploratory Study to Assess the Efficacy and Safety of Different Concentrations of Active Ingredients in the project Formulations of LAS 41004 Compared to a Bland Ointment and to Active Control in a Psoriasis Plaque Test

Investigators and related study site:

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Publication (reference):

Not applicable

Studied period: 10 weeks **First Subject In:** 02.05.2011 **Last Subject Out:** 11.07.2011	**Phase of development:** Phase II

Objectives:

Primary Objective

The primary objective of the study was to gain an initial indication of efficacy for five distinct combinations of betamethasone dipropionate and bexarotene in different concentrations, and one combination of tazarotene and betamethasone dipropionate 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 Visit 1 (defined as Baseline), Visits 4, 8 and 11.

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Secondary Objectives

The 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.
Further secondary objectives were to evaluate the safety by:

- Incidence and severity of Adverse Events/Serious Adverse Events and their relationship to the study medication
- Tolerability assessed by physicians' assessment of tolerability for each of the eight formulations
- Irritation assessed by the irritation score
- Telangiectasia assessed by the telangiectasia score

Methodology:

This was a single center, investigator-blind, randomized, controlled, intra-individual comparator study to evaluate the efficacy, safety and tolerability of five formulations combining different concentrations of bexarotene and betamethasone dipropionate in comparison to:

- Combination of tazarotene and betamethasone dipropionate
- Active comparator (Daivobet® as an ointment formulation) as a positive control
- Vaseline® as a negative control

Treatment took place over 10 days in a time frame up to 14 days (Visit 1 - 10). 1 – 3 days after Visit 10 an additional visit without treatment was performed (Visit 11) for final evaluations. The study was expected to recruit 22 subjects. A total of 22 subjects were screened and randomized and had completed the study. No extension was planned.

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

Diagnosis and 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 12 months
- Psoriatic plaques that were suitable to be defined as target area lesions by the following criteria:

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- Psoriatic plaques had to 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 eight clearly distinguishable (minimum distance between test areas: 1cm) test areas of at least 1 cm² size

- Subject was willing and able to comply with the requirements of the clinical study protocol. In particular, subject had to agree not to use prohibited concomitant therapy in the test areas and had 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:
  - Combined oral, implanted or injectable contraceptives on a stable dose for at least 3 months prior to study entrance, OR
  - Partner who has been sterilized by vasectomy for at least 4 weeks prior to study entrance, OR
  - Intrauterine device inserted for at least 1 month prior to study entrance, AND
  - Barrier methods (e.g. condom, cervical caps, diaphragm)
- Male subjects with sexual partners who were pregnant, possibly pregnant, or who could have been become pregnant had to use condoms during sexual intercourse for the duration of the study and for at least 4 weeks after the last dose of drug

Test product, dose and mode of administration, batch number:

BX: Bexarotene, BDP: Betamethasone dipropionate, TZ Tazarotene

1.0% BX + 0.10% BDP	Once daily application	Topical application in a thin layer and covered by a hypoallergenic patch (semi-occlusive conditions)	Batch No.: 114K02 120K03
0.5% BX + 0.10% BDP	Once daily application	Topical application in a thin layer and covered by a	Batch No.: 114K02 120K03

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		hypoallergenic patch (semi-occlusive conditions)	
1.0% BX + 0.05% BDP	Once daily application	Topical application in a thin layer layer and covered by a hypoallergenic patch (semi-occlusive conditions)	Batch No.: 114K02 120K03
0.5% BX + 0.05% BDP	Once daily application	Topical application in a thin layer and covered by a hypoallergenic patch (semi-occlusive conditions)	Batch No.: 114K02 120K03
0.25% BX + 0.05% BDP	Once daily application	Topical application in a thin layer and covered by a hypoallergenic patch (semi-occlusive conditions)	Batch No.: 114K02 120K03
0.2% TZ + 0.10% BDP	Once daily application	Topical application in a thin layer and covered by a hypoallergenic patch (semi-occlusive conditions)	Batch No.: 114K02 120K03

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.: EE6K079
Merkur® Vaseline	Once daily	Topical	Batch No.:

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(Merkur 791) (Petrolatum, highly refined mixtures of hydrocarbons)	application	application in a thin layer	114K02 120K03

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 22 subjects were randomized. All 22 enrolled subjects were included in the safety analyses. In each subject, eight separate areas with comparable disease severity were treated with the eight test products in an intra-individual design.

Efficacy evaluation:

The analysis of the efficacy parameters was performed on the full analysis set without imputation of missing data. 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)

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Safety evaluation:

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
- 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:
The analysis of the efficacy variables was performed primary on the full analysis set without imputation of missing data. Since few measurements at Visit 1 of one subject were missing, an additional sensitivity analysis was performed and the missing measurements were replaced by the mean of the other measurements of Visit 1.
The primary efficacy endpoint was the area under the curve of width of the echo-lucent band as measured by ultrasound at the Visits 1, 4, 8 and 11. The area under the curve was calculated for each treatment formulation and was summarized using the following descriptive statistics; the number of observations, mean, standard deviation, median, minimum and maximum. No statistical hypotheses were tested.
Due to the level of measurement descriptive statistics such as mean, median, standard deviation, range (minimum, maximum), frequencies and percentages were displayed for the secondary efficacy variables. Summary tables were grouped by treatment formulation and visit, if it is reseaonable.
The distribution of continuous variables was visualized graphically by side-by-side box-and whiskers plots organized in treatment formulations.
Additionally, repeated continuous measurements were presented graphically by plotting the time course of means for symmetric distribution or 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.
All safety data were listed, sorted by subject number and broken down by treatment formulation. Summary tables were grouped by treatment formulation. 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.

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Interim and Subgroup Analysis:
Interim analyses were not planned.
A subgroup analysis was performed for all primary and secondary endpoints as well as for the physicians` assessment of tolerability 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).

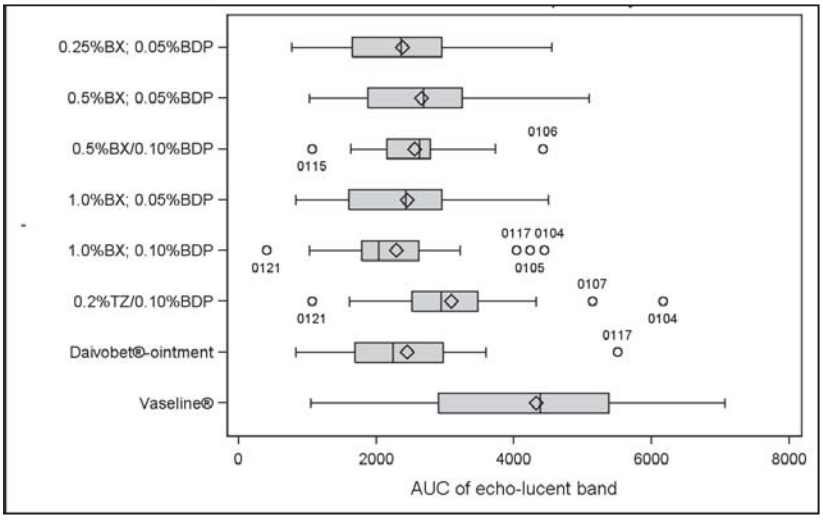
Summary - Conclusions:

Efficacy Results:

In this study, the area under the curve of the width of the echo-lucent band, the width of the echo-lucent band, the scaling score, the erythema score, the induration score and the total score (sum of the individual scaling, erythema and induration scores) were used as efficacy parameters in a Psoriasis Plaque Test. The primary efficacy endpoint is the area under the curve of width of the echo-lucent band measured after Visit 1, 4, 8 and 11.

The highest mean area under the curve of width of the echo-lucent band was observed with Vaseline® followed by 0.2%TZ/0.10%BDP whereas the lowest mean area under the curve of width of the echo-lucent band occurred with 1.0%BX/0.10%BDP followed by 0.25%BX/0.05%BDP. The lowest median area under the curve occurred with 1.0%BX/0.10%BDP, followed by Daivobet® ointment and 0.25%BX/0.05%BDP, whereas the highest median area under the curve was observed with Vaseline®. The results are presented in the Figure 1.

Figure 1: Area Under the Curve of width of echo-lucent band (full analysis set)



The width of the echo-lucent band was considerably higher with Vaseline® from Visit 4 on. At Visit 4, the median width of the echo-lucent band was lowest with 1.0%BX/0.10%BDP. At Visit 8, the median width of the echo-lucent band was comparable between Daivobet®

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ointment and all BX/BDP combination formulations, whereas the median width of echo-lucent band was slightly higher with 0.2%TZ/0.10%BDP formulation. At Visit 11, the lowest median width of the echo-lucent band was observed with 1.0%BX/0.10%BDP. The absolute mean and median percentage change between Visit 11 and Visit 1 was lowest with Vaseline®. The highest absolute mean and median percentage change occurred with 1.0%BX/0.10%BDP, followed by 1.0%BX/0.05%BDP.

The scaling profile at Visit 11 was comparable between all BX/BDP, TZ/BDP treatment formulations and Daivobet® ointment and showed clearly lower scaling scores from Visit 4 on compared with Vaseline®.

The most favorable erythema profile at Visit 11 was observed with 1.0%BX/0.10%BDP followed by 0.5%BX/0.05%BDP, whereas the percentages of test areas without erythema were clearly lowest with 0.2%TZ/0.10%BDP.

The most favorable induration profile at Visit 11 was observed with 1.0%BX/0.10%BDP, followed by 1.0%BX/0.05%BDP and Daivobet® ointment, whereas the percentages of test areas without induration were clearly lowest with Vaseline®.

The lowest mean total score values at Visit 11 was observed with 1.0%BX/0.10%BDP, followed by 0.5%BX/0.05%BDP and 1.0%BX/0.05%BDP. Vaseline® showed the highest mean total score.

With all BX/BDP, TZ/BDP treatment formulations and with Daivobet® ointment, the mean and median area under the curve was higher for test areas located on the lower leg than for test areas at other locations. Nevertheless in both subgroups, the highest mean and median area under the curve of echo-lucent band was observed with Vaseline®. For test areas located on the lower leg, the lowest median area under the curve of the width of echo-lucent band occurred with 1.0BX/0.10%BDP, followed by 0.5%BX/0.10%BDP, whereas for other located test areas the lowest median area under the curve of the width of the echo-lucent band was observed with 1.0%BX/0.1%BDP, followed by Daivobet® ointment.

Safety Results:

All 22 subjects were included in the safety analysis set. 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, one adverse event was observed. This adverse event was judged as not related to the investigational medicinal products or the trial procedure. No deaths, serious adverse events or other significant adverse events occurred.

Physicians` assessment of tolerability at Visit 11 was in all test areas assessed as very good with the exception of one test area assessed as good with 0.5%BX/0.10%BDP, two test areas assessed as good with 0.2%TZ/0.10%BDP and one test area assessed as fair with Vaseline®.

All test areas treated with BX/BDP formulations or Daivobet® ointment were classified according to the study protocol as ‘normal vascular pattern with fine capillary loop under

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highest magnification' from Visit 2 to Visit 10. Single lesions with 0.2%TZ/0.10%BDP and Vaseline® were classified as 'capillary hyperaemia with slight elongation and dilatation of blood vessels not visible to the naked eye' at Visit 4, 7, 8, 9 and 10.

All test areas treated with BX/BDP formulations showed no irritative erythematous reaction from Visit 2 to Visit 10. Single lesions with 0.2%TZ/0.10%BDP, Daivobet® ointment and Vaseline® were classified as 'slight diffuse, partial of follicular erythema' at the Visits 4 to 10.

In all treatment formulations, the physicians` assessment of tolerability was comparable in test areas located on the lower leg and at other locations.

In summary, all combinations of BX/BDP under study showed a favorable safety profile throughout the study which was comparable with the active control Daivobet® ointment.

Conclusion:

In conclusion, the present study indicates that the five distinct combinations containing BX and BDP are largely as effective as Daivobet® ointment, slightly more effective than the formulation containing TZ and BDP and clearly more effective than Vaseline® in the treatment of plaque-type psoriasis.

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

A subgroup analysis evaluated the performance of the study medications at the lower legs and at other locations (arms, trunk and upper legs) separately. In general, lesions on the lower legs responded less to therapy than lesions on other locations. While the performance of the formulation containing 1.0% BX and 0.1% BDP was comparable with Daivobet® ointment at other locations, better values (median AUC, mean absolute percentage change in scaling score, mean and median absolute percentage change in erythema score, mean absolute percentage change in induration score, mean absolute percentage change of total score) could be found for the 1.0% BX and 0.1% BDP formulation than for the approved standard therapy.

Date of report: 06.03.2012