2 SYNOPSIS

Sponsor: Almirall Hermal GmbH **Name of Finished Product:** LAS41004	*(For national Authority Use only)*
Name of Active Ingredients: bexarotene betamethasone dipropionate	

Title of Clinical Trial:	A 29 day, single-center, randomized, vehicle- and comparator-controlled, observer-blind, proof of concept Psoriasis Plaque Test with an intra-individual comparison, to investigate the anti-psoriatic efficacy, tolerability and safety (skin atrophy) of LAS41004 formulations in comparison to a vehicle and an active reference in patients with mild to moderate plaque psoriasis	
Investigator:	[redacted] proDERM Institute for Applied Dermatological Research GmbH	
Study Centre(s):	proDERM Institut für Angewandte Dermatologische Forschung GmbH, Kiebitzweg 2, 22869 Schenefeld	
Publication (reference):	**Dumas KJ, Scholtz ER** (1972) The psoriasis bio-assay for topical corticoid activity. Acta Derm Venerol 53:43-48 G1 **AWMF online** (2011) Leitlinie zur Therapie der Psoriasis Vulgaris, update 2011 Register Nr. 013/001	
Phase of development:	Phase IIa, proof of concept trial	
Studied Period	Date of First Enrollment: 26FEB2014	Date of Last Terminated: 07MAY2014
Objectives:	<u>Primary Objective</u> The primary objective was to gain evidence suggesting efficacy of the investigational products in the treatment of plaque-type psoriasis as assessed by the AUC of the width of the echo-lucent band based on sonography measurements at Day 1 (baseline), Days 4, 8, 12, 22, and 29 to show trends towards superiority for the investigational products to their vehicle and non-inferiority of the investigational products to the comparator, and to support prototype selection and dose finding. <u>Secondary Objectives</u> • Efficacy investigation of the individual scores for erythema and induration at Days 4, 8, 12, 22, and 29 by descriptive comparisons to baseline. • Efficacy investigation of the total score (sum of the erythema and induration scores) at Days 4, 8, 12, 22 and 29 regarding changes of total scores by descriptive	

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	comparisons to baseline. • Efficacy investigation of the width of echo-lucent band over time by calculation of changes to baseline for Days 4, 8, 12, 22 and 29. • Safety investigation of tolerability parameters assessed by a dermatologist at Days 4, 8, 12, 22, and 29. • Safety investigation of skin atrophy assessments at Days 4, 8, 12, 22, and 29 on non-lesional test areas. • Safety investigation of skin atrophy by ultrasound assessments over time by calculation of changes from baseline for post-baseline time points. • Safety investigation by daily assessment of local irritation (dermal reaction). Additionally, the following parameters were documented: • Assessment of AEs and SAEs and their causal relationship to trial medication. • Other safety parameters (blood pressure, heart rate, pregnancy test). • Digital photo documentation at Day 1 and Day 29	
Methodology:	Single-center, randomized, vehicle- and comparator-controlled, observer-blind, proof of concept with intra-individual comparison.	
Number of Patients:	Enrolled: 18	Analyzed: 18 (FAS) 17 (PP)
Diagnosis and Main Criteria for Inclusion:	Male and female patients aged 18 to 75 with mild to moderate chronic plaque psoriasis (plaques with a clinical score of the individual signs, erythema, and induration of ≥ 2 for each sign, and body surface area (BSA) involvement < 10 %), were enrolled.	
Test Products:	3 formulations with the same concentration of betamethasone dipropionate (BDP, 0.064 %) combined with bexarotene (BX) in different concentrations (BX 0.25 % (batch no. 10055323), BX 0.5 % (batch no. 10055321), BX 1 % (batch no. 10055320)), and one bexarotene monoformulation (BX 1 % (batch no. 10055322)): Name: LAS41004 (bexarotene with and without betamethasone dipropionate). Active ingredient: with and without betamethasone dipropionate Route of administration: Topical	
Reference Product:	Name: Daivobet® (betamethasone dipropionate plus calcipotriol)	

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	Active ingredients: Calcipotriol 50 µg/g Betamethasone dipropionate 0.64 mg/g Route of administration: Topical Batch Number: EH2463	
Placebo:	Name: Vehicle of LAS41004 Active ingredient: None Route of administration: Topical Batch Number: 10055324	
Method and Mode of Application:	For each of the test products the amount covering the tip of a spatula was applied once daily for a total of 20 times (5 times per week). The products were applied (gently massaged into the skin) on psoriatic plaques. The test products were assigned to the test areas according to the randomization scheme.	
Duration:	Duration of Treatment: 4 weeks per patient	Duration of Study: 4 weeks (without follow-up period)
Assessment(s):	Clinical evaluations (visually and by palpating the respective test area) regarding erythema and induration were done by the Investigator at Days 1, 4, 8, 12, 22 and 29 according to the following scale for each parameter separately: 0 = none 1 = mild 2 = moderate 3 = severe 4 = very severe Individual Scores and total scores (the sum of the erythema and induration scores) were documented at each assessment day. The total score ranged from 0 to 8. Before each re-application of the products, the study nurse investigated the test area for dermal reactions: Dermal reactions at each test area in comparison to the surrounding plaque, were assessed according to the following scale: 0 = no reactions 1 = slight diffuse, partial or follicular erythema 2 = clear, sharply demarcated erythema 3* = severe erythema with infiltrate and/or epidermal defect (blisters, erosions) 4* = very severe erythema with infiltrate and/or epidermal defects (blisters, erosions) *in case of "3" and higher the Investigator had to be informed and the respective	

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test product had to be prematurely discontinued (LOCF).

The three test areas with non-lesional skin (unaffected by psoriasis) were assessed for safety reasons regarding dermal reactions before re-application.

The local tolerability was judged by a dermatologist at all test areas at Days 4, 8, 12, 22, and 29. The following scale was used:

1 = very good
2 = good
3 = fair
4 = poor
5 = very poor

Assessment of skin atrophy was done at test areas with non-lesional skin, at Days 4, 8, 12, 22 and 29.

Skin atrophy was assessed according to the following scale, taking into account the flattening of skin markings and the increase of skin thinning and transparency as reflected by visibility of the underlying vessels (Frosch and Wendt 1985):

0 = no change
0.5 = slight change
1 = moderate change
2* = severe change
3* = very severe change

* in case of "2" and higher the Investigator had to be informed and the respective test product had to be prematurely discontinued (LOCF).

Instrumental Measurements:	The width of the echo-lucent band of the psoriatic plaque was measured with a 22 MHz ultrasound instrument before the first application of the products at Day 1 (baseline), before application of the products at Days 4, 8, 12, 22, and at Day 29 (end of treatment). Additionally, possible skin atrophy was measured by ultrasound measurement of the skin thickness at the three test areas on the volar forearm. Clinical (digital) photography was performed by using a high resolution digital camera at baseline (Day 1) and at Day 29.
Plan for Data Analysis / Statistics:	Primary endpoint: AUC of width of echo-lucent band from Day 1 (baseline) to Day 29 on lesional skin. Secondary endpoints: a) Scores separately for erythema and induration at Days 1, 4, 8, 12, 22 and 29 on lesional skin, b) Total scores (sum over erythema and induration scores) at

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	Days 1, 4, 8, 12, 22 and 29 on lesional skin. c) Width of echo-lucent band of lesional skin at Days 1, 4, 8, 12, 22, and 29 and its percentage change at Days 4, 8, 12, 22, and 29. d) Tolerability scores assessed by a dermatologist at Days 4, 8, 12, 22, and 29 on lesional skin. e) Skin atrophy scores on non-lesional skin at Days 4, 8, 12, 22 and 29. f) Skin atrophy assessment on non-lesional skin by ultrasound measurements at Days 1, 4, 8, 12, 22, and 29. g) Dermal reaction scores at Days 4, 8, 12, 22, and 29 on both lesional and non-lesional skin.
Safety:	• Physical examination. • Monitoring of blood pressure and pulse rate. • Documentation and analysis of adverse events. • Pregnancy test (for women of child bearing potential). • Assessment of possible skin atrophy on non-lesional skin. • Assessment of local irritation (dermal reaction). • Assessment of local tolerability by dermatologist.
Efficacy Results:	Primary Objective The primary objective was to gain evidence suggesting efficacy of investigational products in the treatment of plaque-type psoriasis as assessed by the AUC of the width of the echo-lucent band based on sonography measurements at Day 1 (baseline), Day 4, 8, 12, 22 and 29 and to show trends towards superiority for the investigational products to their vehicle and non-inferiority of the investigational products to the comparator and to support prototype selection and dose finding. This was done regarding the width of the echo-lucent band as measured by sonography at study Days 1, 4, 8, 12, 22 and 29. The evaluated parameter was the AUC over the course of the study for all treatments. Table 1 shows summary statistics (sorted from highest to lowest mean value) for the AUC calculated on treatment induced changes in width of echo lucent band:

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FAS n = 18	Ultrasound. AUC on Band Width Change to Day 1 (µm*day)					
	N	**mean**	**SD**	**min**	**median**	**max**
Reference	18	-8048.6	4845.1	-19633.6	-5801.8	-2987.0
BX 0.25 % + BDP	18	-6366.3	3507.0	-13633.4	-5680.8	-1556.8
BX 0.5 % + BDP	18	-6296.8	3580.3	-16463.3	-5076.9	-2501.8
BX 1 % + BDP	18	-4739.0	2224.6	-8001.1	-4903.9	-1327.8
BX 1 % mono	18	-1546.5	2266.5	-4646.8	-1768.9	4956.1
Vehicle	18	-601.5	2597.9	-9100.0	-576.2	3376.2

Table 1: Ultrasound AUC on Changes of Width of Echo-Lucent Band to Day 1 (FAS)

The biggest mean reduction regarding the width of the echo-lucent band in the course of this study was achieved by the reference Daivobet®. The formulations containing 0.25% BX, 0.5% BX and 1% BX combined with BDP, BX mono and the Vehicle led to lower mean reduction regarding the width of the echo-lucent band. For the formulations containing 0.25% BX and 0.5% BX combined with BDP the mean reduction regarding width of echo-lucent band were on the same level however for the formulation containing 0.5% BX combined with BDP a higher standard deviation was documented.

Table 2 shows summary statistics (sorted from highest to lowest mean value) for the differences to vehicle of the AUC calculated on changes in width of echo lucent band and the result for the comparison by paired t-Test:

FAS n = 18	Difference to Vehicle for AUC on Band Width Change [µm*day]					
	n	**mean**	**SD**	**Lower CI limit**	**Upper CI limit**	**Results of paired t-Test**
BX 0.25 % + BDP	18	-5764.8	3356.8	-7434.1	-4095.5	<0.0001

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BX 0.5 % + BDP	18	-5695.4	4521.6	-7943.9	-3446.8	<0.0001
BX 1 % + BDP	18	-4137.5	3216.8	-5737.2	-2537.8	<0.0001
BX 1 % mono	18	-945.0	2227.7	-2052.8	162.8	0.0897

Table 2: Ultrasound AUC on Changes of Width of Echo-lucent Band to Day 1, Differences to Vehicle (FAS)

The greatest difference to vehicle regarding width of echo-lucent band in the course of this study was achieved by the formulation containing 0.25% BX combined with BDP followed by the formulations 0.5% BX and 1% BX combined with BDP. The comparison of the formulations to the vehicle by paired t-Test showed significant higher reduction regarding the width of the echo-lucent band in the course of this study for the formulations. The smallest difference to vehicle was detected for BX mono. BX mono was not significantly different from vehicle (paired t-Test). Superiority of BX 0.25 + BDP, BX 0.5 % + BDP and BX 1 % + BHP are shown towards the vehicle indicated by p values smaller than 0.5.

Table 3 shows summary statistics (sorted from highest to lowest mean value) for the ratio to the reference of the AUC calculated on changes in width of echo lucent band and the result for the comparison by paired t-Test:

FAS	**Ratio to Reference for AUC on Band Width Change [µm*day]**					
n = 18	**n**	**mean**	**SD**	**Lower CI limit**	**Upper CI limit**	**Results of paired t-Test**
BX 0.5 % + BDP	18	0.87	0.37	0.68	1.06	0.0960
BX 0.25 % + BDP	18	0.83	0.28	0.69	0.97	0.0254

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BX 1 % + BDP	18	0.69	0.38	0.50	0.88	0.0049

Table 3: Ultrasound AUC on Changes of Width of Echo-lucent Band to Day 1, Ratio to Reference (FAS)

The biggest ratio to reference regarding the width of the echo-lucent band in the course of this study was achieved by the formulation containing 0.5% BX combined with BDP followed by the formulation 0.25% BX and 1% BX combined with BDP. The comparison of the formulations containing 0.25% BX and 1% BX combined with BDP to the Reference by paired t-Test showed significantly higher reduction regarding the width of the echo-lucent band in the course of this study for the reference. 0.5 % BX in combination with BDP was not significantly different compared to the reference. The mean values of ratios to reference and the p-values for the comparison versus reference show hints for superiority of reference over the test products BX 0.25 %, BX 0.5% and BX 1 % combined with BDP.

Secondary Objectives

Secondary objectives were the percentage changes on Days 4, 8, 12, 22 and 29 compared to baseline regarding the width of echo-lucent band.

Hardly any changes (in percent) in the width of the echo-lucent band were seen after application of the vehicle and only marginal changes were seen after application of BX mono. The most pronounced reduction in the width of the echo-lucent band was achieved by the reference product, followed by the other three test combinations of BX in different concentrations in combination with BDP.

Furthermore the efficacy was evaluated by means of visual assessments (erythema and induration). Erythema and induration scores decreased for the reference product and BX 0.25 %, BX 0.5 % and BX 1 %. Minimal changes were seen after application of the vehicle and BX mono. Secondary visual efficacy endpoints were the total score (sum score of erythema and induration) over time (Days 1, 4, 8, 12, 22 and 29) and percentage change of total score. Results were compared to baseline.

A decrease in the total sum score was seen after application of the reference product, while minimal change was seen after application of the vehicle and BX mono. The three test products with different concentrations of bexarotene performed similarly; i.e.

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	after application of all three test products the total sum score was reduced compared to baseline values but to a lesser extent compared to the reference product.
Safety Results:	No dermal reactions were observed after application of the test products, except for the vehicle. After application of the vehicle at Day 4 and Day 5 one dermal reaction at each day was graded with a "1" (slight diffuse, partial follicular erythema). This reaction was no longer present at the following days. In the majority of assessments the local skin tolerability was judged as very good, in a few cases the local tolerability was judged as good. No other grades than very good or good were given. Skin atrophy was assessed visually at test areas with non-lesional skin. Hardly any skin atrophy was assessed after application of the vehicle, BX 1 % combined with BDP and the reference product. A decrease in skin thickness was measured by ultrasound after application of the reference product and to a lesser extent after application of BX 1 % and BDP. 8 non serious adverse events were documented in 3 patients in this study. 6 of these adverse events were of mild severity, while two were judged as moderate. No serious adverse events occurred. In one patient (No. 5) after application of BX 1% in combination with BDP slight erythema and papules were noted. These AEs were product related. However, these AEs were of mild severity and application of the respective product was continued. All other AEs were not product related and all patients recovered without sequelae There were no relevant changes in pulse rate and blood pressure between screening and final visit. All female women of childbearing potential had a negative pregnancy test at screening and at the final visit.
Conclusions:	• The biggest reduction regarding the width of the echo-lucent band (AUC) was achieved after application of the reference product. BX 0.25 %, BX 0.5 %, and BX 1 % combined with BDP, BX mono and the vehicle led to lower reduction of the width of the echo lucent band. • Significant differences in the width of the echo-lucent band (AUC) between vehicle and test products were seen after application of BX 0.25% combined with BDP followed by

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the test products BX 0.5 % and BX 1 % combined with BDP. BX 0.25 %, BX 0.5 %, and BX 1 % combined with BDP show superiority of these products over the vehicle.

- BX mono was not significantly different from the vehicle regarding the reduction of the width of the echo-lucent band (AUC).
- BX 0.5 % was not significantly different from the reference product regarding the width of the echo-lucent band (AUC). Application of the reference product led to higher reduction in the width of the echo-lucent band compared to BX 0.25 % and BX 1 % combined with BDP. The mean values of ratio to reference and the p-values for the comparison versus the reference show hints for superiority of the reference over the test products BX 0.25 %, BX 0.5 % and BX 1 % combined with BDP.
- A decrease in erythema and induration was seen after application of the test products BX 0.25 % + BDP, BX 0.5 % + BDP, BX 1 % + BDP and the reference product. Hardly any decrease was seen after application of the vehicle and BX 1 % mono.
- The total score (sum of erythema and induration) decreased over time for almost all test products (BX 0.25 % + BDP, BX 0.5 % + BDP, BX 1 % + BDP and the reference product) except for BX 1 % mono and the vehicle.
- In the majority of assessments the local skin tolerability was judged as very good, in a few cases the local tolerability was judged as good.
- No dermal reactions were assessed after application of the test products, except for the vehicle once at Day 4 and Day 5.
- Hardly any skin atrophy (non-lesional skin) was assessed visually after application of the vehicle, BX 1 % combined with BDP and the reference product (only tested formulations for skin atrophy).
- A slight reduction in skin thickness was measured after application of the reference product and BX 1 % and BDP by ultrasound (non-lesional skin), however this reduction is considered as clinically not significant.
- 8 non serious adverse events in 3 patients occurred in this study.
- Two of these AEs (slight erythema and papules) were

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related to the application of BX 1 % in combination with BDP. These 2 AEs were of mild severity and the application of the test product was not discontinued.

- All other 6 AEs were not test product related.
- All AEs recovered without sequelae.
- No serious AEs occurred in this study.
- No relevant changes in pulse rate and blood pressure between screening and final visit were seen.