1 TITLE PAGE

Study Title	Randomized, observer-blind, multi-center, reference-controlled phase IIb study to evaluate the efficacy of topically applied LAS41002 lotion in the treatment of scalp psoriasis
Name(s) of Test Drug(s)/ Investigational Product(s)	LAS41002 Lotion/0.1 % mometasone furoate
Reference	Ecural® solution
Indication Studied	Topical treatment of scalp psoriasis
Study Design	Multi-center, randomized, two-arm, observer-blind, phase IIb clinical study, reference controlled
Name of Sponsor	Almirall Hermal GmbH Scholtzstr. 3 21465 Reinbek
Protocol Identification	H 521 000 - 0915
Development Phase of Study	Phase IIb
Study Initiation Date (first patient screened)	January 7, 2010
Date of Early Study Termination	Not applicable
Study Completion Date (last patient completed)	April 19, 2010
Coordinating Investigator	[redacted] proDERM Institut für Angewandte Dermatologische Forschung GmbH, Kiebitzweg 2, 22869 Schenefeld/Hamburg [redacted]
Project Coordinators	[redacted] Almirall Hermal GmbH Scholtzstr. 3 21465 Reinbek
GCP	The study was performed in compliance with GCP (CPMP/ICH/135/95)
Date of Report/Final	August 12, 2010
Previous Reports	Preliminary report: June 21, 2010

2 SYNOPSIS

Sponsor: Almirall Hermal GmbH **Name of Finished Product:** LAS41002 Lotion	*(For Authority Use only)*
Name of Active Ingredients: 0.1 % mometasone furoate	

Title of Study:	Randomized, observer-blind, multi-center, reference-controlled phase IIb study to evaluate the efficacy of topically applied LAS41002 lotion in the treatment of scalp psoriasis
Coordinating Investigator:	[redacted], proDERM Institut für Angewandte Dermatologische Forschung GmbH
Principal Investigators:	[redacted]
Study Centre(s):	proDERM Institut für Angewandte Dermatologische Forschung GmbH, Kiebitzweg 2, 22869 Schenefeld/Hamburg, Germany Universitätsklinikum Schleswig-Holstein Klinik für Dermatologie, Allergologie und Venerologie, Ratzeburger Allee 160, D – 23538 Lübeck Psoriasis Study Center, Dpt. of Dermatology, Venerology and Allergology, Charité-Universitätsmedizin Berlin, CCM, Charitéplatz 1, D – 10117 Berlin Praxis Dr. Scholz, Dr. Sebastian, Dr. Schilling, Bahnhofstraße 1, D – 15831 Mahlow Klinikum der Johann Wolfgang Goethe-Universität, Zentrum der Dermatologie und Venerologie, Theodor-Stern-Kai 7, D – 60590 Frankfurt am Main Klinik und Poliklinik für Hautkrankheiten, Universitätsklinikum Münster, Klinisches Zentrum für innovative Dermatologie (ZiD), Von-Esmarch-Straße 56, 48149 Münster
Publication (reference):	**EMEA Guideline** (2004) Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis. CHMP/EWP/2454/02 November 2004

Sponsor: Almirall Hermal GmbH **Name of Finished Product:** LAS41002 Lotion	*(For Authority Use only)*
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Phase of development:	Phase IIb	
Studied Period	Date of First Enrollment: January 7, 2010	Date of Last Completed: April 19, 2010

Objectives:

The objective of this study was to investigate the efficacy of a topical treatment with mometasone furoate lotion (once daily over a period of 3 weeks) in patients with chronic scalp psoriasis in comparison to a reference product (Ecural® solution).

Primary Objective:

The primary objective of this study was the comparison of test versus reference product. The test product should be non-inferior to the reference product based on relative reduction from baseline in TSS (Total Sign Score) after 3 weeks of treatment (d 22).

Objectives:

Secondary objectives:

a. Non-inferiority of test product to reference product on relative reduction of TSS in comparison to baseline after 1 (d8), and 2 weeks (d15) of treatment.

b. Frequencies of clinically relevant psoriasis reduction (TSS reduction of >50 %, >75 %, >90 %) after 1, 2, and 3 weeks of treatment for test product and reference product.

c. Comparisons for scalp PGA (physicians global assessment) changes to baseline for test and reference product after 1, 2, and 3 weeks of treatment

d. Descriptive statistics for single parameters of TSS (erythema, scaliness, thickness) for each test product and each assessment time point (d1, d8, d15, d22).

e. Subjective assessment of pruritus, burning/stinging by patients at each assessment time point (d1, d8, d15, d22) and for each test product separately.

f. Local tolerability (signs for irritation, 4-point scale) assessed at each assessment time point (d1, d8, d15, d22) and each test product separately.

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Name of Active Ingredients: 0.1 % mometasone furoate	

g. Patient questionnaire regarding product traits

h. Safety parameters were documented and analyzed during treatment

Methodology:	Multi-center, randomized, two-arm, observer-blind, phase IIb clinical study, reference controlled	
Number of Patients:	Enrolled: 70	Analyzed: 70 ITT: 70 PP: 66
Diagnosis and Main Criteria for Inclusion:	70 patients with chronic scalp psoriasis were included in this study.	
Test Product	**LAS41002 lotion** containing 0.1 % mometasone furoate Form: lotion Route of Administration: topically Frequency: once daily Dosage: ad lib. Duration of Treatment: 3 weeks Batch-No.: 947KK09	
Reference Product	**Ecural® solution** containing 0.1 % mometasone furoate Form: solution Route of Administration: topically Frequency: once daily Dosage: ad lib. Duration of Treatment: 3 weeks Batch-No.: 090K359	
Test Procedure	The patients were instructed how to use the products at the scalp. Briefly, a few drops of the lotion or solution had to be applied openly to affected sites at the scalp and had to be massaged lightly until it disappeared. Patients were asked to avoid washing or drying of the hair at least 6 hours after application of the product. Visits at the study centers were done at day 1, 8 ± 2, 15 ± 2 and 22 ± 1. Patients were asked to document time and date of product application in their diary for compliance reasons. TSS and PGA were evaluated at each visit at the test center. Additionally, patients were asked to assess pruritus, and burning/stinging and the investigators looked for signs of skin irritation.	

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Test Procedure (*cont.)*	At the end of the study the patients filled in a questionnaire on product traits. The products were re-weighed for compliance reasons. In case of AEs outside the scheduled visits the patients were asked to report those to the study center.	
Duration:	Duration of Treatment:	Duration of Study:
	3 weeks per patient	4 months

Assessment(s):

According to the EMEA Guideline (2004, Guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis, CHMP/EWP/2454/02) a classification of psoriasis severity should consider the BSA involvement (body surface area), the PASI (psoriasis area and severity index) and PGA (physician's global assessment). Since only scalp psoriasis was investigated a TSS (Total Sign Score), based on the same parameters as the PASI (erythema, thickness, scaliness), was used for the assessment of the severity of the disease. Additionally, local PGA was assessed.

<u>TSS (to assess efficacy)</u>

The Total Sign Score TSS involves the assessment of erythema thickness, and scaliness.

Degree of severity (erythema (E), thickness (T), scaliness (S)) in test area (scalp):

0 = no sign
1 = slight sign
2 = moderate sign
3 = severe sign
4 = very severe sign

The total sign score was calculated by the following formula.

$$TSS = E + T + S$$

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PGA of the scalp (secondary objective)

The physician global assessment score was as follows:

0 = clear (no signs of psoriasis (post-inflammatory hyperpigmentation may be present))
1 = almost clear (intermediate between mild and clear)
2 = mild (slight plaque elevation, scaling and/or erythema)
3 = moderate plaque elevation, scaling and/or erythema
4 = marked plaque elevation, scaling and/or erythema
5 = severe plaque elevation, scaling and/or erythema

Pruritus assessment

0 = no symptoms
1 = slight
2 = moderate
3 = strong
4 = very strong

Burning/stinging

0 = no symptoms
1 = slight
2 = moderate
3 = strong
4 = very strong

Global cutaneous tolerance

0 = no signs of irritation
1 = slight signs of irritation
2 = moderate signs of irritation (obvious increase in redness)
3 = severe signs of irritation (discontinuation of treatment)

Questionnaire on product traits

At the end of the study the patients had to fill in a questionnaire on product traits.

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Clinically Relevant Response	>50 % and >75 % improvements compared to baseline TSS were considered as clinically meaningful improvement. TSS improvement of > 90 % was defined as clear or almost clear.
Plan for Data Analysis/ Statistics:	<u>Primary endpoints:</u> TSS after a treatment of 3 weeks (calculation of 95 % confidence interval for treatment difference test product to reference on relative changes to baseline) <u>Secondary endpoints:</u> • TSS (calculation of 95 % confidence interval for treatment difference test product to reference on relative changes to baseline after treatment times of 1 and 2 weeks) • PGA (comparison of test product and reference on changes to the respective values at baseline after treatment times of 1, 2 and 3 weeks) • Rates of patients with improvements after treatment times of 1, 2 and 3 weeks compared to baseline for TSS (> 90 %, > 75 % and > 50 %) for all test products • Rates of patients with PGA score 0 or 1 (clear or almost clear) after treatment times of 1, 2 and 3 weeks for all test products • Local tolerability after treatment times of 1, 2, and 3 weeks for test product and reference • Descriptive analysis of pruritus and burning/stinging 1, 2, 3 weeks after treatment for test product and reference • Descriptive analysis of patient questionnaire regarding product traits • Safety parameters
Statistical Methods	• Calculation of two-sided 95 % confidence interval for ratio of mean relative reductions test product and reference (non-inferiority test product to reference) • Mann-Whitney-U-Test (comparisons of treatment groups on PGA changes to baseline) • Fisher´s Exact test (comparisons of frequency for clinically relevant improvements TSS and for PGA reduction to 0 or 1 between treatment groups)

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Name of Active Ingredients: 0.1 % mometasone furoate	

	• Descriptive presentation of efficacy and safety data • Power-of-the-mean ANCOVA model (TSS, secondary end point)
Data Management	• All study data were recorded on paper CRFs. • Data was entered into a database and cleaned by appropriate edit checks. • Adverse events and medical history were coded with MedDRA
Safety:	• Physical examination • Monitoring of blood pressure and heart rate • Pregnancy tests for women of childbearing potential (at beginning and end of study) • Documentation and analysis of adverse events

Results:

The primary objective was the comparison of the test product versus reference product (non-inferior to reference product) based on relative reduction from baseline total sign score (TSS) after 3 weeks of treatment (d22).

TSS reduction from baseline in %			95 % confidence intervals for ratio of TSS reduction means			
Day 22	**LAS41002 lotion** mean	**Ecural® solution** mean	**Ratio of means**	**Lower limit 95 % CI**	**Upper limit 95 % CI**	**Non-inferiority ?**
ITT (n=70)	81.82	84.55	0.97	0.85	1.10	yes
PP (n=66)	82.99	85.78	0.97	0.86	1.09	yes

Table 1: TSS reduction from baseline in percent and 95 % confidence intervals for ration of TSS reduction means (all test centers (ITT and PP) at study day 22)

The lower limit of the 95 % confidence interval for the ratio of TSS mean reductions by LAS41002 lotion and Ecural® solution at day 22 was 0.85 (ITT) and 0.86 (PP), respectively. Hence, LAS41002 lotion was non-inferior to Ecural® solution with α=0.025 at a one-sided level.

- Non-inferiority of LAS41002 lotion to Ecural® solution, based on TSS reduction from baseline after 3 weeks of treatment, was shown in this study.

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Name of Active Ingredients: 0.1 % mometasone furoate	

Secondary objective

One secondary objective was the comparison of the test product versus reference product (non-inferior to reference product) based on relative reduction from baseline total sign score (TSS) after 1 (d8) and 2 weeks (d15) of treatment.

TSS reduction from baseline in %			95 % confidence intervals for ratio of TSS reduction means			
Day	**LAS41002 solution** mean	**Ecural® solution** mean	**Ratio of means**	**Lower limit 95 % CI**	**Upper limit 95 % CI**	**Non-inferiority ?**
d8 ITT (n=70)	46.33	41.49	1.12	0.89	1.41	yes
d8 PP (n=66)	48.38	41.25	1.17	0.94	1.48	yes
d15 ITT (n=70)	68.31	69.05	0.99	0.86	1.14	yes
d15 PP (n=66)	70.56	69.34	1.02	0.89	1.16	yes

Table 2: TSS reduction from baseline in percent and 95 % confidence intervals for ration of TSS reduction means (all test centers (ITT and PP) , d8 and d15)

- Non-inferiority of LAS41002 lotion to Ecural® solution was shown at d8 and d15 on a one-sided significance level of α=0.025.

Clinically relevant TSS reduction after 1, 2, and 3 weeks of treatment with LAS41002 lotion and Ecural® solution was assessed. Improvement of TSS of more than 50 % was considered as clinically meaningful, while TSS improvement of > 90 % was defined as clear or almost clear.

The best treatment effect was seen at study day 22 with comparable efficacy of LAS41002 lotion and Ecural® solution. Statistical comparison concerning TSS reduction after treatment with both products did not show any significant differences at any assessment time point (Fisher Exact Test).

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Name of Active Ingredients: 0.1 % mometasone furoate	

These findings were confirmed by assessment of PGA scores ≤ 1 (defined as clear or almost clear). No statistically significant differences were seen between the two different treatment groups. TSS reduction at study days 8, 15, and 22 is summarized in the following table:

ITT		TSS reduction in % > 50	TSS reduction in % > 75	TSS reduction in % > 90	PGA score ≤ 1
d8	Ecural® solution	34.3	2.9	0.0	14.3
	LAS41002 lotion	34.3	5.7	0.0	17.1
d15	Ecural® solution	80.0	40.0	8.6	54.3
	LAS41002 lotion	74.3	42.9	8.6	57.1
d22	Ecural® solution	91.4	71.4	45.7	88.6
	LAS41002 lotion	85.7	77.1	42.9	80.0

Table 3: Frequency of subjects [%] achieving clinical relevant TSS reduction at study days 8, 15 and 22 (ITT)

- A comparable good efficacy of LAS41002 lotion and Ecural® solution was seen during the whole study period.

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Name of Active Ingredients: 0.1 % mometasone furoate	

The results of the comparison for PGA (physician global assessment on a 6 point scale) changes after treatment with test and reference product at d1, d8, d15, and d22 are given in the following table:

		Physician Global Assessment Score (PGA)			
		ITT (n=70)		PP (n=66)	
		Mean	SD	Mean	SD
d1	Ecural® solution	3.37	0.65	3.36	0.65
	LAS41002 lotion	3.34	0.59	3.30	0.59
d8	Ecural® solution	2.29	0.89	2.27	0.91
	LAS41002 lotion	2.14	0.81	2.09	0.77
d15	Ecural® solution	1.51	0.95	1.52	0.91
	LAS41002 lotion	1.46	0.82	1.39	0.79
d22	Ecural® solution	0.74	0.92	0.70	0.85
	LAS41002 lotion	0.80	1.02	0.79	1.02

Table 4: Mean PGA scores at study days 1, 8, 15 and 22 (ITT and PP)

- Statistical comparison concerning PGA after treatment with both products did not show significant differences at any assessment time point (Mann-Whitney-U-Test).

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Name of Active Ingredients: 0.1 % mometasone furoate	

Each single **TSS parameter** (erythema, thickness and scaling) was analyzed descriptively at each assessment time point. In the following the main results for the ITT population are listed.

Erythema:
97.1 % of patients treated with Ecural® solution and 91.4 % of patients treated with LAS41002 lotion had no or only slight signs of erythema at study day 22, while at study day 1 nearly all patients in both treatment groups had at least moderate signs of erythema (only 3 patients treated with Ecural® had only slight signs of erythema). At study day 8 45.7 % of patients treated with Ecural® solution and 60 % of patients treated with LAS41002 solution had no or slight signs of irritation.

Thickness:
At study start about 70 % of all patients showed moderate to very severe signs of thickness. In nearly all patients signs of thickness were no longer present or only described as slight at the last study day (d22).

Scaliness:
About 90 % of all participating patients showed no or slight signs of scaliness at study day 22 with comparable results for the reference and verum treated group.

A subjective assessment by the patients of pruritus was done at study days 1, 8, 15 and 22.

Pruritus:
While more than half of the study population assessed pruritus as moderate to very strong at beginning of the study about 90 % of all patients experienced no or only slight pruritus at the last study day (d22) in both treatment groups. Clearly less pruritus was already observed at study day 8 in both treatment groups.

Tolerability of reference and LAS41002 lotion was assessed regarding the parameters burning/stinging (subjective assessment by patients) and global cutaneous tolerance (assessed by investigator

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Name of Active Ingredients: 0.1 % mometasone furoate	

Burning/stinging:
The majority of patients did not experience burning/stinging after application of either verum or reference product. One patient complained about strong burning/stinging at study day 22 after application of LAS41002 lotion, all other patients had no stinging symptoms.

Global cutaneous tolerance:
At the end of the study (d22) none of the patients showed any sign of skin irritation. During the study period only slight signs of skin irritation were observed in a very low number of patients.

- The tolerability of LAS41002 lotion, based on assessments of burning/stinging and global cutaneous tolerance was very good and comparable with the tolerability of Ecural® solution

At the end of the study patients were asked to fill in a questionnaire on **product traits** including tolerability, comparability with previously used products, absorption, scent and application of product, and the suitability for psoriasis treatment.

The overall tolerability was judged by almost all patients as good to very good, based on burning/stinging, tension feeling, impression of dryness, dull and brittle hair, and smooth and supple scalp.

Other product traits, such as ease of application, absorption, scent, and viscosity were judged in general as good to very good.

LAS41002 lotion and the reference solution were judged as suitable for the treatment of psoriasis by almost all patients.

- The product traits of LAS41002 lotion and Ecural® solution were judged as equally good.

Safety: 21 AEs in 20 patients occurred during this study. 3 of these AEs were serious (pancreatitis, infectious enterocolits, cholelithiasis), while 18 were non-serious AEs. In all reported AEs no or an unlikely relation to the study drug was described. All but 3 patients recovered without sequelae, in these 3 patients the condition was improving.

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19 female patients of childbearing potential were tested negative for pregnancy at screening. In all other patients a pregnancy test was not applicable.

There were no clinically relevant changes in blood pressure and heart rate between screening and final visit.

No negative aspects regarding safety were observed in this study, neither after application of LAS41002 lotion nor the reference product.

Conclusions:

The study was conducted as planned. The primary objective of the study to prove non-inferiority of LAS41002 lotion compared to the reference product Ecural® solution was achieved based on clinical assessments of TSS after 3 weeks of treatment.

Non-inferiority of LAS41002 lotion compared to reference Ecural® solution was also confirmed after 1 (d8) and 2 weeks (d15) of treatment based on clinical assessments of TSS.
These results are based on assessments of erythema, thickness and scaliness.

PGA scores were also comparable in both treatment groups after 1, 2, and 3 weeks of treatment.

Pruritus decreased considerably from d1 to d22 in both treatment groups comparably in this study.

An equally good skin tolerance of LAS41002 lotion and reference Ecural® solution was confirmed in this study.

Product traits were generally judged as good to very good by patients in both treatment groups

3 serious and 18 non-serious AEs occurred during the study. No or an unlikely relation to the study conduct was assessed for all AEs. Most patients recovered without sequelae (18 AEs), while in 3 patients the condition was improving.

There were no clinically significant changes in blood pressure and heart rate between screening and final visit.

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In summary, the primary objective (non-inferiority of LAS41002 lotion compared to Ecural® solution at day 22) was proven in this study in patients with chronic scalp psoriasis.

All secondary objective;

- TSS (treatment difference of test product to reference on relative changes to baseline af ter treatment times of 1 and 2 weeks)
- PGA (comparison of test product and reference on changes to the respective values at baseline after treatment times of 1, 2 and 3 weeks)
- Rates of patients with improvements after treatment times of 1, 2 and 3 weeks compared to baseline for TSS (> 90 %, > 75 % and > 50 %) for all test products
- Rates of patients with PGA score 0 or 1 (clear or almost clear) after treatment times of 1, 2 and 3 weeks for all test products
- Local tolerability after treatment times of 1, 2, and 3 weeks for test product and reference
- Analysis of pruritus and burning/stinging 1, 2, 3 weeks after treatment for test product and reference
- Analysis of patient questionnaire regarding product traits

showed that treatment with LAS41002 lotion had a comparable efficacy compared to Ecural® solution in this study.

Skin tolerability of both, LAS41002 lotion and reference Ecural® solution, was equally good. The assessment of product traits was also comparable between the two treatment groups. No negative aspects regarding safety were seen under the study conditions.