1 TITLE PAGE

Study Title	A 12 day placebo- and reference-controlled, double-blind, single center, randomized, phase II clinical study with an intraindividual comparison, investigating the anti-psoriatic efficacy and the tolerability of LAS41002 lotion in a psoriasis plaque test
Name(s) of Test Drug(s)/ Investigational Product(s)	LAS41002 Lotion/0.1 % mometasone furoate
Reference/Placebo	Ecural® cream/Placebo to LAS41002 Lotion
Indication Studied	Topical treatment of psoriasis
Study Design	Randomized, single center, double-blind, phase II clinical trial, reference- and placebo- controlled, intra-individual comparison
Name of Sponsor	Almirall Hermal GmbH Scholtzstr. 3 21465 Reinbek
Protocol Identification	H 521 000 - 0914
Development Phase of Study	Phase II
Study Initiation Date (first patient screened)	February 11, 2010
Date of Early Study Termination	Not applicable
Study Completion Date (last patient completed)	March 05, 2010
Principal 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 3, 2010
Previous Reports	Preliminary report: April 13, 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:	A 12 day placebo- and reference-controlled, double-blind, single center, randomized, phase II clinical study with an intraindividual comparison, investigating the anti-psoriatic efficacy and the tolerability of LAS41002 lotion in a psoriasis plaque test	
Principal Investigator:	[redacted], proDERM Institut für Angewandte Dermatologische Forschung GmbH	
Investigators:	[redacted]	
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	
Phase of development:	Phase II	
Studied Period	Date of First Enrollment: February 22, 2010	Date of Last Completed: March 05, 2010

Objectives:

The objective of this study was to investigate the efficacy (ability to reduce a psoriatic plaque) of a topical treatment with mometasone furoate (LAS41002 lotion) in patients with psoriasis in comparison to a reference product (Ecural® cream) and a placebo.

Primary Objective:

Clinical examination (visually and by palpating the respective test area): LAS41002 lotion better than (superior to) placebo at study day 12.

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Objectives:	Secondary objectives: a. Clinical examination (visually and by palpating the respective test area): at study day 5, LAS41002 lotion compared to placebo. b. Clinical examination (visually and by palpating the respective test area) at study days 5 and 12, LAS41002 lotion compared to the reference product Ecural® cream (non-inferiority) c. Relative changes (given in %) from baseline ultrasound measurements at study day 5 and study day 12: LAS41002 lotion in comparison to placebo and reference product Ecural® cream d. Global tolerability of the LAS41002 lotion, reference product and placebo, assessed at the last study day e. Digital photography at each assessment time point f. Safety parameters were documented and analyzed during treatment	
Methodology:	Randomized, single center, double-blind, phase II clinical trial, reference- and placebo- controlled, intra-individual comparison	
Number of Patients:	Enrolled: 24	Analyzed: 24 ITT: 24 PP: 23
Diagnosis and Main Criteria for Inclusion:	male and female patients with mild to moderate chronic plaque psoriasis, aged 18-75	

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Products and Batch Numbers: Test Product	LAS41002 Lotion containing 0.1 % mometasone furoate (Batch-No.: 948KK09)
Placebo	Placebo to LAS41001 (Batch-No.: 947KK03)
Reference Product	Ecural® cream containing 0.1 % mometasone furoate (Batch-No.: 9NGKFA50)

Test Procedure:	100 µl of LAS41002 lotion, the placebo and reference product was applied occlusive with large Finn-Chambers (inner diameter 11 mm) for altogether 9 times for 24 ± 2 hours during the week and for 72 ± 4 h during the weekend. Before the first application of the products baseline assessments of ultrasound measurements and baseline digital photography was performed. At study day 5 and study day 12 clinical examinations and ultrasound measurements were done after removal of all three products. Additionally, digital photography was done at these days. At all study days, before reapplication of LAS41002 lotion, reference and placebo the test areas were investigated regarding intolerance reactions for safety issues. At the final visit test areas were assessed regarding local tolerability by the investigator.

Duration:	Duration of Treatment:	Duration of Study:
	11 days per patient	12 days

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Assessment(s):

Clinical examinations (visually and by palpating the respective test area) regarding plaque reduction were done by the investigator at day 5 and day 12, always 15 to 45 minutes after patch removal according to the following scale:

0 = no effect
1 = slight plaque reduction
2 = moderate plaque reduction
3 = strong plaque reduction
4 = complete reduction of plaque to skin surface level

Before each reapplication of LAS41002 lotion, the reference product and the placebo, the study nurse investigated the test areas for papules and vesicles, increasing erythema (in comparison to the surrounding psoriatic skin) and edema to detect potential intolerance reactions for safety reasons. In case of intolerance reactions the investigator had to decide about further applications or discontinuation of the respective product application.

The following score was used (taking the underlying disease into account) to assess possible intolerance reactions for safety reasons:

0 = no skin intolerance reaction
+ = doubtful skin intolerance reaction
++ = slight skin intolerance reaction*
+++ = moderate skin intolerance reaction*
++++ = strong skin intolerance reaction*

* in case of "++" or higher, the investigator has to decide about further procedure, product discontinuation or further product application.

The global tolerability was judged by the investigator at the final visit. Since the skin under examination is not healthy, the local tolerability of LAS41002 lotion, placebo and reference product cannot be clearly determined. However, at the end of the study the investigator looked for signs of local intolerance reactions other than caused by the psoriasis.

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Instrumental Measurements	Skin thickness of the psoriatic plaque was measured with a 22 MHz ultrasound instrument before first application of the products at day 1 (baseline), before application of the product at day 5 and additionally at the last study day (day 12). Clinical (digital) photography was performed by using a high resolution digital camera at study day 1 and day 5 (before application of the products) and day 12.
Plan for Data Analysis/ Statistics:	<u>Primary endpoints:</u> • Analysis of superiority of the test product LAS41002 to placebo with respect to clinical examinations (visually and by palpating the respective test area) at study day 12 <u>Secondary endpoints:</u> • Analysis of superiority of LAS41002 to placebo with respect to clinical examination (visually and by palpating the respective test area) at day 5 • Analysis of LAS41002 in comparison to reference product Ecural® cream based on clinical examination (visually and by palpating the respective test area) at study days 5 and 12 (non-inferiority) • Descriptive statistics of LAS41002, placebo and reference at days 5 and 12 with respect to relative ultrasound changes to baseline • Descriptive presentation of global tolerability parameters • Safety parameters
Statistical Methods	• Wilcoxon matched pairs signed rank test (clinical examination) • Two-sided 95 % confidence intervals • Paired t-test (ultrasound)

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Data Management

- All study data were recorded on paper CRFs
- Data were entered directly into a database and cleaned by appropriate edit checks
- Adverse events and medical history were coded with MedDRA

Safety:

- Physical examination focused on the skin
- Monitoring of blood pressure and heart rate
- Documentation and analysis of adverse events
- Pregnancy test (for women of child bearing potential)

Results:

The primary objective was to show that LAS41002 lotion was better in the reduction of a psoriatic plaque than placebo at study day 12, based on clinical examination (visually and by palpating the respective test area). The results, absolute and relative frequencies of different scores, are summarized in the following table (primary objective in bold letters):

ITT, n=24	**Plaque Reduction (clinical examination), day 12**					
	no effect	Slight reduction	moderate reduction	strong reduction	complete reduction	Total
Placebo	**8 (33.3 %)**	**9 (37.5 %)**	**2 (8.3 %)**	**0 (0 %)**	**5 (20.8 %)**	**24 (100 %)**
LAS41002	**2 (8.3 %)**	**0 (0 %)**	**0 (0%)**	**2 (8.3 %)**	**20 (83.3 %)**	**24 (100 %)**
Ecural® cream	0 (0 %)	1 (4.2 %)	0 (0 %)	2 (8.3 %)	21 (87.5 %)	24 (100 %)

Table 1: **Plaque reduction (clinical examination) at day 12, LAS41002 and Placebo (primary objective; bold) and reference (secondary objective)**

LAS41002 lotion had a statistically significant benefit (p=0.0016)

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over placebo (Wilcoxon Signed Rank Test, one-sided significance level of □=0.025) at study day 12. With this the primary objective of the study was proven.

- LAS41002 lotion was superior to placebo as assessed clinically (visually and by palpating the respective test area) at study day 12

As a secondary objective LAS41002 lotion and the reference product (Ecural® cream) were compared at study day 12:

LAS41002 lotion vs Ecural® cream: p=0.5781

No statistically significant difference in plaque reduction (assessed by clinical examination) was observed at study day 12 at the test areas treated with LAS41002 lotion compared to the reference product Ecural® cream.

When calculating the 95 % confidence interval for the difference in plaque reduction between LAS41002 lotion and reference product Ecural® cream the following conclusion was drawn:

- LAS41002 lotion was non-inferior to reference product Ecural® cream as assessed clinically (visually and by palpating the respective test area) at study day 12.

In the following table plaque reduction, based on clinical examination, is illustrated at study day 5 for placebo, reference and LAS41002 lotion:

ITT, n=24	**Plaque reduction (clinical examination), day 5**					
	no effect	slight reduction	moderate reduction	strong reduction	complete reduction	Total
Placebo	10 (41.7 %)	7 (29.2 %)	4 (16.7 %)	3 (12.5 %)	0 (0 %)	24 (100 %)
Ecural® cream	0 (0 %)	4 (16.7 %)	2 (8.3 %)	7 (29.2 %)	11 (45.8 %)	24 (100 %)
LAS41002	2 (8.3 %)	3 (12.5 %)	5 (20.8%)	6 (25 %)	8 (33.3 %)	24 (100 %)

Table 2: Plaque reduction (clinical examination) at day 5, placebo, reference (Ecural® cream), and LAS41002

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Reference (Ecural® cream) and LAS41002 lotion performed clearly better than placebo. When comparing LAS41002 lotion with placebo and reference, the following results were obtained (p-values from Wilcoxon Signed Rank Test):

LAS41002 lotion vs placebo: $p=0.0001^{sign}$
LAS41002 lotion vs reference: $p=0.1210^{ns}$

sign: statistically significant on a one-sided significance level of □=0.025
ns: statistically not significant

- LAS41002 lotion was superior to placebo as assessed clinically (visually and by palpating the respective test area) at study day 5
- LAS41002 lotion was not statistically significant inferior to reference as assessed clinically (visually and by palpating the respective test area) at study day 5

Besides clinical examinations of plaque reduction, ultrasound measurements of skin thickness of the psoriatic plaques were performed on study days 1 (baseline), 5 and 12. Changes to baseline were calculated in % and are illustrated in the following table:

ITT, n=24	**Ultrasound changes to baseline in %**			
	Day 5		**Day 12**	
	mean	sd	mean	sd
Placebo	-0.75	12.57	-7.84	16.56
Reference Ecural® cream	-19.58	9.31	-31.43	7.84
LAS41002	-16.28	11.68	-25.81	14.20

Table 3: Skin thickness measurements (ultrasound), changes from baseline in %)

A clear decrease in skin thickness at psoriatic plaques treated with LAS41002 lotion and the reference product Ecural® cream was seen already at study day 5. This decrease was even more pronounced at study day 12 for these two products, while treatment with placebo had only a slight effect on the thickness reduction of a psoriatic plaque. When comparing the test product LAS41002 lotion with reference and placebo (paired t-Test) the following p-values were

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obtained:

LAS41002 lotion vs	**Comparison of ultrasound changes to baseline in % (p-values of paired t-Test)**	
	day 5	day 12
Placebo (ITT)	0.0004 sign.	0.0005 sign.
Reference (ITT)	0.2112 ns	0.0318 sign
Placebo (PP)	0.0009 sign.	0.0010 sign.
Reference (PP)	0.0377 sign.	0.0148 sign.

Table 4: Statistical comparison of ultrasound changes to baseline in %

A significantly more pronounced reduction in plaque thickness was measured at test areas treated with LAS41002 lotion compared to areas treated with placebo at study days 5 and 12.

No statistically significant differences in skin thickness were analyzed between LAS41002 lotion and reference after 5 days of treatment in the ITT population. When analyzing the PP population at study day 5, reference performed statistically significantly better in reducing a psoriatic plaque than LAS41002 lotion. At study day 12, skin thickness was significantly more reduced after treatment with reference compared to LAS41002 lotion (ITT and PP).

- LAS41002 lotion superior to placebo based on plaque reduction as measured by ultrasound at day 5 and day 12
- LAS41002 lotion was not statistically significantly different to reference based on plaque reductions as measured by ultrasound at day 5 (ITT population)
- Reference showed a statistically significantly higher reduction in skin thickness compared to LAS41002 lotion as measured by ultrasound at day 5 (PP population) and day 12 (ITT and PP population)

Another secondary objective was the assessment of skin tolerability assessed by the investigator at study day 12. No intolerance reactions were seen, neither for LAS41002 lotion, nor for the reference product nor for the placebo (always in comparison to the surrounding psoriatic skin), indicating a good skin tolerability of all three products. This was confirmed by the tolerability assessment, which was done on study days 2, 3, 4, 5, 8, 9, 10 and 11 for safety

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reasons always before re-application.

- An equally good skin tolerability of LAS41002 lotion, placebo and reference product was seen in this study

Safety:

1 non serious adverse event and no serious adverse events were documented in this study. This non serious adverse event (tooth pain) was graded as severe and was unrelated to the study. Concomitant medication was altered and the condition improved.

One female patient of childbearing potential was 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.

Conclusions:

It was the primary objective of this study to show that LAS41002 lotion was superior to placebo in reducing a psoriatic plaque as assessed by clinical examination (visually and by palpating the respective test area) at study day 12. This primary objective was fulfilled in this study. These findings were confirmed by clinical assessments at study day 5 and ultrasound measurements of skin thickness at days 5 and 12.

No statistically significant treatment differences between LAS41002 lotion and reference (Ecural® cream) were assessed by clinical examinations at study days 5 and 12. LAS41002 lotion performed equally well in reduction of a psoriatic plaque compared to reference.

Ultrasound measurements of skin thickness were assessed as secondary objective. Treatment of LAS41002 lotion and reference reduced skin thickness statistically significantly more pronounced compared to placebo. When comparing LAS41002 lotion with reference, skin thickness was significantly more reduced after application of the reference product compared to treatment with LAS41002 lotion. When interpreting these results it has to be kept in mind, that clinical assessment and ultrasound measurements assess

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different parameters. While, ultrasound measurement is a very sensitive method to assess the epidermal thickness and inflammatory infiltrate, scaling which is easily assessed clinically is not detected by ultrasound. Since ultrasound measurements are able to detect slight decreases in skin thickness, these slight changes may clinically not be palpable. These findings explain the different efficacy results obtained by clinical assessments and by ultrasound (reference and LAS41002 lotion): More pronounced decreases in skin thickness after application of the reference product compared to LAS41002 lotion were measured by ultrasound but were not detected clinically (visual assessment and palpating of test area). On the other hand, scaling, assessed visually was not measured by ultrasound. Since treatment compliance of patients is based on the visual improvement of skin conditions (e.g. combination of redness, infiltration, and scaling) the clinical assessment was chosen as primary parameter and has a stronger impact on treatment compliance.

In this study design the base formulation of the test product was a lotion and was compared to a reference product with a cream basis with identical active ingredients. Previous studies have shown that the effect of skin thickness reduction may be due to occlusion (Bangha and Elsner, 1996). Since a cream is more occlusive than a lotion, the more pronounced skin thickness reduction after application of the reference product as assessed by ultrasound is probably due to the basis of the reference product.

No intolerance reactions were observed during the full course of the study, indicating an equally good skin tolerability of LAS41002 lotion, the respective placebo and the reference product.

1 non serious and no serious adverse event occurred during this study conduct. This AE was not study related.

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

All female patients of childbearing potential were tested negative for pregnancy.

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Overall Conclusions:

In general LAS41002 lotion was equally effective in reducing a psoriatic plaque as the reference product in this study. An equally good skin tolerability of LAS41002 lotion and placebo compared to the reference was shown in this study. The more pronounced reduction in skin thickness, as assessed by ultrasound measurements, was probably due to the two different base formulations of verum and reference with different occlusive properties.

No negative aspects regarding safety were seen in this study.