2 SYNOPSIS

Sponsor: Almirall Hermal GmbH	*(For national Authority Use only)*
Name of Finished Product: 0.10 % TZ + 0.10 % BDP 0.05 % TZ + 0.10 % BDP 0.10 % TZ + 0.05 % BDP 0.05 % TZ + 0.05 % BDP 0.025 % TZ + 0.05 % BDP	
Name of Active Ingredients: tazarotene betamethasone	

Title of Study:	A 22 day bland ointment and reference-controlled, investigator-blind, single center, randomized, proof of concept clinical study with an intraindividual comparison investigating the anti-psoriatic efficacy and the tolerability of an ointment containing a retinoid and a steroid in different concentrations 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, [redacted] Schenefeld	
Publication (reference):	**Dumas KJ, Scholtz ER** (1972) The psoriasis bio-assay for topical corticoid activity Acta Derm Venerol 53:43-48 **AWMF online** (2011) Leitlinie zur Therapie der Psoriasis Vulgaris, update 2011 Register Nr. 013/001	
Phase of development:	Proof of Concept	
Studied Period	Date of First Enrollment: August 22nd, 2011	Date of Last Completed: September 12th, 2011
Objectives:	The objective of the study was to investigate the efficacy and tolerability of 5 ointment formulations containing fixed combinations of different concentrations of tazarotene and betamethasone dipropionate <u>Primary Objective:</u> Psoriasis was assessed by ultrasound measurements of skin thickness (distance between the lower border of the entry echo of the skin and the lower border of the dermis as well as the width of the echo-lucent band) at study days 1, 8, 15 and 22.	

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	Secondary Objectives: a) Efficacy of different treatments was clinically assessed (visually and by palpating the test area) at study days 8, 15 and 22 compared to baseline (scaling, erythema, induration, total sum score) b) Ultrasound measurements as changes to baseline (in percent) c) Tolerability of different treatments was assessed at study days 8, 15, and 22 by a physician d) Assessment of teleangiectasia and erythema at each study visit (safety) e) Assessment of AEs and SAEs and their relationship to study medication f) Other safety parameters (blood pressure, heart rate, pregnancy test) g) Digital photography for documentation	
Methodology:	Randomized, single center, investigator-blind, proof of concept clinical trial, reference- and bland ointment- controlled, intra-individual comparison	
Number of Subjects:	Enrolled: 24	Analyzed: 24 (SP) 24/21 (FAS/Reference) 18/17 (PPS/Reference)
Diagnosis and Main Criteria for Inclusion:	24 male and female patients with mild to moderate chronic plaque Psoriasis, aged 18-75, were included in this study so that at least 20 patients finished the study	
Test Products and Batch Numbers:	**Test products:** 0.10 % TZ + 0.10 % BDP Batch-No.: 129K02 0.05 % TZ + 0.10 % BDP Batch-No.: 129K02 0.10 % TZ + 0.05 % BDP Batch-No.: 129K02 0.05 % TZ + 0.05 % BDP Batch-No.: 129K02 0.025 % TZ + 0.05 % BDP Batch-No.: 129K02	

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Name of Active Ingredients: tazarotene betamethasone	

Additional ingredients:	Paraffin, white soft Paraffin, liquid Diisopropyl adipate Citricacid Sodium citrate Propylene glycol Monopalmitosearate Purified water Butylhydroxytoluene
Reference product:	
Name:	Daivobet®
Active ingredients:	Calcipotriol 50µg/g Betamethasone dipropionate 0.5mg/g
Other ingredients:	Viscous paraffin α-tocopherol α-hydro-ω-octadecyloxypoly(oxy-propylen)-15 White Vaseline
Batch number:	EE8K527
Bland ointment:	
Name:	Petroleum jelly (Vaseline®)
Batch number:	129K02

Method and Mode of Application:	The amount covering the tip of a spatula of the 5 formulations, the reference and the bland ointment was applied once daily for altogether 15 times (5 times per week). The products were massaged gently into the skin. Each test area was defined and marked with a skin marker at baseline (marks were renewed at each visit). The applied test products were covered with a non-occlusive, hypoallergenic tape. Before the first product application, baseline ultrasound measurements and baseline digital photography were performed. At study day 8, 15 and 22 clinical examinations and ultrasound measurements were done after removal of all products. Additionally, digital photography was done at these days. At all study days, before reapplication of the products (including reference and bland ointment), the test areas were investigated regarding erythema and telangiectasia for safety issues. At days 8, 15 and 22 test areas were assessed regarding local tolerability by investigator.

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Name of Active Ingredients: tazarotene betamethasone	

Duration:	Duration of Treatment:	Duration of Study:
	21 days per subject	22 days

Assessment(s):

Efficacy of the different treatments was assessed by ultrasound measurements and clinical evaluations.

Clinical examinations (visually and by palpating the respective test area) regarding scaling, erythema and induration were done by the investigator at study day 8, 15 and 22, always 15 to 45 minutes after patch removal according to the following scale for each parameter separately:

0 = none
1 = mild
2 = moderate
3 = severe
4 = very severe

A total score was calculated for each assessment day by the sum of erythema, scaling and induration. The total score ranged from 0 to 12.

Before each reapplication of the products the study nurse investigated the test areas for erythema and telangiectasia.

Dermal reactions in each test area were assessed according to the following scale before test products were reapplied:

0 = no reaction
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 defect (blisters, erosions)

In the event that a score of "3" or higher was recorded the investigator had to be informed and the respective test product was prematurely discontinued.

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	Telangiectasia were assessed according to the following scale: 0 = normal vascular pattern with fine capillary loop under highest magnification 1 = capillary hyperaemia with slight elongation and dilation of blood vessels not visible to the naked eye 2 = moderate telangiectasia just visible to the naked eye 3 = severe telangiectasia with marked reduction of capillary loops 4 = very severe telangiectasia with large blunt vessels and absence of capillary loops In the event that a score of "2" or higher was recorded the investigator had to be informed and the respective test product was prematurely discontinued. The tolerability was judged by a physician at study days 8, 15, and 22. Since the skin under examination was not healthy, the local tolerability of the 5 formulations, the bland ointment and the reference product could not be clearly determined. The following scale was used for assessment of tolerability: 1 = very good 2 = good 3 = fair 4 = poor 5 = very poor
Instrumental Measurements:	Skin thickness 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 products at day 8, 15 and additionally at the last study day (day 22). Clinical (digital) photography was performed by using a high resolution digital camera at study days 1, 8, 15 (before application of the products) and day 22.

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Plan for Data Analysis/ Statistics:	Primary endpoints: AUC of skin thickness (distance between lower border of the entry echo of the skin and the lower border of the dermis as well as the echo-lucent band) at study days 1, 8, 15 and 22. Secondary endpoints: • Skin thickness at day 1, 8, 15 and 22 • Percentage change in skin thickness as measured by ultrasound at study day 22 compared to baseline • Percentage change of scaling, erythema and induration score at day 22 compared to baseline • Scaling, erythema and induration score over time (days 1, 8, 15 and 22) • Total score (sum score of scaling, erythema and induration) over time (days 1, 8, 15 and 22) • Descriptive presentation of global tolerability parameters (as assessed by a physician at study days 8, 15 and 22) • Descriptive presentation of safety parameters, i.e. erythema and telangiectasia at all study days • Other safety parameters, i.e. adverse events
Safety:	• Physical examination • Monitoring of blood pressure and heart rate • Pregnancy tests for women of childbearing potential • Assessment of possible intolerance reactions (erythema and telangiectasia) • Assessment of tolerability by physician at study days 8, 15 and 22 • Documentation and analysis of adverse events
Results:	Primary Objective The primary objective was the assessment of skin thickness as measured by ultrasound (distance between lower border of the entry echo of the skin and the lower border of the dermis) as well as the width of the echo-lucent band at study days 1, 8, 15 and 22 (AUC on changes to day 1). Baseline data are provided in table 1 and the

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results for changes of skin thickness (distance lower border of the entry echo to lower border dermis) to day 1 are shown in table 2, listed from highest to lowest:

Product	n	mean	sd
Reference (Daivobet®)	21*	2192	411.7
0.050% TZ + 0.10% BDP	24	2156	459.5
0.025% TZ + 0.05% BDP	24	2093	418.0
0.100% TZ + 0.05% BDP	24	2156	519.1
0.100% TZ + 0.10% BDP	24	2126	417.0
0.050% TZ + 0.05% BDP	24	2166	515.4
Bland Ointment (Vaseline)	24	2104	497.3

* not all subjects were treated with the reference product

Table 1: Baseline data on skin thickness (µm*day)

Product	n	mean	sd
Reference (Daivobet®)	21*	-9114.70	5369.20
0.050% TZ + 0.10% BDP	24	-8528.74	4580.12
0.025% TZ + 0.05% BDP	24	-8172.38	4677.53
0.100% TZ + 0.05% BDP	24	-7857.41	5920.17
0.100% TZ + 0.10% BDP	24	-7415.19	5688.77
0.050% TZ + 0.05% BDP	24	-7148.78	4857.17
Bland Ointment (Vaseline)	24	-3283.03	6400.49

* not all subjects were treated with the reference product

Table 2: AUC on changes to day 1 regarding skin thickness (distance skin border to dermis border (FAS))

The most pronounced reduction in skin thickness was seen after application of the reference product Daivobet® followed by the products 0.050 % TZ + 0.10 % BDP and the products 0.025% TZ + 0.05% BDP and 0.100% TZ + 0.05% BDP, based on numerical data.

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In the following table (table 3) assessment of skin thickness based on ultrasound results on AUC of the width of the echo-lucent band are illustrated:

Product	n	mean	sd
Reference (Daivobet®)	21*	-3951.87	1889.60
0.025% TZ + 0.05% BDP	24	-3827.57	1922.87
0.050% TZ + 0.05% BDP	24	-3788.11	1816.80
0.050% TZ + 0.10% BDP	24	-3777.32	1865.12
0.100% TZ + 0.05% BDP	24	-3722.37	1867.00
0.100% TZ + 0.10% BDP	24	-3385.05	2069.76
Bland Ointment (Vaseline)	24	-1269.69	1850.44

* not all subjects were treated with the reference product

Table 3: AUC on changes to day 1 regarding width of echo-lucent band (FAS)

The most pronounced reduction in the measurement of the echo-lucent band was seen after application of the reference product Daivobet®. In contrast to the skin thickness ultrasound analysis, the next most efficient product was 0.025% TZ + 0.05% BDP followed by 0.050 % TZ + 0.05 % BDP and 0.05% TZ + 0.10% BDP and 0.10% TZ + 0.05% BDP.

Secondary Objectives

Secondary objectives were the percentage of changes in skin thickness at study days 8, 15 and 22 compared to skin thickness at study day 1. Again changes of thickness (distance lower border entry echo and lower border of the dermis) and changes in the width of the echo-lucent band were analyzed. The results for changes of skin thickness are given in table 4:

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Product	n	Day 8 mean ± sd	Day 15 mean ± sd	Day 22 mean ± sd
Reference (Daivobet®)	21*	-15.4±16.6	-27.5±9.1	-29.8±11.3
0.050% TZ+0.10% BPD	24	-16.7±9.0	-24.0±12.3	-27.1±10.9
0.025% TZ+0.05% BDP	24	-15.0±13.9	-24.0±11.8	-30.1±12.09
0.100% TZ+0.05% BDP	24	-12.2±14.1	-23.3±5.2	-24.0±17.4
0.100% TZ+0.10% BDP	24	-12.4±14.9	-21.0±16.8	-25.7±15.4
0.050% TZ+0.05% BDP	24	-10.8±13.7	-21.5±11.7	-25.7±11.7
Bland ointment (Vaseline)	24	-1.8±17.4	-9.5±13.7	-11.5±15.7

* not all subjects were treated with the reference product

Table 4: Changes to day 1 in skin thickness (distance skin border to dermis border) in %

The maximum decrease in skin thickness (based on lower border of the entry echo of the skin and the lower border of the dermis) was seen at study day 22 for all products applied in this study.

In the following table (table 5) changes of the width of the echo-lucent band are summarized:

Product	n	Day 8 mean ± sd	Day 15 mean ± sd	Day 22 mean ± sd
Reference (Daivobet®)	21*	-61.8±18.2	-85.7±17.6	-95.8 ± 8.9
0.025% TZ+0.05% BPD	24	-60.9±24.3	-81.8±14.7	-93.3±10.2
0.050% TZ+0.05% BDP	24	-61.7±19.0	-76.1±19.7	-88.6±14.4
0.050% TZ+0.10% BDP	24	-64.0±22.0	-79.5±15.4	-90.3±13.9
0.100% TZ+0.05% BDP	24	-61.0 ±17.9	-74.3±15.5	-82.9±15.3

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Bland ointment (Vaseline)	24	-8.0±41.1	-23.9±38.7	-33.0±36.6

* not all subjects were treated with the reference product

Table 5: Changes to day 1 width of echo-lucent band in %

Again the most pronounced reduction in echo lucent band was seen at study day 22 for all products applied in this study.

Clinical assessments of efficacy based on scaling, erythema and induration was another secondary objective. A total score (sum of erythema, induration and scaling) was calculated for each assessment time point. The results were as follows (table 6):

Product	n	Day 1 mean	Day 8 mean	Day 15 mean	Day 22 mean
Reference (Daivobet®)	21*	5.6	3.2	1.5	0.5
0.025% TZ+0.05% BPD	24	5.5	2.9	1.8	0.8
0.050% TZ+0.10% BDP	24	5.5	2.8	2.1	1.2
0.05 % TZ+0.05% BDP	24	5.2	3.0	2.2	1.2
0.100% TZ+0.10% BDP	24	5.5	2.9	2.3	1.5
0.100% TZ+0.05% BDP	24	5.4	3.0	2.4	1.8
Bland ointment (Vaseline)	24	5.2	4.9	4.4	4.3

* not all subjects were treated with the reference product

Table 6: Clinical assessment of efficacy (total score; erythema + scaling + induration) FAS

Clear improvements in psoriasis parameters after application of all products, except for the bland ointment, were seen until day 22.

Global tolerability parameters (erythema and telangiectasia) were assessed at each visit as further secondary objectives. In one subject severe erythema after application of 4 products (0.05%

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TZ+0.05% BDP, 0.1% TZ+0.1% BDP, 0.05% TZ+0.1% BDP and 0.1% TZ + 0.05% BDP) led to discontinuation of the respective product. Although these 4 products induced severe erythema after application in other subjects, no additional product discontinuations occurred. The best tolerated product was the reference product and the bland ointment Vaseline followed by 0.025% TZ+0.05% BDP.

No telangiectasia were seen during the 22 days of study conduct. At study days 8, 15 and 22 a global assessment of tolerability was done by a physician. The following results were obtained (table 7):

Product	very good	good	fair	poor	very poor
0.050%TZ+0.05% BDP	98.6	0	0	0	1.4
Reference (Daivobet®)	100	0	0	0	0
0.100% TZ+0.1% BDP	98.6	0	0	0	1.4
Bland ointment (Vaseline)	97.2	1.4	1.4	0	0
0.050% TZ+0.1% BDP	97.2	1.4	0	0	1.4
0.025% TZ+0.05% BDP	100	0	0	0	0
0.100% TZ+0.05% BDP	97.2	0	0	0	2.8

Table 7: Global tolerability in % as assessed by physician

In all subjects the global tolerability of the reference product and test product containing 0.025% TZ + 0.05% BDP was judged as very good.

Safety:

In 4 subjects non-serious adverse events (AEs) occurred during the study. Two subjects (no. 3 and 9) suffered from headaches of mild severity, in one subject (subject no. 20) plaster reactions of moderate severity were seen and in one additional subject (subject no. 23) skin reactions (moderate severity) after application of 4 test products (0.1 % TZ+0.1% BDP, 0.1 % TZ+0.05 % BDP, 0.05 % TZ+0.1 % BDP, 0.05 % TZ+0.05 % BDP) occurred which led to discontinuation of the respective products. In two subjects the AEs (headache) were not study related, while the plaster reactions in subject no. 20 were study procedure related and the skin reactions observed in subject no. 23 were definitely product related. 3 subjects recovered without

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sequelae, while in subject no. 23 the condition was improving. No serious AEs occurred in the study.

There were no relevant changes in heart rate and blood pressure between screening and final visit. All female women of childbearing potential had a negative pregnancy test at screening.

Conclusions:

- The reference product was the most effective product (non statistical comparison was performed, based only on numerical data) in this study regarding measurements of skin thickness and clinical parameters.
- Product 0.025 % TZ+0.05 % BDP was also effective in reduction of skin thickness, erythema, scaling and induration and total score.
- The bland ointment Vaseline was not very effective in reduction of skin thickness, erythema, induration and scaling.
- No clear grading of the 5 different formulations containing different concentrations of tazarotene and betamethasone dipropionate can be made. Based on numerical data without consideration of the standard deviation there was a tendency that the products containing 0.05 % tazarotene were slightly more effective compared to the products containing 0.1 % tazarotene.
- The reference product and 0.025 % TZ+0.05 % BDP were both well tolerated.
- Non-serious AEs in 1 subject which led to product discontinuation occurred after application of 4 products containing 0.05 % and 0.1 % tazarotene.