2. Synopsis

Name of Company: Almirall Hermal GmbH	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Combinations of Panretin® Gel 0.1 %, Zorac® Gel 0.1%, Targretin® Gel 1 %, with Diprosis® Gel		
Name of Active Ingredients: Alitretinoin 0.1 %, tazarotene 0.1 %, bexarotene 1 % combinated with betamethasone dipropionate 0.064 %		

Title of Study: A phase I, single-center, randomized, observer-blind controlled study to determine the antipsoriatic efficacy of combinations of topical formulations in a psoriasis plaque test	
Investigator(s): [redacted]	
Study center(s): bioskin GmbH, Berlin, Germany	
Publication (reference): Not applicable to this study	
Studied period (years): 2008	Phase of development: I
Objectives: Demonstration of antipsoriatic efficacy of a combination of topical formulations in subjects with psoriasis vulgaris	
Methodology: Twenty-two occlusive treatments (mornings and evenings) over a study period of 12 days. Sonography and chromametry were made at baseline (day 1) and on study days 4, 8 and 12, clinical assessments were made on study days 4, 8 and 12, photodocumentation was made on study days 1 and 12	
Number of subjects (planned and analyzed): 15 male subjects planned and randomized, there were no dropouts, data of all 15 subjects were valid for analysis	
Diagnosis and main criteria for inclusion: Male or female subjects with chronic plaque type psoriasis, aged 18 to 75 years	
Test product(s), dose and mode of administration, batch number: Panretin® Gel 0.1 %, batch no.: K0553/08 Zorac® Gel 0.1%, batch no.: K0197/08 Targretin® Gel 1 %, batch no.: K0553/09 Diprosis® Gel, batch no.: K0553/07 Occlusive application of approximately 200 µl to test field	
Duration of treatment: 12-day study period (11 morning applications of Panretin® Gel 0.1 %, Zorac® Gel 0.1%, Targretin® Gel 1 % to one test field, respectively, 11 evening applications of Diprosis® Gel to four test fields)	
Reference therapy or controls, dose and mode of administration, batch number: White petrolatum (Control), batch no.: K0553/11 Psorcutan® Beta (Comparator), batch no.: K0553/06 Occlusive application of approximately 200 µl to test field	
Duration of treatment: 12-day study period (11 morning applications of control to two test fields, 11 evening applications of comparator to one test field)	

2. Synopsis (continued)

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Criteria for evaluation:

Efficacy: Primary efficacy variable for statistical evaluation was the area under the time curve (AUC) calculated from USE-index differences to baseline calculated for the three measurement points following the baseline visit, separately.

Secondary variables were the USE-index, infiltrate thickness (sonography), skin color (chromametry) and the clinical assessment (scores) assessed or measured at the various test points.

Safety: Screening and final clinical examinations, recording of adverse events.

Statistical Methods:

Analysis populations

The Full Analysis Set consisted of all subjects randomized into the study who received at least one application of study drug. To be included in the efficacy analysis data from at least one post-baseline measurement had to be available. The Last Observation Carried Forward (LOCF) method was applied for missing efficacy measurements and assessments. The intention-to-treat analysis was based on the Full Analysis Set.

The Valid-Cases Set included all subjects in the Full-Analysis Set, excluding subjects with major protocol violations or significant protocol deviations.

Major protocol violations included but were not limited to:

- inappropriate enrollment
- the use of prohibited concomitant medication
- reaching a major exclusion criterion during the trial

Significant protocol deviations included:

- missing visits on days 4, 8 or 12
- identified protocol violations or significant deviations during the "Subject Data Inclusion" meeting

The per-protocol analysis was based on the Valid-Cases Set.

The Safety Set included all randomized subjects who received at least one application of study medication. All safety analyses were based on the Safety Set.

Analysis variables

Subject characteristics:

- Demographic and background characteristics
- Prior and concomitant medications

Efficacy part:

- AUC of the USE differences from baseline
- USE index and differences from baseline
- Infiltrate thickness and differences from baseline
- Chromametry measurements and differences from baseline
- Clinical assessment of efficacy
- Global clinical assessment

Safety data:

- Adverse events
- Physical examination
- Vital signs

2. Synopsis (continued)

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Statistical Methods (continued):

Analysis of demographic data

Demographic and background data were summarized using descriptive statistical methods. Continuous data were summarized by mean, standard deviation, median and range. Categorical demographic data were summarized by frequency tables.

Analysis of efficacy data

Calculation of the USE-Index and differences to baseline:

$$\textbf{USE-Index} = [T + Da^* * K_{Da}]/K_{Ges}$$

where:

T = infiltrate depth in µm

Da* = color difference to healthy skin (arbitrary unit): $Da^* = a^*_{\text{test field}} - a^*_{\text{healthy skin}}$

K_{Da} = 3 (correction factor for redness)

K_{Ges} = 18 (total correction factor).

The correction factors allow for adjustment in accordance with the pathophysiological significance of the individual observations. The division factor KGes 18 is a "cosmetic" value which serves to ensure that most of the calculated values remain below 100.

Differences to baseline were calculated for study days 4, 8 and 12 as

$$dUSE_X = USE_X - USE_1 \qquad \text{where } x = (4, 8, 12).$$

Calculation of the AUC of the USE-Index:

$$AUC = dUSE_4 \times 2 + (dUSE_4 + dUSE_8) \times 2 + (dUSE_8 + dUSE_{12}) \times 2$$

Statistical analysis

If the efficacy analyses sets differed by more than two subjects, the outlined analyses were performed separately as intent-to-treat and per-protocol analyses.

Skin redness, infiltrate thickness, the calculated USE index, the USE index differences to baseline and the AUC of the USE index differences were summarized by test point and treatment using descriptive statistics (N, mean, standard deviation, median, min, max) as applicable. If appropriate, the different treatments were compared using the paired t-test (two-sided, alpha = 5 %). However, obtained p-values were descriptively interpreted.

Clinical efficacy assessment was descriptively evaluated. The scores were presented in frequency tables for each test point as well as the pooled total effect over all test points. Score sums for clinical assessment were also calculated for the pooled total effect over the study period. The antipsoriatic efficacy was derived from the frequency of scores and score sums.

Analysis of safety data

Adverse events including narrative description of skin irritation in the treatment areas and skin irritation outside the treatment area were summarized descriptively, photographs were taken of local adverse events.

Tables with adverse events were presented as appropriate.

Vital signs were summarized by time point with mean, standard deviation, median, minimum and maximum.

No hypotheses were formulated for this exploratory proof-of-concept study. All results gained from inferential statistical methods were descriptively interpreted.

An interim analysis was not planned.

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Summary, conclusions:

Efficacy results:

Under the conditions in this study three combinations of formulations (Panretin® Gel 0.1 %, Targretin® Gel 1 % and Zorac® Gel 0.1 %, each combined with Diprosis® Gel, respectively) demonstrated antipsoriatic efficacy.

The lowest effect was noted for Panretin® Gel 0.1 % / Diprosis® Gel which showed the highest mean AUC of the USE differences from baseline (-58.7) and the lowest reductions in mean USE-Index (32.48 %) and mean infiltrate thickness (37.52 %).

A clear improvement was noted for Zorac® Gel 0.1 % / Diprosis® Gel and Targretin® Gel 1 % / Diprosis® Gel. The mean AUC was -119.1 for Zorac® Gel 0.1 % / Diprosis® Gel and -99.4 for Targretin® Gel 1 % / Diprosis® Gel. The mean USE-Indexes of Zorac® Gel 0.1 % / Diprosis® Gel and Targretin® Gel 1 % / Diprosis® Gel were reduced by 55.18 % and 49.57 % and the mean infiltrate thicknesses were reduced by 60.37 % and 54.52 % after twelve days of treatment, respectively.

A similar effect was seen for the comparator combination treatment Vaseline / Psorcutan® Beta with a mean AUC of -122.1. The mean USE-Index was reduced by 62.95 % and the mean infiltrate thickness by 65.54 % after twelve days of treatment with Vaseline / Psorcutan® Beta.

The greatest effect was observed for control combination treatment Vaseline / Diprosis® Gel which demonstrated the lowest mean AUC (-135.9) and the greatest reductions in mean USE-Index (66.50 %) and mean infiltrate thickness (69.22 %).

The statistical comparisons between the treatments showed that the mean AUC for Panretin® Gel 0.1 % / Diprosis® Gel was significantly higher than for all four other treatment combinations. A statistically significant higher mean AUC was also for found for the comparison Targretin® Gel 1 % / Diprosis® Gel versus Vaseline / Diprosis® Gel. The other comparisons showed no statistically significant differences.

In the chromametry measurements Panretin® Gel 0.1 % / Diprosis® Gel showed an increase in mean skin redness of 17.27 % on study day 12. No relevant changes in mean skin redness were observed for Zorac® Gel 0.1 % and Targretin® Gel 1 %, each combined with Diprosis® Gel (3.97 % and 4.97 %, respectively). A clear decrease in skin redness was noted after twelve days of treatment with Vaseline / Psorcutan® Beta and Vaseline / Diprosis® Gel (18.85 % and 24.59 %, respectively).

The subordinate global clinical assessment did not reveal an improvement in the fields treated with Panretin® Gel 0.1 % / Diprosis® Gel and Targretin® Gel 1 % / Diprosis® Gel after twelve days of treatment, even worsening was noted in most of the subjects treated with Panretin® Gel 0.1 % / Diprosis® Gel and in six subjects treated with Targretin® Gel 1 % / Diprosis® Gel. Slight improvement was noted in most of the subjects treated with Zorac® Gel 0.1 % / Diprosis® Gel, however, worsening was noted in the test fields of three of the subjects. Clear improvement but no complete healing was noted in most of the subjects treated with the comparator and control combinations.

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Summary, conclusions (continued):

Safety results:

Mild to moderate irritant reactions (erythema and/or erosions) were seen in the test fields treated with the three study preparation combinations: in all subjects after treatment with Panretin® Gel 0.1 % / Diprosis® Gel, in most of the subjects after treatment with Targretin® Gel 1 % / Diprosis® Gel and in six subjects after treatment with Zorac® Gel 0.1 % / Diprosis® Gel. Treatments were discontinued prematurely due to AEs in the nine test fields treated with Panretin® Gel 0.1 % / Diprosis® Gel and in four test fields treated with Targretin® Gel 1 % / Diprosis® Gel.

These reactions were not unexpected since irritant reactions are described as a frequent side effect for topical treatment with retinoids.

There were no other AEs or relevant observations related to safety in this study.

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Summary, *conclusions (continued)*:

Conclusion:

The purpose of this study was the demonstration of antipsoriatic efficacy of a combination of topical formulations in subjects with psoriasis vulgaris.

In the present study a relevant antipsoriatic effect was found for the three study preparation combinations (Panretin® Gel 0.1 %, Targretin® Gel 1 % and Zorac® Gel 0.1 %, each combined with Diprosis® Gel, respectively) on the basis of the sonographic measurements.

The favorite of the three combinations was Zorac® Gel 0.1 % / Diprosis® Gel which demonstrated the greatest improvement, comparable to the comparator combination Vaseline / Psorcutan® Beta, and the best tolerability with less irritant reactions compared to the other two combinations. The effect of Targretin® Gel 1 % / Diprosis® Gel also nearly reached the effect seen for the comparator combination but most of the subjects showed irritant reactions. The lowest effect and the worst tolerability was noted for Panretin® Gel 0.1 % / Diprosis® Gel. This combination showed the highest mean AUC of the USE differences from baseline, the lowest reductions in mean USE-Index and mean infiltrate thickness and irritant reactions in all subjects. The statistical comparisons between the treatments showed that the mean AUC for Panretin® Gel 0.1 % / Diprosis® Gel was significantly higher than for all four other treatment combinations.

The greatest improvement with the lowest AUC and the greatest reduction in mean USE-Index and mean infiltrate thickness was seen for the control combination Vaseline / Diprosis® Gel.

In the chromametry measurements Panretin® Gel 0.1 % / Diprosis® Gel showed a relevant increase in mean skin redness. No relevant changes in mean skin redness were observed for Zorac® Gel 0.1 % and Targretin® Gel 1 %, each combined with Diprosis® Gel. A clear decrease in skin redness was noted following treatment with comparator and control combinations.

The subordinate global clinical assessment did not reveal an improvement in the fields treated with Panretin® Gel 0.1 % / Diprosis® Gel and Targretin® Gel 1 % / Diprosis® Gel after twelve days of treatment, even worsening was noted in most of the subjects treated with Panretin® Gel 0.1 % / Diprosis® Gel and in six subjects treated with Targretin® Gel 1 % / Diprosis® Gel. Slight improvement was noted in most of the subjects treated with Zorac® Gel 0.1% / Diprosis® Gel, however, worsening was noted in the test fields of three of the subjects. Clear improvement but no complete healing was noted in most of the subjects treated with the comparator and control combinations.

Mild to moderate irritant reactions were seen in the test fields treated with the three study preparation combinations: in all subjects after treatment with Panretin® Gel 0.1 % / Diprosis® Gel, in most of the subjects after treatment with Targretin® Gel 1 % / Diprosis® Gel and in six subjects after treatment with Zorac® Gel 0.1% / Diprosis® Gel. Treatments were discontinued prematurely due to AEs in the nine test fields treated with Panretin® Gel 0.1 % / Diprosis® Gel and in four test fields treated with Targretin® Gel 1 % / Diprosis® Gel. The irritant potential of these retinoids is well known, therefore these reactions were not unexpected.

There were no other AEs or relevant observations related to safety in this study.

Date of the report: September 9, 2008