Clinical Study Report

Sponsor:	**GALENpharma GmbH**
Trial No.:	**310409BS**
EudraCT-No.:	**2011-002571-42**
Title:	Phase IIa, multi-center, randomized, double-blind, vehicle-controlled study for assessment of clinical skin condition and effects on barrier impairment of a topical formulation containing tarenflurbil on lesional skin in subjects with mild to moderate atopic eczema
Investigational Products:	**IMP 1:** Tarenflurbil Spray 4 % **IMP 2:** Active ingredient-free vehicle to IMP 1
Clinical Phase:	**IIa**
Indication:	**Atopic eczema**
Objectives:	**Primary objective:** To evaluate efficacy of Tarenflurbil Spray 4 % on lesional skin by clinical assessment of skin condition in subjects with mild to moderate atopic eczema **Secondary objective:** To assess the effect of Tarenflurbil Spray 4 % on barrier impairment by measurement of transepidermal water loss (TEWL) in subjects with mild to moderate atopic eczema
Description:	This was a multi-center, randomized, double-blind, vehicle-controlled trial with intraindividual comparison and random assignment of the treatments to the test field areas. A total of 40 male or female subjects aged 18 years or older, with mild to moderate atopic dermatitis meeting Hanifin and Rajka's criteria were randomized and included in the safety evaluation set (SES) and in the full analysis set (FAS). 37 subjects were included in the valid cases set (VCS). Three subjects were excluded from the VCS due to major protocol deviations. Altogether two comparable lesional areas (30 – 40 cm^2, each) were examined per subject (difference in modified local SCORAD not > 2). All subjects performed treatment with Tarenflurbil Spray 4 % and the active ingredient-free vehicle. The comparison of the IMPs was performed intraindividually. The treatment areas were treated twice daily over a 4-week treatment period. Clinical assessments (erythema, edema/ papulation, oozing/crusts, excoriations, lichenification, and dryness) by scoring and measurements of TEWL to determine the epidermal barrier impairment were performed on Days 1, 8, 15, and 29.
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GCP Compliance:	The clinical trial was conducted in compliance with Good Clinical Practice incl. the archiving of essential documents.
Trial Period:	January 03 to April 19, 2012
Date of Report:	July 03, 2012

2. Synopsis

Name of Company: GALENpharma GmbH	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Not applicable		
Name of Active Ingredient: Tarenflurbil		

Title of Study:
Phase IIa, multi-center, randomized, double-blind, vehicle-controlled study for assessment of clinical skin condition and effects on barrier impairment of a topical formulation containing tarenflurbil on lesional skin in subjects with mild to moderate atopic eczema

Investigator(s):
Coordinating investigator: W. Wigger-Alberti, M.D. (center 01)
Principal investigators: U. Kroencke (center 02), M.D, Y. Frambach (center 03), M.D., D. Thaci, M.D.(center 04)

Study center(s):
Center 01: bioskin GmbH, Berlin, Germany
Center 02: bioskin GmbH, Hamburg, Germany
Center 03: University Hospital of Schleswig Holstein, Campus Luebeck, Germany
Center 04: Johann Wolfgang Goethe University Hospital Frankfurt, Germany

Publication (reference):
Not applicable to this trial

Studied period (years):	Phase of development:
2012	IIa

Objectives:
Primary objective: To evaluate efficacy of Tarenflurbil Spray 4 % on lesional skin by clinical assessment of skin condition in subjects with mild to moderate atopic eczema
Secondary objective: To assess the effect of Tarenflurbil Spray 4 % on barrier impairment by measurement of transepidermal water loss (TEWL) in subjects with mild to moderate atopic eczema

Methodology:
Altogether two comparable lesional areas (30 – 40 cm^2, each) were examined per subject (difference in modified local SCORAD not > 2). All subjects performed treatment with Tarenflurbil Spray 4 % and the active ingredient-free vehicle. The comparison of the IMPs was performed intraindividually. The treatment areas were treated twice daily over a 4-week treatment period. Clinical assessments (erythema, edema/papulation, oozing/crusts, excoriations, lichenification, and dryness) by scoring and measurements of TEWL to determine the epidermal barrier impairment were performed on Days 1, 8, 15, and 29.

Number of subjects (planned and analyzed):
40 male or female subjects with mild to moderate atopic dermatitis were planned, randomized and included in the SES and FAS. 37 subjects were included the VCS. Three subjects were excluded from the VCS due to major protocol deviations.

Diagnosis and main criteria for inclusion:
Male or female subjects, aged 18 years or older with mild to moderate atopic dermatitis meeting Hanifin and Rajka´s criteria; at least two comparable lesional areas (TEWL in the lesional areas at least 12 g/m²h, modified local SCORAD at least 4)

Test product(s), dose and mode of administration, batch number:
IMP 1: Tarenflurbil Spray 4 % (daily dosage: approx. 8.8 mg tarenflurbil, total dosage: approx. 246.4 mg tarenflurbil), batch no.: C1110009
IMP 2: Active ingredient-free vehicle to IMP 1, batch no.: C1110009
Topical application of one puff at the distance of approximately 10 cm per treatment area (30 – 40 cm^2) twice daily

2. Synopsis (continued)

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Duration of treatment:
4-week treatment period (56 treatments)

Reference therapy or controls, dose and mode of administration, batch number:
n.a.

Duration of treatment:
n.a.

Criteria for evaluation:

Primary efficacy variable:	Clinical assessment using a 4-point scale (modified local SCORAD intensity criteria: erythema, edema/papulation, oozing/crusts, excoriations, lichenification, and dryness)
Secondary efficacy variable:	Epidermal barrier impairment by measurement of TEWL

Assessments and measurements were performed on Days 1, 8, 15, and 29.

Other efficacy/tolerability variables:	Subjective assessment of itching (24 hours prior to the treatments on Days 1, 8, 15, and 29) and burning (directly after the treatments on Days 1, 8, 15) using a 10-point scale
Safety and baseline variables:	Medical history, physical examination of the skin and vital signs at screening, urine pregnancy test (Day 1), extent of exposure to IMP, recording of adverse events, final physical examination of the skin

Statistical Methods:

Study populations

Intent-to-treat (ITT)

The full analysis set (FAS) included all randomized subjects who received at least one dose of IMP and had at least one post-baseline assessment. The ITT analysis was based on the FAS.

Per-protocol (PP)

The valid cases set (VCS) included all subjects of the FAS

- without any major protocol violation including violation of inclusion criteria;
- who did not use any prohibited concomitant medication;
- who had 28 ± 1 application days, except for a treatment discontinuation due to reaching criteria for treatment discontinuation and at least a possibly treatment related adverse event or lack of efficacy;
- with available values of the primary endpoint, i.e. with no imputed values, except for treatment discontinuation due to reaching criteria for treatment discontinuation, and at least a possibly treatment related adverse event or lack of efficacy.

The per-protocol analysis was based on the VCS.

Safety evaluation set (SES)

The SES was comprised of all subjects who received any IMP at least once. All safety analyses were based on the SES.

2. Synopsis (continued)

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Statistical Methods (continued)

Efficacy analyses

The efficacy analyses are given for the intent-to-treat and the per-protocol analysis sets.

Statistical analyses

This trial was evaluated in an exploratory manner. All inferential comparisons were interpreted descriptively with respect to the type I error rate of 5 %. Descriptive statistics of the outcomes and their changes from baseline are provided by treatment and time point for the modified local SCORAD and TEWL. Scores of the components of the modified local SCORAD are additionally presented by frequency tables. All efficacy analyses specified below are additionally provided by site.

Primary efficacy endpoint

The primary efficacy endpoint was the comparison of active IMP vs. vehicle with respect to the change from baseline in modified local SCORAD on Day 29. The change from baseline in modified local SCORAD was determined as the difference of the score on Day 29 minus the score at baseline.

The comparison was performed using descriptive statistics for the mean treatment effect including a 95 % confidence interval and the corresponding p-value of the two-sided paired t-test. The treatment effect was determined as the difference between the active IMP and the vehicle in change from baseline of the modified local SCORAD.

Secondary efficacy analyses

The onset of treatment effect with respect to the change from baseline in modified local SCORAD was assessed along the lines of the primary analysis for the Days 8 and 15.

The onset of treatment effect with respect to the change from baseline in modified local SCORAD for the Days 8 and 15 and the change from baseline in TEWL for the Days 8, 15 and 29 were assessed along the lines of the primary analysis.

Safety analyses

Safety was evaluated by tabulations of medical history, physical examination of the skin, vital signs, urine pregnancy test (Day 1), extent of exposure to IMP, AEs, subjective assessment of tolerability (itching and burning).

Other efficacy/tolerability analyses

Descriptive statistics by treatment and time point are provided for the subjective assessments of itching and burning and changes from baseline for the subjective assessments of itching. Scores of the subjective assessments of itching and burning are additionally presented by frequency tables.

2. Synopsis (continued)

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Summary, conclusions:

Efficacy results:

Under the conditions in this trial, with twice daily topical application to lesional skin in subjects with mild to moderate atopic eczema over a 4-week treatment period, Tarenflurbil Spray 4 % showed no clinically relevant treatment effect either on clinical skin condition or on barrier impairment.

The primary efficacy analysis showed a statistically significant less mean change from baseline to Day 29 (end of trial) in modified local SCORAD for Tarenflurbil Spray 4 % when compared to the vehicle ($p = 0.0217$). The change from baseline of the mean modified local SCORAD was comparable on Day 15 (-1.2 and -1.3, respectively), but was slightly lower for Tarenflurbil Spray 4 % and greater (more negative) for the vehicle at the end of the trial (-0.8 vs. -1.6).

Overall, the clinical assessment showed no clinically relevant changes for the individual parameters erythema, edema/palpulation, oozing/crusts, lichenification and dryness following treatment with Tarenflurbil Spray 4 % or the vehicle.

The TEWL measurements showed no clinically relevant changes in mean TEWL-values following treatment with Tarenflurbil Spray 4 % or the vehicle over the trial period (change from baseline to Day 29 = 3.1 and 0.4 g/m²h, respectively). Statistically significant differences in TEWL without clinical relevance were noted for Tarenflurbil Spray 4 % on Days 8 and 15 when compared to the vehicle ($p = 0.0119$ and 0.0321, respectively). No statistically significant difference was found at the end of the trial ($p = 0.0606$).

In the subjective assessment no clinically relevant changes were assessed by the subjects for the symptoms itching and burning following treatment with Tarenflurbil Spray 4 %. The vehicle also showed no clinically relevant change in itching, but the number of subjects with burning had decreased.

Safety results:

In total, nine non-serious TEAEs were experienced by seven subjects. None of the AEs corresponded to a specific test field and all nine AEs were considered to be unlikely related to IMPs. None of the nine TEAEs had led to a premature trial discontinuation and all TEAEs had recovered at the end of the trial.

There were no other relevant observations to safety in this trial.

Conclusion:

The purpose of this trial was to assess the clinical skin condition and the effects on barrier impairment of a topical formulation containing tarenflurbil on lesional skin in subjects with mild to moderate atopic eczema.

Twice daily topical application over a 4-week treatment period with Tarenflurbil Spray 4 % showed no clinically relevant treatment effect either on clinical skin condition or on barrier impairment which was confirmed by clinical and subjective assessments and measurement of transepidermal water loss.

The primary efficacy analysis showed a statistically significant less mean change from baseline to end of the trial in the modified local SCORAD for Tarenflurbil Spray 4 % when compared to the vehicle. No clinically relevant changes were seen for Tarenflurbil Spray 4 % in the clinical assessment for the individual parameters (erythema, edema/palpulation, oozing/crusts, lichenification and dryness), in the TEWL measurements for the mean TEWL-values and in the subjective assessment for the symptoms itching and burning. In general, the results for Tarenflurbil Spray 4 % were similar to those of the vehicle.

In total, nine treatment-emergent adverse events (TEAEs) which were not related to IMP were noted in seven subjects. There were no safety concerns based on the results of this trial.

Date of the report: July 03, 2012