Clinical Study Report

Sponsor:	GALENpharma GmbH
Trial No.:	**310603BS**
EudraCT-No.:	**2011-003807-39**
Title:	A phase II, single-center, randomized, observer-blind, vehicle-controlled trial to determine clinical equivalence of MomeGalen Cream (mometasone furoate 0.1 %) to Ecural® Fettcreme (reference drug) and superiority to the active ingredient-free vehicle by evaluation of the anti-psoriatic efficacy in a psoriasis plaque test
Investigational Medicinal Product/s (IMPs):	**IMP 1** (Generic formulation): MomeGalen Cream (0.1 % mometasone furoate) **IMP 2** (Vehicle to IMP 1): Active ingredient-free vehicle to MomeGalen Cream **IMP 3** (Reference listed drug; RLD): Ecural® Fettcreme (0.1 % mometasone furoate)
Clinical Phase:	II
Objective:	**Primary objective:** To demonstrate clinical equivalence of MomeGalen Cream (mometasone furoate 0.1 %) to Ecural® Fettcreme (RLD) in anti-psoriatic efficacy by sonographic measurement of psoriatic infiltrate in subjects with chronic psoriasis vulgaris **Secondary objective:** To evaluate the anti-psoriatic efficacy of MomeGalen Cream (mometasone furoate 0.1 %) by clinical assessment in subjects with chronic psoriasis vulgaris
Description:	This phase II trial was performed as a single-center, randomized, observer-blind, vehicle-controlled trial with intraindividual comparison and random assignment of the treatments to the test fields. In total, 30 male or female subjects aged 18 to 75 years with stable psoriatic plaques were included in this trial and were valid for the safety and full analyses sets (SES, FAS). Twenty-nine subjects were included in the valid cases set (VCS). One subject was excluded from the VCS due to a protocol violation. Altogether three test fields were examined per subject (MomeGalen Cream 0.1 %, the active ingredient-free vehicle to MomeGalen Cream and the marketed product Ecural® Fettcreme). The test fields were treated occlusively over 11 days. Experimental measurements by 20 MHz sonography were performed at baseline (Day 1) and on Days 4, 8, and 12. On Days 4, 8, and 12 clinical assessments of the test fields were performed using a 5-point score. Additionally, photographic documentation was made at baseline (Day 1) and on Day 12.
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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:	October 17 – November 25, 2011
Date of Report:	February 16, 2012

2. Synopsis

Name of Company: GALENpharma GmbH	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product: MomeGalen Cream	Volume: Page:	
Name of Active Ingredient: mometasone furoate		

Title of Study:

A phase II, single-center, randomized, observer-blind, vehicle-controlled trial to determine clinical equivalence of MomeGalen Cream (mometasone furoate 0.1 %) to Ecural® Fettcreme (reference drug) and superiority to the active ingredient-free vehicle by evaluation of the anti-psoriatic efficacy in a psoriasis plaque test

Investigator(s):

U. Kroencke, M.D.; W. Wigger-Alberti, M.D.; Y.-L. von Mackensen, M.D.

Study center(s):

bioskin GmbH, Hamburg, Germany

Publication (reference):

Not applicable to this trial

Studied period (years):	Phase of development:
2011	II

Objectives:

The primary objective of this trial was to demonstrate clinical equivalence of MomeGalen Cream 0.1 % to Ecural® Fettcreme in anti-psoriatic efficacy by sonographic measurement of psoriatic infiltrate in subjects with chronic psoriasis vulgaris.

The secondary objective was to evaluate the anti-psoriatic efficacy of MomeGalen Cream 0.1 % by clinical assessment in subjects with chronic psoriasis vulgaris.

Methodology:

Approximately 200 µl of each IMP were occlusively applied to altogether three test fields using special test chambers over an 11-day treatment period (10 applications on Days 1 - 6 and 8 - 11). The IMPs were applied in chambers and seated in holes punched in a hydrocolloid dressing. The hydrocolloid dressing stayed in place for a maximum of 4 days and was renewed on Days 4 and 8. Experimental measurements by 20 MHz sonography were performed at baseline (Day 1) and on Days 4, 8, and 12. Clinical assessments of the test fields were performed using a 5-point score on Days 4, 8, and 12. Additionally, photographic documentation was made at baseline (Day 1) and on Day 12.

Number of subjects (planned and analyzed):

Thirty male or female subjects were planned and included in this trial. Data from all 30 subjects were valid for the SES and FAS and 29 subjects for the VCS (protocol violation in one subject).

Diagnosis and main criteria for inclusion:

Male or female subjects aged 18 to 75 years with chronic plaque type psoriasis in a stable phase and an area sufficient for three treatment fields

Test product(s), dose and mode of administration, batch number:

IMP 1 (Generic formulation): MomeGalen Cream (0.1 % mometasone furoate), batch no.: 11371A

IMP 2 (Vehicle to IMP 1): Active ingredient-free vehicle to MomeGalen Cream, batch no.: 11371B

Occlusive, topical application of approximately 200 µl of formulation per treatment to one test field each (1.1 cm^2) once daily

Duration of treatment:

11-day treatment period (10 treatments)

2. Synopsis (continued)

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Name of Active Ingredient: mometasone furoate		

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

IMP 3 (Reference listed drug [RLD]): Ecural® Fettcreme (0.1 % mometasone furoate), batch no.: 1NGFA60001

Occlusive, topical application of approximately 200 µl of formulation per treatment to one test field (1.1 cm^2) once daily

Duration of treatment:

11-day treatment period (10 treatments)

Criteria for evaluation:

Efficacy:

Primary variable: Change in psoriatic infiltrate thickness over the treatment period (Day 1 to Day 12)

Primary endpoint: The area under the curve (AUC) of the changes from baseline in infiltrate thickness over the treatment period

Secondary variables: Changes in psoriatic infiltrate thickness on days 4, 8, and 12,
Clinical assessment using a 5-point score on days 4, 8, and 12.

Safety: Relevant medical history; adverse events; physical examination of the skin and vital signs were collected during the two weeks before the baseline visit and on Day 12.

Statistical Methods:

Study populations

- *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 intention-to-treat analysis (ITT) was based on the FAS. The last observation carried forward (LOCF) principle was applied for missing efficacy data.
- *The valid cases set (VCS)* included all subjects
  - without any major protocol violation including violation of inclusion criteria;
  - who received the full trial medication doses;
  - with available values of the primary variables at all days, i.e. with no imputed values.

The per-protocol (PP) analysis was based on the VCS.

- *The safety evaluation set (SES)* included all subjects who received any trial medication at least once; all safety analyses were based on the SES.

Efficacy analyses

Hypotheses

For the primary analysis all following three co-primary hypotheses had to be rejected:

Co-primary hypothesis 1:

The clinical equivalence of IMP 1 to the reference listed drug (RLD) with respect to the area under the curve (AUC) of change in infiltrate thickness will be assessed testing the hypothesis

H_{01}: mean $AUC_{IMP\ 1}$ / mean AUC_{RLD} < 0.8 or mean $AUC_{IMP\ 1}$ / mean AUC_{RLD} > 1.25

against the alternative

H_{11}: 0.8 ≤ mean $AUC_{IMP\ 1}$ / mean AUC_{RLD} ≤ 1.25

2. Synopsis (continued)

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Statistical Methods (continued)

Co-primary hypothesis 2:

The clinical superiority of IMP 1 vs. the vehicle to IMP 1 with respect to the AUC of change in infiltrate thickness was assessed testing the hypothesis

H_{02}: mean $AUC_{IMP\ 1}$ = mean $AUC_{Vehicle}$

against the alternative

H_{12}: mean $AUC_{IMP\ 1} \neq$ mean $AUC_{Vehicle}$

Co-primary hypothesis 3:

The clinical superiority of RLD vs. the vehicle to IMP 1 with respect to the AUC of change in infiltrate thickness was assessed testing the hypothesis

H_{03}: mean AUC_{RLD} = mean $AUC_{Vehicle}$

against the alternative

H_{13}: mean $AUC_{RLD} \neq$ mean $AUC_{Vehicle}$

Statistical analyses

The efficacy analyses will be given for the Intent-To-Treat and the Per-Protocol analysis sets.

Primary analyses

The clinical equivalence of IMP 1 to RLD with respect to the AUC of change in infiltrate thickness was assessed applying Locke's method (1) by calculation of the 90 % confidence interval for the ratio (mean $AUC_{IMP\ 1}$ / mean AUC_{RLD}). Hypothesis H_{01} was to be rejected for the IMP if the lower limit was greater or equal 0.8 and the upper limit less or equal 1.25.

The clinical superiority of IMP 1 (and RLD) vs. the vehicle to IMP 1 with respect to the AUC of change in infiltrate thickness was assessed applying the two-sided paired t-test with an error type I of 5 %.
If the obtained p-value was less than 0.05 and the mean AUC for IMP 1 (or RLD) was less than the mean AUC for the vehicle to IMP 1, then the superiority of the IMP 1 (or RLD) vs. vehicle was established.

Secondary analyses

The calculated AUC, the absolute values of infiltrate thickness and their changes from baseline were summarized by treatment and time point using descriptive statistics (N, mean, standard deviation, median, minimum, maximum).
Clinical efficacy assessment was evaluated descriptively. The scores are presented by treatment for each time point using frequency tables and descriptive statistics (N, mean, standard deviation, median, min, max, sum). Additionally, the cumulative total score over all time points was summarized descriptively by treatment.

Safety analyses

Safety was evaluated by tabulations of relevant medical history, physical examination of the skin, extent of exposure to IMP, adverse events (AEs) and vital signs.

2. Synopsis (continued)

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Summary, conclusions:

Efficacy results: In the present psoriasis plaque test with once daily occlusive application over an 11-day treatment period clinical equivalence of MomeGalen Cream (IMP 1) to the reference listed drug (RLD) Ecural® Fettcreme could be demonstrated. Furthermore, superiority of both 0.1 % mometasone furoate-containing creams vs. active ingredient-free vehicle was shown.

The sonographic measurements showed a nearly identical great reduction of infiltrate thickness following treatment with MomeGalen Cream and the reference (Day 12: % mean change in infiltrate thickness = approximately 80 %). For both creams a great comparable negative mean AUC of change in infiltrate thickness was calculated (-3174 and -3258 µm day), representing clear antipsoriatic efficacy.

No effect was seen for the vehicle of MomeGalen Cream (% mean change in infiltrate thickness = 1 %, mean AUC = 134 µm day).

All three co-primary hypotheses could be rejected and therefore the primary trial aim was achieved:

The clinical equivalence was significant with an observed confidence interval (CI) for the ratio (mean $AUC_{IMP\ 1}$/mean AUC_{RLD}) ranging from 91 – 104 % which was completely covered by the 90 % CI ranging from 80 - 125 % (co-primary analysis 1).

For MomeGalen Cream and Ecural® Fettcreme superiority vs. vehicle was established since the obtained p-values ($p< 0.0001$, each) were less than 0.05 and the mean AUC of both active creams was less than the mean AUC for the vehicle (co-primary analyses 2 and 3).

In general, the clinical assessment data underscored the sonographic results. Over the trial period a clear continuous improvement was seen for both formulations. At the end of the trial “completely healed” (score 3) was noted in the respective test fields of all 30 subjects. No effect was seen in the vehicle-treated test fields in most of the subjects. A slight improvement was noted in two subjects and in a further subject worsening was noted following treatment with the vehicle

Safety results: There were two non-serious treatment-emergent AEs noted in two subjects which were considered to be unlikely related to any of the IMPs. Both TEAEs (PT: headache) were of mild to moderate intensity. The two TEAEs recovered without sequelae and no action with IMP was taken.

The physical examinations of the skin did not show relevant findings in any of the patients and there were no other relevant observations to safety in this trial.

Conclusion: The aim of this trial was to determine clinical equivalence of MomeGalen Cream (mometasone furoate 0.1 %) to Ecural® Fettcreme (reference listed drug) and superiority to the active ingredient-free vehicle by evaluation of the anti-psoriatic efficacy in a psoriasis plaque test.

Under the present trial conditions clinical equivalence of MomeGalen Cream to Ecural® Fettcreme could be demonstrated and superiority to the active ingredient-free vehicle was shown in the primary analysis of the AUC of change in infiltrate thickness.

A nearly identical clear antipsoriatic effect was seen for both mometasone furoate 0.1 %-containing creams following once daily occlusive application over an 11-day treatment period. This was confirmed by sonographic measurement showing a mean percent reduction in infiltrate thickness of 80 % and by clinical assessment evaluating complete healing in the test fields treated with the MomeGalen Cream and Ecural® Fettcreme in all subjects.

No treatment effect was seen for the vehicle in the present trial.

Overall, all three IMPs were well tolerated. Two non-serious treatment-emergent AEs were reported in two subjects and were considered to be unlikely related to any of the IMPs. There were no safety concerns based on the results of this trial.

Date of the report: February 16, 2012