Clinical Study Report

Sponsor:	**Medice Arzneimittel Pütter GmbH & Co. KG**
Trial No.:	**6520-9170-08 / 310827BS**
EudraCT-No.:	**2011-001175-38**
Title:	**A phase II, multi-center, randomized, double-blind trial with intraindividual comparison to assess superiority of topically applied Soventol HydroCort 0.5 % Cremogel versus vehicle on lesional skin in patients with mild atopic eczema, seborrheic eczema or stasis dermatitis and to assess safety of Soventol HydroCort 0.5 % Cremogel**
Investigational Medicinal Product/s (IMP):	**IMP 1:** Soventol HydroCort 0.5 % Cremogel (topical formulation with 0.5% hydrocortisone acetate) **IMP 2:** Active ingredient-free vehicle to IMP 1
Clinical Phase:	II
Indication:	Atopic eczema, seborrheic eczema, stasis dermatitis
Objective:	The objectives were to assess superiority of Soventol HydroCort 0.5 % Cremogel versus vehicle and to assess the safety of Soventol HydroCort 0.5 % Cremogel.
Description:	This phase II trial was performed as a multi-center, randomized, double-blind vehicle-controlled trial with intraindividual comparison and random assignment of the treatments to the test areas. A total of 34 male or female patients aged 18 years or older, with mild atopic dermatitis meeting Hanifin and Rajka's criteria, seborrheic eczema or stasis dermatitis were randomized in the trial. Thirty-two patients completed the trial as planned. All 34 patients were included in the safety evaluation set (SES). Data from 32 patients were valid for the full analysis set (FAS) and the data from 27 patients for the valid cases set (VCS). Two patients were excluded from the FAS since they had no post-baseline assessment. Five additional patients were excluded from the VCS due to major protocol violations. Altogether two comparable lesional areas (of at least 2 cm^2 each) were examined per patient. All patients performed treatment with Soventol HydroCort 0.5 % Cremogel and the active ingredient-free vehicle three times daily (morning, noon and evening) during a 2-week treatment period. Clinical assessment (erythema, edema/-papulation, oozing/-crusting, excoriations, scaling and lichenification) by scoring was performed on Days 1, 4, 8 and 15. The comparison of the IMPs was performed intraindividually.
Coordinating Investigator:	Swarna Ekanayake-Bohlig, M.D. MENSINGDERMA research GmbH Heegbarg 4, 22391 Hamburg, Germany Tel.: +49-40-602 98 472, Fax: +49-40-603 30 25
Project Manager (Sponsor):	Armin Engels, Ph.D. MEDICE Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37, 58638 Iserlohn, Germany Tel.: +49-2371 937-368, Fax: +49-2371 937-360
GCP Compliance:	The clinical trial was conducted in compliance with Good Clinical Practice (GCP) including the archiving of essential documents.
Trial Period:	February 06 – March 26, 2012
Date of Report:	August 14, 2012

2. Synopsis

Name of Company: MEDICE Arzneimittel Pütter GmbH & Co. KG	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: Soventol HydroCort 0.5 % Cremogel		
Name of Active Ingredient: 0.5 % hydrocortisone acetate		

Title of Study:	
A phase II, multi-center, randomized, double-blind trial with intraindividual comparison to assess superiority of topically applied Soventol HydroCort 0.5 % Cremogel versus vehicle on lesional skin in patients with mild atopic eczema, seborrheic eczema or stasis dermatitis and to assess safety of Soventol HydroCort 0.5 % Cremogel	
Investigator(s):	
Swarna Ekanayake-Bohlig, M.D.; Christian Mensing, M.D.; Cornelius Mensing, M.D.; Martin Miehe, M.D.; Sören Baeblich, M.D.; Ulrike Serfling, M.D.; Thomas Stavermann, M.D.; Beate Ziethen, M.D.	
Study center(s):	
Three study centers in Germany: MENSINGDERMA research GmbH, Hamburg; Dermatological Practice, Martin Miehe, M.D., Berlin and Dermatological Practice, Thomas Stavermann, M.D., Berlin	
Publication (reference):	
Not applicable to this trial	
Studied period (years):	Phase of development:
2012	II
Objectives:	
The objectives were to assess superiority of Soventol HydroCort 0.5 % Cremogel versus vehicle and to assess the safety of Soventol HydroCort 0.5 % Cremogel.	
Methodology:	
Altogether two comparable lesional areas (of at least 2 cm^2 each) were examined per patient. Topical application of up to 3 fingertip units (FTU) corresponding to approximately 1.5 g of each IMP per treatment area was performed three times daily (morning, noon and evening) during a 2-week treatment period (42 treatments). Clinical assessment (erythema, edema/papulation, oozing/crusting, excoriations, scaling and lichenification) by scoring was performed on Days 1, 4, 8 and 15.	
Number of patients (planned and analyzed):	
A total of 34 patients were randomized in the trial. Thirty-two patients completed the trial as planned. All 34 patients were included in the safety evaluation set (SES). Data from 32 patients were valid for the FAS and data from 27 patients for the valid cases set (VCS). Two patients were excluded from the FAS since they had no post-baseline assessment. Five additional patients were excluded from the VCS due to major protocol violations.	
Diagnosis and main criteria for inclusion:	
Male or female patients, aged 18 years or older with mild atopic dermatitis or seborrheic eczema or stasis dermatitis	
Test product(s), dose and mode of administration, batch number:	
IMP 1: Soventol HydroCort 0.5 % Cremogel (topical formulation with 0.5 % hydrocortisone acetate), batch no. PL 5256 **IMP 2:** Active ingredient-free vehicle to IMP 1, batch no. PL 5256 topical application of up to 3 FTU corresponding to approximately 1.5 g of IMP 1 per treatment area (at least 2 cm^2) three times daily (morning, noon and evening)	
Duration of treatment:	
2-week treatment period (42 treatments)	

2. Synopsis (continued)

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

Duration of treatment:
n.a.

Criteria for evaluation:

Efficacy:

Primary efficacy variable
Clinical assessment of erythema using a five-point scale

Secondary efficacy variables
Clinical assessment of edema/papulation, oozing/crusting, excoriations, scaling and lichenification using a five-point scale

Safety:

Medical history, physical examination of the skin, vital signs, recording of adverse events (AEs), extent of exposure

Statistical Methods:

Study Populations

Intent-To-Treat (ITT)
The FAS included all randomized patients who received at least one dose of IMP, and had at least one post-baseline assessment. The intention-to-treat analysis was based on the FAS.

Per-Protocol (PP)
The valid-cases set (VCS) included all patients of the FAS

- without any major protocol violation including violation of inclusion criteria;
- who did not use any prohibited concomitant medication;
- who received the full trial medication doses, except for treatment discontinuation due to reaching criteria for treatment discontinuation, an at least 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, an at least possibly treatment related adverse event or lack of efficacy.

Prior to breaking the blind, other additional criteria might have been added to the list to accommodate for unforeseen events that occurred during the conduct of the trial that resulted in noteworthy protocol violations. The relevance of protocol violations was determined in a blinded analysis meeting, prior to database closure.

The PP analysis was based on the VCS.

(continued)

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Statistical Methods (continued):

Safety population:
The safety evaluation set (SES) was comprised of all patients who received any IMP at least once. All safety analyses were based on the SES.

Efficacy analyses:
The primary efficacy analysis was based on the FAS. A sensitivity analysis was performed in the VCS.

Hypotheses
The clinical superiority of IMP 1 vs. the vehicle to IMP 1 with respect to the area under the curve (AUC) was assessed testing the hypothesis

H_0: mean $AUC_{IMP\ 1}$ = mean $AUC_{Vehicle\ to\ IMP\ 1}$

against the alternative

H_1: mean $AUC_{IMP\ 1} \neq$ mean $AUC_{Vehicle\ to\ IMP\ 1}$

If the obtained p-value was less than 0.05 and the mean AUC for IMP 1 was less than the mean AUC for the vehicle to IMP 1 then the superiority of the IMP 1 vs. vehicle could be established.

Statistical analyses
Efficacy analyses are provided for the FAS and the VCS. Safety analyses are provided for the SES.

Primary efficacy endpoint
The clinical superiority of IMP 1 vs. the vehicle to IMP 1 with respect to the AUC of baseline corrected erythema scores was assessed testing the Hypothesis H_0 against the alternative H_1 applying the two-sided paired t-test with a type I error of 5 %. If the obtained p-value was less than 0.05 and the mean AUC for IMP 1 was less than the mean AUC for the vehicle to IMP 1 then the superiority of the IMP 1 vs. vehicle was established.

Secondary efficacy analyses
Clinical assessment of edema/papulation, oozing/crusting, excoriations, scaling and lichenification was evaluated descriptively following the primary analysis.

Safety analyses
Safety was evaluated by tabulations of extent of exposure to IMP, AEs, medical history and assessment of vital signs.

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Summary, conclusions:

Efficacy results:

Under the conditions of this trial with topical application three times daily over a 2-week treatment period (42 applications) Soventol HydroCort 0.5 % Cremogel showed a treatment effect in patients with mild atopic eczema, seborrheic eczema or stasis dermatitis.

The clinical superiority of Soventol HydroCort 0.5 % Cremogel to the active ingredient-free vehicle was shown in the robust analysis (Wilcoxon signed-rank test), but was just barely missed in the planned primary parametric analysis (paired t-test).

The primary analysis showed that one part of the definition for superiority was met: The mean AUC-value of baseline corrected erythema scores for Soventol HydroCort 0.5 % Cremogel (FAS: -15.0 a.u., VCS: -15.3 a.u.) was less (more negative) than the mean AUC-value for the vehicle (FAS and VCS: -10.4 a.u., each). However, the obtained p-value was marginally greater than 0.05 (FAS: $p = 0.0577$, VCS: $p = 0.0518$) and therefore, no superiority of Soventol HydroCort 0.5 % Cremogel vs. vehicle could be shown missed in the parametric analysis (paired t-test).

Due to this borderline outcome of the primary endpoint and the unexpected high standard deviation of the estimate of the treatment effect, additional analyses to evaluate the robustness of the primary outcome were performed. The diagnostic analysis of the residuals suggested a parametric analysis, but a more detailed analysis of the primary endpoint revealed a few suspicious outlying results showing weak verum but strong vehicle effects. Therefore, a robust analysis of the primary endpoint was recommended. The Wilcoxon signed-rank test showed a significant effect ($p = 0.0321$) with superiority vs. vehicle.
In general, the clinical assessment showed a slightly greater reduction of erythema following treatment with Soventol HydroCort 0.5 % Cremogel when compared to the vehicle (mean change from baseline to Day 15: -1.7 vs. -1.3). Similar courses in mean scores were also seen for the parameters edema/papulation, oozing/crusting, excoriations, scaling and lichenification, also demonstrating somewhat greater reductions for Soventol HydroCort 0.5 % Cremogel than for the vehicle. The calculated mean AUC-values were slightly less for Soventol HydroCort 0.5 % Cremogel than for the vehicle, but a p-value < 0.05 were not found for any of these clinical assessment parameters in the parametric analysis.

Safety results:

In total, nine non-serious TEAEs were experienced by eight patients (application site pain: N = 6, nasopharyngitis: N = 1, dysmenorrhoea: N = 1).

Seven TEAEs corresponded to a specific test field (application site pain): Three TEAEs were assessed to be probably related to Soventol HydroCort 0.5 % Cremogel and four TEAEs to the vehicle (in one of the patients application site pain was reported in both test fields). In these six patients skin burning occurred shortly after the application and generally disappeared after a short time. In four of the patients skin burning was only noted on Day 1, in one patient on Days 1 - 3 and in another patient on Days 1 - 6.

The two other TEAEs were considered to be unlikely related to any of the IMPs.

None of the nine TEAEs had led to a premature trial discontinuation and all TEAEs had recovered without sequelae at the end of the trial.

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

2. Synopsis (continued)

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Summary, conclusions:

Conclusion:

The purpose of this phase II, multi-center, randomized, double-blind and vehicle-controlled trial with intraindividual comparison was to assess the superiority of Soventol HydroCort 0.5 % Cremogel versus the active ingredient-free vehicle on lesional skin in patients with mild atopic eczema, seborrheic eczema or stasis dermatitis and to assess the safety of Soventol HydroCort 0.5 % Cremogel.

Under the present trial conditions Soventol HydroCort 0.5 % Cremogel demonstrated efficacy in the treatment of mild atopic eczema, seborrheic eczema or stasis dermatitis which was confirmed by clinical assessment.

The calculated mean AUC-value of baseline corrected erythema scores for Soventol HydroCort 0.5 % Cremogel was less than the mean AUC-value for the vehicle.

The clinical superiority of Soventol HydroCort 0.5 % Cremogel to the active ingredient-free vehicle was shown in the robust analysis (Wilcoxon signed-rank test), but was just barely missed in the planned parametric analysis (paired t-test) since the obtained p-value was marginally greater than 0.05. To reduce the influence of extreme values in the evaluation of the central tendency of the treatment effect a robust test was considered more appropriate for the evaluation of the treatment effect than the parametric test.

In general, the clinical assessment of erythema, edema/papulation, oozing/crusting, excoriations, scaling and lichenification showed a slightly greater reduction of erythema following treatment with Soventol HydroCort 0.5 % Cremogel when compared to the vehicle.

Overall, it should be taken into consideration that also the vehicle showed a positive treatment effect in this clinical trial.

There were nine non-serious TEAEs experienced by eight patients. Seven of these AEs were probably (application site pain) and two AEs were unlikely related to any of the IMPs. No safety concerns were found in this trial.

Date of the report: August 14, 2012