1 Title Page

Study Title	A placebo-controlled, multicentre, double-blinded, intra-individual comparison to gain evidence of the safety, tolerability and efficacy of Prednicarbat cream and ointment in patients with active atopic dermatitis
Protocol No.	071-007
EudraCT No.	2009-012028-98
Investigational medicinal products (IMPs)	IMP 1: Prednicarbat cream (O/W), containing 2.5 mg/g prednicarbate IMP 2 Prednicarbat ointment, containing 2.5 mg/g prednicarbate Placebo 1: Prednicarbat cream (O/W), containing no active compound Placebo 2: Prednicarbat ointment, containing no active compound
Indication	Active atopic dermatitis, active atopic dermatitis was defined by an Investigator's Global Assessment (IGA)-Score between 1 and 4
Design	A placebo-controlled, multicentre, double-blinded study to gain evidence of the safety, tolerability and efficacy of Prednicarbat cream (O/W) and ointment in the intra-individual comparison to a placebo. Treatment took place over 21 days.
Development Phase	II
Sponsor	Dr. Jörg Mehnert GALENpharma GmbH Wittland 13 24109 Kiel
Coordinating Investigator	Prof. Dr. Kristian Reich SCIderm GmbH Esplanade 6 20354 Hamburg
Author of Report	Dr. Konstanze Henning SCIderm GmbH Esplanade 6 20354 Hamburg
Study Initiation Date	FPI: 13 July 2009
Study Completion Date	LPO: 28 August 2009
Date of Report	Final Version 25 November 2009
ICH/GCP- Declaration:	This study was performed in compliance with Good Clinical Pratices (GCP), including the archiving of essential documents.

2 Synopsis

<table>
<tr><td>Name of Sponsor/Company:
GALENpharma GmbH</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Prednicarbat cream (O/W)
Prednicarbat ointment</td></tr>
<tr><td>Name of Active Ingredient:
2.5 mg/g prednicarbate</td></tr>
<tr><td colspan="3">Title of study:
A placebo-controlled, multicentre, double-blinded, intra-individual comparison to gain evidence of the safety, tolerability and efficacy of Prednicarbat cream and ointment in patients with active atopic dermatitis</td></tr>
<tr><td colspan="3">Investigators:
<table><tr><td>Site 1
SCIderm GmbH:

Prof. Dr. K. Reich (LKP)
Dr. K. Shakery
Dr. C. Kahl
Dr. L. Grams</td><td>Site 2
Hautarztzentrum Tegel:

Dr. M. Miehe [Principle Investigator (PI)]
Dr. S. Baeblich</td><td>Site 3
Gemeinschaftspraxis Mahlow:

Dr. M. Sebastian (PI)
Dr. H. Scholz
Dr. S. Schilling</td></tr></table></td></tr>
<tr><td colspan="3">Study centres:
<table><tr><td>SCIderm GmbH
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15831 Mahlow</td></tr></table></td></tr>
<tr><td colspan="3">Publication (reference): None</td></tr>
<tr><td colspan="2">Studied period:

Date of first enrolment:
13 July 2009
Date of last completed:
28 August 2009</td><td>Phase of development: Phase II</td></tr>
<tr><td colspan="3">Objectives:

Primary objective was to gain evidence of the safety and local tolerability of Prednicarbat cream (O/W)/Prednicarbat ointment compared to placebo, assessed by the severity, nature and frequency of adverse events/serious adverse events (AEs/SAEs) and the relationship to study medication, vital signs and subjective and objective skin symptoms by physicians' and patients' assessment of tolerability (PAT, PaAT).</td></tr>
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Name of Sponsor/Company: GALENpharma GmbH	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Name of Finished Product: Prednicarbat cream (O/W) Prednicarbat ointment	Volume:	
Name of Active Ingredient: 2.5 mg/g prednicarbate	Page:	

The patients' assessment of tolerability was rated at all visits based on the following symptoms: itching, burning, stinging and tightness of the skin before and after application of the IMPs. The physicians' assessment of tolerability was rated at all visits based on the occurrence of the following symptoms: occurrence of folliculitis, bruise (ecchymosis), whitehead (milia), dermal atrophy, telangiectasia, local infections, local allergic reactions before and after application of the IMPs.

The secondary objectives were to gain evidence of the tolerability and efficacy of Prednicarbat cream (O/W)/Prednicarbat ointment compared to placebo evaluated by physical examination, the patients' and physicians' global assessment of tolerability and as efficacy parameter modified EASI.

Methodology:

This was a placebo-controlled, multicentre, double-blinded study to gain evidence of the safety, tolerability and efficacy of Prednicarbat cream (O/W) and ointment in the intra-individual comparison to a placebo. Treatment took place twice daily over a period of 21 days.

Number of patients (planned and analysed):

planned:	50	analysed safety: safety population	50
screened:	50		
randomized:	50	analysed efficacy: Intention-to-treat	50
completed:	50	(ITT) population	

Diagnosis and main criteria for inclusion:

The study population consisted of 50 patients with active atopic dermatitis. Active atopic dermatitis was defined by an IGA-Score between 1 and 4.

Inclusion criteria:

- Male or female patients with a diagnosis of atopic dermatitis for ≥ 6 months, in active stage (active stage means severity as measured by IGA-Score between 1 and 4)
- At least two comparable areas of stable atopic eczema on bilateral symmetric corresponding sides of the extremities or the body (except for head and genital area), each of at least 10 cm^2, with a modified EASI score of the test areas > 6 and at least 60 % of the defined test areas afflicted with atopic dermatitis (definition of modified EASI in chapter 9.5.1.1)
- Age between 18 and 75 years
- A patient of childbearing potential agreed to use one of the following contraceptive

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Name of Finished Product: Prednicarbat cream (O/W) Prednicarbat ointment	Volume:	
Name of Active Ingredient: 2.5 mg/g prednicarbate	Page:	

methods for the duration of the study:

- Strict abstinence (exception: male partner with a vasectomy at least 3 months prior to study entry was allowed)
- Combined oral, implanted or injectable contraceptives on a stable dose for at least 3 months prior to study entrance
- Intrauterine device (IUD) inserted at least 1 month prior to study entrance

- Patient was willing and able to comply with the requirements of the clinical study protocol. In particular, patient had to adhere to concomitant therapy prohibitions of the test areas and had to agree to avoid intense ultraviolet (UV) exposure of the test areas during the study
- Written Informed Consent

Test product, dose and mode of administration, batch number:

Prednicarbat cream (O/W), containing 2.5 mg/g prednicarbate	Twice-daily application (total max. dose 50 g)	cutaneous application	Batch no.: 08061
Prednicarbat ointment, containing 2.5 mg/g prednicarbate	Twice-daily application (total max. dose 50 g)	cutaneous application	Batch no.: 09101

Duration of treatment: 21 days

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

Prednicarbat cream (O/W), containing no active compound	Twice-daily application (total max. dose 50 g)	cutaneous application	Batch no.: 08352
Prednicarbat ointment, containing no active compound	Twice-daily application (total max. dose 50 g)	cutaneous application	Batch no.: 08384

Criteria for evaluation:

All 50 patients who were randomized were included in the ITT and safety population. The analysis of the efficacy parameter was performed on ITT population, the analysis of the safety data was based on the safety population.

Efficacy:

The efficacy was assessed by modified EASI (Eczema Area and Severity Index) at visit 1

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Name of Finished Product: Prednicarbat cream (O/W) Prednicarbat ointment	Volume:	
Name of Active Ingredient: 2.5 mg/g prednicarbate	Page:	

(day 0), visit 2 (day 7) and visit 3 (day 21).

Safety:

Safety and tolerability of Prednicarbat cream (O/W)/Prednicarbat ointment compared to placebo were assessed by the severity, nature, the relationship to study medication and frequency of AEs/SAEs, vital signs, physical examination, patients' assessment of tolerability (PaAT), physicians' assessment of tolerability (PAT) and patients' and physicians' global assessment of tolerability (PaGA and PGA) .

Statistical methods:

The Statistical Analysis Plan defined the statistical analyses for all study evaluations.

The efficacy parameter modified EASI was summarized using descriptive statistics (N, mean, median, standard deviations, minimum and maximum). Summary tables are presented by treatment and visit.

Safety analyses of the nature, severity and relationship of AEs to study medication were summarized by preferred term and system organ class (SOC) and presented in frequencies and percentages broken down by treatment group, if appropriate. Safety parameters were summarized according to the level of measurement by frequencies and percentages, broken down by treatment group. Vital signs and physical examination were analyzed by listing abnormal values.

Summary - Conclusions:

<u>Efficacy Results:</u>

The efficacy was assessed by modified EASI.

At the beginning of the study (visit 1, day 0) a similar modified EASI value was assessed for the test areas treated with Prednicarbat cream (O/W) or placebo cream (36.2±7.48 and 36.1±7.90 respectively). During the course of the study the modified EASI values decreased continuously for both test areas, but at the end of the study (visit 3, day 21) the test areas treated with Prednicarbat cream (O/W) showed a notable superiority compared to the test areas treated with placebo cream (11.2±10.62 vs. 24.1±16.04).

Those test areas that were treated with Prednicarbat ointment or placebo ointment also showed a similar modified EASI value at visit 1 (37.0±8.52 and 40.1±10.99, respectively). During the course of the study the modified EASI values decreased continuously for both test

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Name of Active Ingredient: 2.5 mg/g prednicarbate	Page:	

areas, but the test areas treated with Prednicarbat ointment showed a notable superiority compared to the test areas treated with placebo ointment (12.4±9.89 and 23.3±16.63 after 21 days, visit 3).

Safety Results:

The safety and tolerability was assessed by the occurrence of AEs/SAEs, by vital signs, physical examination, patients' assessment of tolerability (PaAT), physicians' assessment of tolerability (PAT) and patients' and physicians' global assessment of tolerability (PaGA and PGA).

Two patients who were treated with Prednicarbat cream (O/W, patient R27) and placebo cream (patient R16) reported *related* AEs. These AEs consisted of subjective ('application site pruritus' and 'skin tightness') symptoms, showed no objective signs and were resolved after one day or in one case after 14-day duration, with no AE related alterations of the use of study medication. An AE that was *related* to the study medication was not recorded for any of the patients who were treated with Prednicarbat ointment and placebo ointment. No SAE occurred. No change of dose or treatment frequency was necessary regarding the investigational products and no event occurred that led to withdrawal of a patient from the study.

Regarding the results of physical examinations and vital signs, no clinically significant alteration or new findings were reported during the treatment period in comparison with visit 1 (day 0).

The physicians' assessment of tolerability as well as the patients' assessment of tolerability showed a very good safety profile for both Prednicarbat cream (O/W) and Prednicarbat ointment comparable to that of the placebo treatments.

The overall tolerability of both Prednicarbat cream (O/W) and Prednicarbat ointment was most often judged to be either 'very good' or 'good' by both the physicians (96% in both treatment groups) and the patients (92% and 88%, respectively) .

Conclusion:

Assessing the risk-benefit relationship, this study gave first evidence that the benefit of treatment with Prednicarbat cream (O/W) or ointment as performed in this study showed a higher efficacy than placebo treatment while offering an equally favourable risk profile.

Date of report: Final Version 25 November 2009