Clinical Study Report

LEO 19123 Cream in the Treatment of Atopic Dermatitis

A Phase II, proof of concept study, testing once daily use of two dose-combinations of LEO 19123 cream (calcipotriol and LEO 80122) in the treatment of atopic dermatitis

An international, multi-centre, prospective, randomised, double-blind, 3 arm, vehicle-controlled, parallel group, 3 week phase II clinical study

Synopsis

LEO Pharmaceutical Products Ltd. A/S
(LEO Pharma A/S)
Medical Department

LEO 19123-C21
Final
EudraCT Number: 2006-001472-20
05-FEB-2008

1 CLINICAL STUDY REPORT APPROVAL FORM

The following persons have approved this Clinical Study Report using electronic signatures as presented on the last page of this document

[redacted], International Clinical Development, LEO

[redacted] Biostatistics Department, LEO HQ

1.1 APPROVAL STATEMENT INVESTIGATORS

On behalf of all Investigators, the International Co-ordinating Investigator approves the Clinical Study Report.

The International Co-ordinating Investigator

[redacted], Professor, MD

has approved this report as presented on the International Co-ordinating Investigator Clinical Study Report Approval Form adjoined as a separate page to this document.

2 REPORT STATEMENTS

2.1 COMPLIANCE WITH GOOD CLINICAL PRACTICE

This Clinical Study Report is designed to comply with the standards issued by the International Conference on Harmonisation (ICH) (E3 Structure and Content of Clinical Study Reports; E6 Good Clinical Practice; and E9 Statistical Principles for Clinical Trials).

2.2 STUDY AUTHENTICATION

LEO Pharma Medical Department	GCP 1-SOP 02

AUTHENTICATION FORM

Protocol Code Number:	Report Date (dd-mmm-yyyy):	TF Index No.:
LEO 19123-C21	05-Feb-2008	16.1.

Report Title:
LEO 19123 Cream in the Treatment of Atopic dermatitis

This study was performed in compliance with the Good Clinical Practice (GCP) standard issued by the International Conference on Harmonisation (ICH), the Declaration of Helsinki with subsequent amendments, and respecting national rules/regulations.

The study was performed in accordance with the approved Study Protocol and with LEO Pharma Standard Operating Procedures for GCP. The report provides a true and accurate record of the results obtained.

Authorised by: PCPC

[redacted] [redacted] Date 05-Feb-2008

Printed Name Signature dd-mmm-yyyy

Version: 01-May-2003	Distribution: Original → Trial Master File (as part of Final Study Report)	Printed: 05-Feb-2008 Page 1 of 1

3 SYNOPSIS

Name of Sponsor/Manufacturer: LEO Pharma A/S	Location of study report in Regulatory Dossier for authorities	
Name of Investigational Product/ Finished Product, if available: Not applicable	Volume:	
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Title of study/Protocol Code Number:
LEO 19123 Cream in the Treatment of Atopic Dermatitis / LEO 19123-C21

International Co-ordinating Investigator:
[redacted], Professor, MD, [redacted], Denmark.

Centre details:
Multicentre study conducted at 15 recruiting centres (Canada: 5; Denmark: 6; Finland: 1; United Kingdom: 3).

Publication references:
To be decided.

Study period details:	Phase of development:
First patient included 03 October 2006 Last patient attended last visit 04 July 2007	Phase II

Objectives/hypothesis, if applicable:
To compare the clinical efficacy and safety of LEO 19123 cream (calcipotriol 50 mcg/g and LEO 80122 0.6 mg/g; henceforth referred to as LEO 19123 50/0.6), LEO 19123 cream (calcipotriol 15 mcg/g and LEO 80122 0.2 mg/g; henceforth referred to as LEO 19123 15/0.2), and LEO 19123 cream vehicle alone (henceforth referred to as LEO 19123 vehicle), in patients with atopic dermatitis after once daily treatment for three weeks.

Study methodology:
An international, multi-centre, prospective, randomised, double-blind, 3 arm, vehicle-controlled, parallel group, 3-week phase II clinical study in patients with atopic dermatitis. Patients were treated on all atopic dermatitis lesions on trunk and limbs only, once daily in the evening for 3 weeks with either a) LEO 19123 50/0.6 or b) LEO 19123 15/0.2 or c) LEO 19123 vehicle.
Following a screening visit (Visit 0) up to 28 days prior to randomisation, study visits were performed at baseline (Visit 1) and after 3 (Visit 2), 7 (Visit 3), 14 (Visit 4), and 21 (Visit 5) days. A follow-up visit (Visit 6) at day 35 was performed for those patients who completed the 3 week treatment period and for those patients who withdrew prematurely due to a

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treatment-related adverse event (possible, probable or not assessable). Prior to randomisation (Visit 1) a washout period was to be completed if the patient was treated, or had recently been treated with atopic dermatitis treatments or other relevant medication, as defined by the exclusion criteria.
Efficacy assessments including the Investigator's global assessment of disease severity (IGA), Investigator's assessment of the clinical signs for the Total Severity Score (TSS) on the arms (erythema, induration/papulation, oozing/crusting, excoriation, lichenification) and the Eczema Activity and Severity Index (EASI) (erythema, induration/papulation, excoriation, lichenification), the Patient's overall assessment of disease severity and the Patient's assessment of pruritus were performed at all visits (1 to 6). Safety assessments were performed at all post-baseline visits (2 to 6). Blood samples for haematology and clinical chemistry assessment were taken at baseline at days 7, 21; at follow-up (Visits 1, 3, 5 and 6) and at early withdrawal (Visits 2 and 4). Total IgE was measured at baseline (Visit 1). Cosmetic acceptability was assessed by the patient after 7 days treatment (Visit 3).

Number of patients enrolled :

A total of 75 patients were planned (25 patients in each of the three treatment groups).
A total of 83 were enrolled and 74 were randomised: 23 to LEO 19123 50/0.6, 26 to LEO 19123 15/0.2, and 25 to LEO 19123 vehicle.

Diagnosis and main criteria for patient selection:

Male hospital out patients or patients attending the private practice of the dermatologist, aged between 18 and 50 years, with a clinical diagnosis of atopic dermatitis amenable to topical treatment and with moderate disease at baseline (Visit 1) i.e. severity score of at least 2 at baseline (Visit 1) for each of the signs erythema, induration/papulation, excoriation and lichenification, (four of the five clinical signs in the TSS). Informed consent given. Exclusions were current diagnosis of exfoliative erythrodermia or clinical infection (impetiginised atopic dermatitis) on the treatment area, systemic treatment with immunosuppressive drugs (e.g. methotrexate, cyclosporine, azathioprine) or corticosteroids or PUVA or UVB within 4 weeks of randomisation, topical treatment with immunomodulators (pimecrolimus, tacrolimus) or WHO group III or IV corticosteroids within 2 weeks of randomisation or other topical therapy on the treatment area (except for the use of emollient and use of hydrocortisone cream 1% on lesions on head and neck) within 1 week of randomisation. Use of

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antihistamines or any other kind of treatment (drug, non-drug) for atopic dermatitis (other than study treatment) was excluded during the study period.

Investigational product, dose, method of administration, lot numbers:

LEO 19123 50/0.6 : calcipotriol 50 mcg/g and LEO 80122 0.6 mg/g. Lot numbers: 06 247 6101, 06 367 6101 and 07 111 6101

LEO 19123 15/0.2: calcipotriol 15 mcg/g and LEO 80122 0.2 mg/g. Lot numbers: 06 242 6101, 06 311 6101 and 07 104 6101

Both products were applied topically to affected areas on trunk and limbs once daily to a maximum of 60 g per week.

Reference product, dose, method of administration, lot numbers:

LEO 19123 vehicle. Lot numbers: 06 241 6101 and 06 309 6101

The reference product was applied topically to affected areas on trunk and limbs once daily to a maximum of 60 g per week.

Duration of treatment:

Up to 3 weeks.

Criteria for evaluation

Efficacy :

Primary response criterion:

Absolute change in TSS from baseline to the end of treatment (EOT) on the arms.

Secondary Response Criteria:

IGA on trunk and limbs at EOT.

The absolute change in EASI on trunk and limbs from baseline to EOT.

Patient's assessment of pruritus on trunk and limbs at EOT.

Patients with 'controlled disease' ('clear' or 'almost clear' for patients with at least moderate disease at baseline; 'clear' for patients with mild disease at baseline) according to IGA at EOT.

Patient's overall assessment of disease severity on trunk and limbs at EOT.

Safety:

Any reported adverse events (AEs) or adverse drug reactions (ADRs). Reasons for withdrawal from the trial. The absolute change in the laboratory values from baseline to each visit and relative change by categorising the values as low, normal, or high.

Statistical methodology

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The primary response criterion was analysed based on the full analysis set and the per protocol set. The absolute change in TSS from baseline to EOT was analysed in a dose-response linear model with concentrations 0, 1, 3 as covariate and centre as a factor. For each treatment comparison, the difference in least square (ls)-means, its 97.5% confidence interval, and a P-value was estimated from the analysis of variance with treatment group and centre as factors. A 97.5% confidence interval (CI) was chosen to account for multiplicity using the Bonferroni method. For the secondary response criteria the Hochberg correction was used to account for multiplicity and 95% CIs were estimated for descriptive purposes only. The absolute change in EASI from baseline was analysed in the same way as the primary response criterion, the IGA, patient's overall assessment of disease severity and the patient's assessment of pruritus were analysed using the proportional odds model with concentrations 0, 1, 3 as covariate and centre as a factor and 'controlled disease' was analysed using a dose-response logistic regression model with concentrations 0, 1, 3 as covariate and centre as a factor.

Summary – Conclusions

Efficacy results:

The mean TSS on the arms at baseline was 10.0 (range: 8-14) in the LEO 19123 vehicle group, 9.7 (range: 8-13) in the LEO 19123 15/0.2 group and 9.9 (range: 8-15) in the LEO 19123 50/0.6 group.

The primary response criterion was the absolute change in TSS on the arms to EOT (Day 21, last observation carried forward [LOCF], full analysis set). The absolute change in TSS from baseline to EOT was −1.9 (SD 2.7) in the LEO 19123 vehicle group, compared to −2.7 (SD 3.3) in the LEO 19123 15/0.2 group and −2.3 (SD 3.6) in the LEO 19123 50/0.6 group. The response was minimal and similar in all three treatment groups. The overall difference between the groups was not statistically significant (difference per unit increase −0.24; 95% CI −0.80 to 0.31; P=0.38). Furthermore the pairwise comparisons between each of the two active treatments and the vehicle group were also not statistically significant. For the LEO 19123 15/0.2 group the difference was −0.57; 97.5% CI −2.41 to 1.28; P=0.49 and for the LEO 19123 50/0.6 group the difference was −0.78; 97.5% CI −2.72 to 1.16; P=0.36. The per-protocol analysis confirmed these results.

There were five secondary efficacy response criteria, which were all assessments of atopic

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eczema on trunk and limbs. None of the secondary efficacy response criteria (IGA, EASI, patient's overall assessment of disease severity, patient's assessment of pruritus and patients with 'controlled disease') demonstrated statistical significance nor a tendency to efficacy for either of the active treatments. The similar and not statistically significantly different response across treatment groups also appeared to be consistent across age, centre and baseline disease severity.

Safety results:

The proportion of patients with AEs did not differ significantly across the treatment groups (P=0.28) and most AEs in all groups were reported in the SOC 'skin and subcutaneous tissue disorders'. Among the cutaneous adverse events more patients in the LEO 19123 50/0.6 reported this type of event (14 patients versus 8 for LEO 19123 15/0.2 and 9 for LEO 19123 vehicle) and the number of cutaneous events per patient was higher. The most common preferred terms reported were 'erythema', 'pruritus', 'rash scaly' and 'skin irritation' in the in the LEO 19123 50/0.6 group and 'eczema' in the LEO 19123 15/0.2 group. Similarly the number of patients with ADRs was greater in the LEO 19123 50/0.6 group than in the other two groups (14 patients versus 7 for LEO 19123 15/0.2 and 10 for LEO 19123 vehicle). There were also more ADRs per patient and the intensity was more severe in the LEO 19123 50/0.6 group. In addition, more patients in the LEO 19123 50/0.6 group withdrew early due to unacceptable AEs (9 patients versus 5 for LEO 19123 15/0.2 and 6 for LEO 19123 vehicle). No clinically relevant changes in laboratory parameters over time in the active treatment groups relative to vehicle treated group were observed. There were no deaths and two SAEs; one (atopic dermatitis aggravated) possibly related in the LEO 19123vehicle group and one (impetigo) not related to study treatment in the LEO 19123 50/0.6 group.

Conclusion:

Neither of the active treatments (LEO 19123 15/0.2 nor LEO 19123 50/0.6) was more effective than the LEO 19123 vehicle in the treatment of atopic dermatitis over 3 weeks. No statistically significant difference (or trend towards a difference) in efficacy was seen between the two active LEO 19123 treatments compared to the vehicle. More adverse skin reactions were seen with active treatment than with vehicle and the number observed tended to increase with dose. Proof-of-concept was not demonstrated in this GCP study.

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3.1 SCHEDULE/CHART OF STUDY PROCEDURES

Visit	**0 Screening** [a)]	**1 Randomi-sation (baseline)**	**2**	**3**	**4**	**5 or Early withdrawal**	**6 Follow-up** [b)]
Day	**-28 to -1**	**0**	**3**	**7**	**14**	**21**	**35**
Visit window (days)			**±1**	**±1**	**±2**	**±2**	**±2**
Informed consent	x						
Patient demographics (incl. height and weight)	x						
In/exclusion criteria	x	x					
Concomitant treatment	x	x	x	x	x	x	x
Medical history	x	x					
Randomisation		x					
Adverse event(s)			x	x	x	x	x
Haematology		x		x		x	x
Blood chemistry		x		x		x	x
Total IgE		x					
Clinical photographs [c)]		x	x	x	x	x	x
Investigator's global assessment		x	x	x	x	x	x
Investigator's clinical assessments for Total Severity Score, EASI		x	x	x	x	x	x
Patient's overall assessment		x	x	x	x	x	x
Patient's assessment of pruritus		x	x	x	x	x	x
Patient's cosmetic acceptability				x			
Dispensing of investigational product		x		x	x		
Dispensing of other treatment [d)]	x	x		x	x	x	
Compliance		x	x	x	x	x	
Return of used/unused investigational product				x	x	x	
End of Trial Form		x [e)]				x [e)]	x

a) The screening period was defined as the time between Visit 0 and Visit 1. The screening period included any washout period. This period varied between 1 to 28 days depending on whether the patient was using a treatment for AD.
b) Follow-up (FU) Visit was applicable for all randomised patients who had completed the 3 week treatment. If a patient was prematurely withdrawn from the trial due to an adverse event classified as possibly or probably related to the investigational product or not assessable in relation to the investigational product a follow-up visit was to be completed.
c) Clinical photographs were obtained from one designated site.
d) Other trial medication: hydrocortisone cream 1%, Locobase® fatty cream and Essex® cream. This was to be dispensed on an individual basis per patient as needed.
e) If a patient was not randomised or when a patient was ending the trial, the End of Trial Form was to be completed.