Clinical Study Report

Cromoglicate in Mastocytosis

A phase II exploratory study evaluating the efficacy of topical cromoglicate solution (20mg/ml) compared to topical solution vehicle in the treatment of mastocytosis

An exploratory, prospective, randomised, double-blind, vehicle-controlled, left/right comparison study with twice daily topical administration for 14 days

LEO Pharma A/S
Clinical Development and Safety

LP0074-33
23-Jan-2014
2011-006275-20

Clinical Study Report Statement

Approval Statement, Sponsor

The following persons have approved this Clinical Study Report on behalf of LEO Pharma A/S using electronic signatures:

[redacted]
[redacted] Biostatistics and Data Management

[redacted]
[redacted] Medical Department

Approval Statement, Investigator

The Co-ordinating Investigator approves the Clinical Study Report by manually signing the International Co-ordinating Investigator Clinical Study Report Approval Form, which is a separate document adjoined to this report (Appendix 1.5).

The following person has approved this Clinical Study Report:

Prof. Dr. med. [redacted]
Co-ordinating Investigator

SYNOPSIS

Name of Sponsor/Company: LEO Pharma A/S

Name of Finished Product: Not applicable

Name of Active Ingredient: Cromoglicate

Title of study:
Cromoglicate in Mastocytosis. A phase II exploratory study evaluating the efficacy of topical cromoglicate solution (20mg/ml) compared to topical solution vehicle in the treatment of mastocytosis

Investigators:
The Principal Investigator was Dr. med. [redacted], Germany.
The International Coordinating Investigator was Prof. Dr. Med [redacted], Germany.

A list of investigators and CV for the International Coordinating Investigator is in Appendix 1.4.

Trial Centre(s):
There was one centre: [redacted], Germany

Publication(s) based on the study:
None at the time of this clinical study report.

Study Period:	Phase of Development:
Date of first enrolment (informed consent signed and CRF started): 29-Oct-2012 Date of last subject completed: 01-Feb-2013. The trial was terminated on 20-Feb-2013 due to a lack of suitable subjects meeting the inclusion criteria.	II

Objectives:

The primary objective of this exploratory trial was to investigate the clinical efficacy on pruritus of treatment with topical cromoglicate solution in patients with mastocytosis. The secondary objectives were to investigate the safety of treatment with topical cromoglicate solution in patients with mastocytosis, and to investigate and identify pharmacodynamic parameters related to pruritus and to cromoglicate mode of action.

Methodology:

This was a single centre, exploratory, prospective, randomised, double-blind, vehicle-controlled, left/right comparison trial evaluating the efficacy of topical cromoglicate solution (20mg/ml) compared to topical solution vehicle in the treatment of pruritis associated with mastocytosis.

The trial consisted of a screening visit, a wash-out period if needed, a treatment period of 14 days, and if applicable, a follow-up visit (or telephone contact).

Subjects attended a screening visit to determine their eligibility for participation in the trial within 28 days of starting treatment with investigational product (IP). Administration of IP began on Day 0 (Visit 1) and continued to Day 14 (Visit 2). IP was administered topically, twice-daily (morning and evening) on each of the two target lesions.

At the Screening Visit, and at Days 0 and 14, standardised provocation of the Darier's sign (wheal and flare type skin reaction) and clinical (investigator) and subject assessments of itch and skin reactions were performed.

Ten of the planned 30 subjects were to have 4 skin biopsies collected (6 mm punch biopsies) at Day 0 (pre-provocation/left-side lesion and post-provocation/right-side lesion) and Day 14 (post-provocation/left-side lesion and post-provocation/right-side lesion).

Information on adverse events was collected on an ongoing basis during the treatment phase. If an adverse event (serious or non-serious) classified as possibly or probably related to study treatment or not assessable in relation to the study treatment

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was ongoing at Visit 2 a follow-up visit/contact took place 28 (±2) days after that visit.

Full details on the methodology of the trial can be found in the Clinical Study Protocol which is appended to this report (Appendix 1.1). A blank sample CRF can be found in Appendix 1.2.

Number of Subjects (Planned and Analysed):

A total of 30 randomised subjects was planned for this trial. Prior to the early termination of the trial 10 subjects were screened, and 7 of these 10 were randomised.

Diagnosis and Main Criteria for Inclusion:

In order to be eligible for the trial, subjects needed to have a diagnosis of chronic stable symptomatic maculopapulous cutaneous mastocytosis or indolent systemic mastocytosis with skin involvement and a positive Darier's Sign.

Main criteria for inclusion:

1. Signed informed consent has been obtained
2. Chronic stable symptomatic maculopapulous cutaneous mastocytosis or indolent systemic mastocytosis with skin involvement and a positive Darier's Sign
3. Age between 18 and 70 years
4. Either sex

Main criteria for exclusion:

1. The presence of autoimmune and infectious disease including aggressive systemic mastocytosis
2. Medical history or presence of epilepsy, significant neurological disorders, cerebrovascular attacks or ischemia
3. Medical history or presence of myocardial infarction or cardiac arrhythmia which requires drug therapy, hyper/hypokalemia
4. Evidence of severe renal dysfunction (creatinine >1.5 times upper reference value)
5. Evidence of significant hepatic disease (liver enzymes >2 times upper reference value)
6. Presence of active cancer which requires chemotherapy or radiation therapy
7. Intake of antihistamines or leukotriene antagonists within 7 days prior to the beginning of the trial
8. Intake of oral corticosteroids within 14 days prior to randomisation
9. Use of depot corticosteroids or chronic systemic corticosteroids within 21 days prior to randomisation
10. Radiation therapy of target areas including UV therapy within 4 weeks prior to randomisation
11. Confounding other dermatological diseases or conditions that can affect the symptoms of the target areas

Investigational Product, Dose and Mode of Administration, Batch Number:

Route of administration: topical, applied two-times daily (morning and evening) with a daily maximum of 0.5 mL (on each of the two target lesions). The topical cromoglicate solution was Cromo-Stulln® UD with batch number 110916.

Duration of Treatment:

14 days.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Route of administration: topical, applied two-times daily (morning and evening) with a daily maximum of 0.5 mL (on each of the two target lesions). The topical solution vehicle was blink® refreshing Eyedrops with batch number ML243.

Criteria for Evaluation:

The primary efficacy response criterion was the change from baseline to last observation on an investigator-rated composite score (maximum of 9 points) evaluating wheal, erythema, and itch on a 4-point scale (0=no, 1=mild, 2= moderate, 3=severe) and on a subject-rated visual-analogue scale (VAS) of "subjective complaints".

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The secondary efficacy response criterion was the change from baseline to last observation as evaluated by volumetric and thermographic analyses, gene expression, and immunohistochemistry.

Safety:

Evaluation of safety was based on any reported adverse events (AEs), any reported adverse drug reactions (ADRs), and reasons for withdrawal from the trial.

Statistical Methods:

All randomised subjects with at least one application of the study medication were to be included into the primary efficacy analysis population (ITT population). The safety population was to include all subjects with at least one application of the study medication. This population will be used for all safety analyses and baseline characteristics. Missing values would not be imputed. All statistical tests were to be one-sided with a significance level of 5%, two-sided 90% confidence intervals will be calculated if applicable.

The outcome of any statistical tests applied in the analysis of this trial are to be regarded as exploratory. Changes from baseline until the last observation in the composite lesion score was planned to be compared between the cromoglicate and placebo test area using a paired Wilcoxon test. Due to the early termination of the trial with only 7 of the planned 30 subjects randomised, no formal statistical analyses were conducted.

Summary – Conclusions

Study Population:

7 subjects were treated with both topical cromoglicate solution (20mg/ml) and topical solution vehicle with at least one application of investigational product, and all 7 subjects completed the trial. The trial was terminated early due to a lack of suitable subjects meeting the inclusion criteria..

Efficacy Summary:

Efficacy analyses are included in the Statistical Report (including individual subject listings) which is appended to this CSR Synopsis (Appendix 2.9). Due to termination of the study after only 7 of the planned 30 subjects had been treated, no conclusions have been drawn from the efficacy analyses. The skin biopsy samples were not analysed.

Safety Summary:

There were no deaths, serious adverse events, or significant safety issues in the trial. One adverse event was recorded in the trial: a [redacted], had high blood pressure, described as moderate in intensity and not related to study medication. The event started on [redacted] and ended on [redacted]. The subject had a 15-year prior history of hypertension, and type II diabetes since 2006. Further information on this subject can be found in the Statistical Report which is appended to this CSR Synopsis (Appendix 2.9).

Conclusion:

No conclusions can be drawn regarding the primary or secondary objectives of this trial due to the early termination of the trial after 7 of the planned 30 subjects were treated. No significant or unexpected safety issues occurred during the trial.

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ELECTRONIC SIGNATURES

Electronic signature made within eDoc LEO by LEO Pharma A/S employees or employees of any LEO Pharma A/S affiliate located anywhere in the world, are to be considered to be legally binding equivalent of traditional handwritten signatures.

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
[redacted]	[redacted] Biostatistics Approval	23-Jan-2014 12:04 GMT+01
[redacted]	[redacted] Department, Medical Approval	23-Jan-2014 13:28 GMT+01