Clinical Study Report Synopsis

A phase 2a proof of concept study comparing three doses of an oral solution of LEO 22811 with a placebo oral solution for the treatment of psoriasis vulgaris

An international, multi-centre, prospective, randomised, double-blind, 4–arm, placebo controlled, parallel group study with 12 weeks once daily oral treatment in subjects with psoriasis vulgaris

LEO Pharmaceutical Products Ltd. A/S
(LEO Pharma A/S)
Clinical Development

Trial ID: LEO 22811-S22
19-July-2012
EudraCT No. 2009-01785812

CLINICAL STUDY REPORT SYNOPSIS APPROVAL

APPROVAL STATEMENT

On behalf of LEO, only the Head of International Clinical Development and the Head of Biostatistics, LEO HQ are authorised to approve the main Clinical Study Report. The Head of Medical Department has approved this CSR in lieu of the Head of International Clinical Development as per SOP deviation

All LEO approvers will be identified on a signature page of the pdf-file of the final Clinical Study Report Synopsis when the last LEO approval is obtained. The time and date of their e-signatures are likewise presented on the approval page.

The following persons have approved this Clinical Study Report Synopsis using electronic signatures:

[redacted] Biostatistics and Data Management

[redacted] Medical Department

APPROVAL STATEMENT INVESTIGATORS

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

The following person has approved this Clinical Study Report Synopsis

[redacted] MD, [redacted] Canada
International Co-ordinating Investigator

SYNOPSIS

Name of Sponsor/Company: LEO Pharma A/S	Individual Trial Table Referring to Part of the Dossier	
Name of Finished Product: LEO 22811	Volume:	
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Title of trial:
A phase 2a proof of concept study comparing three doses of an oral solution of LEO 22811 with a placebo oral solution for the treatment of psoriasis vulgaris

Investigators:
International and National co-ordinating investigator for Canada:
[redacted], MD, [redacted], Canada
National co-ordinating investigator for France:
[redacted], MD, [redacted], France

Trial centre(s):
The trial was conducted at 11 centres: five in Canada and six in France

Publication (reference):
None

Trial period: date of first enrolment: 14-May-2010 date of last completed: 25-Jul-2011	Phase of development: Phase 2a

Objectives:
Primary Objective:
To compare the clinical efficacy of three different doses (0.5 mg, 1.5 mg and 3.0 mg) of an oral solution of LEO 22811 with a placebo oral solution all administered once daily for up to 12 weeks in subjects with psoriasis vulgaris.
Secondary Objective:
To investigate the safety of the three different doses of LEO 22811 (mentioned above) in subjects with psoriasis vulgaris

Methodology:
This was a multi-centre, double-blinded, 4-arm, placebo-controlled, parallel group study with 12 weeks once daily oral treatment with LEO 22811 in three different doses in subjects with psoriasis vulgaris. There were a total of 8 study visits. Study visits were performed at Day 0 (baseline/ randomisation) and at week 1, 2, 4, 6, 8, 10 and 12. A wash-out period (up to 30 days) was completed if the subject was treated, or had recently been treated, with anti-psoriatic treatments or other relevant medication, as defined in the exclusion criteria. Finally a follow up visit / visit 9 were performed 28 days after the subject's last on-treatment for follow-up of reproductive hormone levels following cessation of treatment. A follow up visit was also conducted if an adverse event (serious or non-serious) classified as possibly or probably related to the study medication or not assessable in relation to the study medication was ongoing at the subject's last on-treatment visit or if the subject had any laboratory values that were outside the reference range at the last on-treatment visit. The FU visit may be conducted at the same time as Visit 9.

Number of subjects (planned and analysed):
A total of 64 subjects were to be randomised to the four treatment groups in a 1:1:1:1 ratio, i.e. 16 subjects in each of the LEO 22811 0.5 mg, 1.5 mg and 3.0 mg groups and 16 subjects in the placebo group. 104 subjects were screened for the trial out of wich 63 were randomised. Full analysis set and safety analysis set comprised 63 subjects, per protocol analysis set comprised 61 subjects and the biomarker analysis set comprised 33 French subjects.

Diagnosis and main criteria for inclusion:
The trial population included subjects at least 18 years of age with psoriasis vulgaris for at least 6 months prior to

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randomisation and covering at least 10% of the body surface area and candidate for systemic anti-psoriatic treatment. Psoriasis Area and severity Index (PASI) should be ≥ 10 and disease severity were moderate, severe or very severe according to the Investigators' Global Assessment of disease severity (IGA). Subjects were males or surgically sterile or post menopausal females.

Test product, dose and mode of administration, batch number:
LEO 22811, 0.0625 mg/mL, 0.1875 mg/mL and 0.3750 mg/mL, oral solution, batch / lot numbers: 09 302 72 01, 09 304 74 01, 09 306 76 01, 102997201, 103007301, and 103017401.

Duration of treatment:
Each subject received treatment for up to 12 weeks

Reference therapy, dose and mode of administration, batch number:
Placebo, oral solution, batch / lot number: 09 301 71 01 and 10 298 71 01

Criteria for evaluation:

Efficacy:

Primary Response Criterion

The percentage change in PASI from baseline to Week 12.

Secondary Response Criteria

Subjects with PASI 75 (i.e. at least 75% reduction in PASI from baseline) at Week 12

Percentage change in PASI from baseline to Weeks 1, 2, 4, 6, and 8

Subjects with PASI 75 at Weeks 1, 2, 4, 6, and 8

Subjects with "controlled disease" (defined as "Clear" or "Almost clear") according to the IGA at Week 12

Subjects with "controlled disease" according to the IGA at Weeks 1, 2, 4, 6, and 8

Safety:

Evaluation of (Serious) Adverse Events

Any adverse events reported.

Any adverse drug reactions reported.

Reasons for withdrawal from the study.

Evaluation of Laboratory Data

Change in haematology parameters from baseline to Week 12

Change in clinical chemistry parameters from baseline to Week 12

Change in reproductive hormone levels from baseline to Week 12

Evaluation of Other Observations

Change in biomarker levels in the skin biopsies from baseline to Week 12

Statistical methods:
Baseline characteristics and safety were presented by descriptive statistics.
Primary response criterion: For each dose level of LEO 22811 and placebo, the difference between least square-means, the 95% confidence interval of the difference and p-value was estimated from the analysis of variance (ANOVA) with treatment group and centre as factors. A test for treatment homogeneity across centres was performed in a separate analysis by testing the treatment-by-centre interaction term as a fixed effect in the analysis of variance model.
The dose response was investigated using a linear model with treatment group (LEO 22811 0.5 mg, 1.5 mg and 3.0 mg) as a covariate and centre as a factor.
Robustness of the results was verified using the Wilcoxon rank sum test.

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The number and proportion of subjects who achieve "controlled disease" (subjects classified as clear or almost clear according to the IGA) at end of treatment was compared between each active group and the placebo group using the Cochran-Mantel-Haenszel test adjusting for the effect of centre. The Cochran-Mantel-Haenszel adjusted odds ratio, the corresponding 95% confidence interval and p-value was calculated for each comparison. The Breslow-Day test for homogeneity of the odds ratios across centres was performed.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

- For the primary analysis population, the mean percentage change in PASI from baseline to Week 12 (end of treatment) was -5.6 in the placebo group compared to -7.6 in the 0.5 mg dose group, -0.3 in the 1.5 mg group and -12.7 in the 3.0 mg group. The change was not statistically significantly different from placebo and there was no statistically significant dose response
- A clear dose related exposure of LEO 22811 was detected in blood
- LEO 22811 was undetectable in skin from patients
    - Concentration below approximately 10 nM in the skin
- There were no statistical differences from placebo in the biomarkers investigated in the skin although at the highest dose there could be indications in individuals that some immune modulation was ongoing

SAFETY RESULTS:

- •The overall frequency of subjects with AEs tended to be higher in the 3.0 mg dose group compared to the lower dose groups and placebo (71.4% [placebo], 68.8% [0.5 mg], 73.3% [1.5 mg], 83.3% [3.0 mg])
- The number of subjects having AEs assessed by investigator as related to trial treatment was comparable in the two lowest dose groups and placebo but was higher in the 3.0 mg dose group. Especially events within the nervous system (dizziness, tremor, headache and migraine) as well as skin and subcutaneous tissue disorders (rash, pruritus, psoriasis flare up) showed a trend towards dose dependency and these events were not reported in the placebo group.
- Seven subjects withdrew from the trial due to AEs. The reason for discontinuing the trial was mainly worsening of psoriasis. All subjects who withdrew were in the active treatment groups
- There were no conspicuous findings regarding change in haematological or clinical chemistry parameters during the trial

CONCLUSION: The efficacy of LEO22811 could not be established. There were no statistical differences from placebo in the biomarkers investigated in the skin although at the highest dose there could be indications in individuals that some immune modulation was ongoing. LEO22811 was generally well tolerated with no unexpected toxicity.

Date of the Report:
19-Jul-2012

LEO 22811-S22 Clinical Study Report Synopsis - English

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] Department, Medical Approval	20-jul-2012 10:26 GMT+020
[redacted]	[redacted] Biostatistics Approval	20-jul-2012 10:41 GMT+020