Clinical trial report synopsis
Full version for regulatory submission

LEO 32731 for the treatment of moderate to severe psoriasis vulgaris

Design of trial:

A phase 2a proof of concept study comparing an oral tablet formulation of LEO 32731 with a corresponding placebo tablet in patients with moderate to severe psoriasis vulgaris

A multi-centre, prospective, randomised, double-blind, 2-arm, placebo-controlled, parallel-group study with 16 weeks twice times daily oral treatment

The clinical trial, including the archival of essential documents, was conducted in compliance with the clinical trial protocol, GCP, and the applicable regulatory requirement(s).
Clinical trial report synopsis statement

Approval statement, LEO Pharma A/S

The following persons have approved this clinical trial report synopsis using electronic signatures as presented on the last page of this document:

PPD, MSc
PPD, Global Clinical Operations

PPD, MD
PPD, Translational Medicine

Approval statement, signatory investigator

The signatory investigator has approved this clinical trial report synopsis by manually signing the Signatory Investigator Clinical Trial Report Synopsis Approval Form, which is a separately adjoined document.

The following person has approved this clinical trial report synopsis:

Sandra Philipp, PhD

Signatory investigator
**Trial registration number**
NCT02888236

**EudraCT number**
2015-005279-25

**Title of trial**
LEO 32731 for the treatment of moderate to severe psoriasis vulgaris

**Investigators**
Sandra Philipp, PhD, Head of Psoriasis study centre, Charité Universitätsmedizin Berlin, Department of Dermatology, Germany, was appointed as signatory investigator

**Trial centres**
This trial was conducted at 7 centres in 1 country (Germany) and coordinated at the Psoriasis study centre, Charité Universitätsmedizin Berlin, Department of Dermatology.

**Publications**
None at the time of the final clinical trial report.

**Clinical trial period**
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**Objectives and endpoints**

**Objectives**

**Primary objective**
- To investigate the efficacy of LEO 32731 30 mg compared with that of placebo after 16 weeks of oral treatment of psoriasis vulgaris.

**Secondary objectives**
- To investigate the effect on psoriasis symptoms during 16 weeks of twice daily treatment with LEO 32731 30 mg or placebo.
- To investigate the effect on itch intensity after 16 weeks of twice daily treatment with LEO 32731 30 mg or placebo.
- To investigate the safety and tolerability during 16 weeks of twice daily treatment with LEO 32731 30 mg or placebo.

**Endpoints**

**Primary endpoint**
- Psoriasis Area and Severity Index (PASI) at Week 16

**Secondary endpoints**
- Treatment success (defined as clear or almost clear) according to Physician’s Global Assessment of disease severity (PGA) at Week 16
- Itch numeric rating scale (NRS) at Week 16

**Methods**
This was a phase 2a, multi-centre, prospective, randomised, double-blind, 2-arm, placebo-controlled, parallel-group trial. Subjects were randomised in a 1:1 ratio to twice daily treatment with either 30 mg LEO 32731 or placebo for 16 weeks. The trial consisted of 3 periods: screening/washout (up to 35 days), treatment (1-week dose escalation followed by 15-week full dose treatment), and follow-up (2 weeks). The maximum duration of the trial for each subject was 23 weeks (161 days).

**Number of subjects planned and analysed**
36 subjects were planned and 36 subjects were allocated to treatment.
Diagnosis and main criteria for inclusion
- Clinical diagnosis of psoriasis vulgaris with or without psoriatic arthritis (maximum 4 joints with active arthritis) for ≥6 months prior to screening.
- Moderate to severe psoriasis vulgaris as defined by:
  - PASI >10.
  - Covering >10% of the body surface area.
  - Disease severity of moderate or worse (PGA ≥3).
- Aged between 18 and 65 years.
- Men or women of non-childbearing potential.
- Candidates of systemic anti-psoriatic treatment or phototherapy.

Test product, dose and mode of administration, batch numbers
LEO 32731, 10 mg tablets (batch number P15030/W029883) and 30 mg tablets (batch number P15031/W029890), administered orally as follows:
- Days 1–3: 10 mg twice daily.
- Days 4–6: 20 mg twice daily.
- Day 7 onwards: 30 mg twice daily.

Duration of treatment
16 weeks (1-week dose escalation, 15-week full dose)

Control product, dose and mode of administration, batch number
Placebo tablets (batch number P15029/W029897), administered orally twice daily from Day 1 onwards.

Statistical methods
Efficacy
The primary endpoint (PASI at Week 16) was analysed for the full analysis set and the per protocol analysis set. The full analysis set was regarded as primary. PASI score at Week 16 was compared for LEO 32731 and placebo using an analysis of covariance (ANCOVA) model. Missing data were imputed using last observation carried forward (LOCF). An additional sensitivity analysis was performed using a mixed model of repeated measures (MMRM).

The secondary endpoints were analysed for the full analysis set. PGA treatment success at Week 16 was analysed by means of logistic regression, with missing data imputed using LOCF. Itch NRS score at Week 16 was analysed by means of an ANCOVA model, with missing values imputed using LOCF. A sensitivity analysis was performed using an MMRM.

Safety
Safety evaluations were based on the safety analysis set and were descriptive only.

Summary of results
Trial population
Subject disposition
36 subjects (18 in each treatment group) were treated with at least 1 dose of investigational medicinal product and 17 subjects (8 in the LEO 32731 group and 9 in the placebo group) completed the trial. In the LEO 32731 group, all but 1 withdrawal (a voluntary withdrawal by the subject) were related to adverse events (AEs). In the placebo group, 5 subjects withdrew because of unacceptable treatment efficacy, 3 subjects withdrew because of AEs, and 1 subject was lost to follow-up.

Protocol deviations
There were 5 major protocol deviations: 3 related to use of prohibited concomitant medication, 1 related to dosing error, and 1 GCP violation. (The GCP violation involved repeated haematology analyses prior to randomisation, which may be interpreted as rescreening. According to the site, the analyses were not performed for rescreening purposes but for follow-up on leucocytes values, and the subject would have been randomised regardless, based on the initial screening results.) 2 subjects were excluded from the per protocol analysis set owing to 3 major protocol deviations (prohibited medication and dosing error) that were deemed to potentially affect efficacy assessments.
Demographics and baseline characteristics
The trial population comprised mostly men (91.7%), and all but 1 subject were white. The median age at baseline was 46.5 years (range 20–61 years). The mean BMI was in the overweight category (28.2 kg/m²), and the BMI ranged from normal to obese. At baseline, the majority of subjects had moderate and some had severe psoriasis vulgaris. The mean PASI score was 14.9 and the median duration of the disease was 14 years (range 3–47).

Efficacy results
- The PASI score (least-squares means) at Week 16 was 7.1 in the LEO 32731 group and 13.1 in the placebo group. The difference between the treatment groups of -6.0 (95% CI -10.0 to -2.0) was statistically significant (p=0.005).
- The success rate (based on LOCF) according to PGA at Week 16 was 7 of 18 subjects (38.9%) in the LEO 32731 group and 1 of 18 subjects (5.6%) in the placebo group. The odds of achieving PGA treatment success were higher for subjects in the LEO 32731 group than for subjects in the placebo group (odds ratio: 12.3 [95% CI: 1.7–256.1]), and the difference was statistically significant (p=0.032).
- The itch score (least-squares means) at Week 16 was 3.4 in the LEO 32731 group and 5.7 in the placebo group. The treatment difference of -2.3 (95% CI -4.6 to 0.0) was not statistically significant (p=0.053).

Safety Results
- 127 AEs were reported for 17 subjects (94.4%) in the LEO 32731 group and 57 AEs were reported for 16 subjects (88.9%) in the placebo group. 106 of the AEs reported in the LEO 32731 group and 28 of the AEs reported in the placebo group were assessed as possibly or probably related to the treatment.
- The most common AEs in the LEO 32731 group were within the SOC gastrointestinal disorders, in particular nausea and diarrhoea, most of which were considered treatment-related.
- Most AEs were mild or moderate. 1 subject in the LEO 32731 group had 1 severe AE (increased alanine aminotransferase, considered possibly related to the IMP). 2 subjects in the placebo group had a total of 3 severe AEs (toothache, abdominal pain, and abdominal cramps).
- No subjects died during the trial. 3 serious AEs (SAEs) were reported: 2 subjects in the LEO 32731 group had 1 SAE each (ureterolithiasis, considered not related to the IMP, and erysipelas on the arm, considered possibly related to the IMP) and 1 subject in the placebo group had 1 SAE (“condition aggravated”, relating to pre-existing Scheuermann’s disease and considered not related to the IMP).
- AEs leading to withdrawal from the trial were reported for 9 subjects (50.0%) in the LEO 32731 group and 3 subjects (16.7%) in the placebo group. In the LEO 32731 group, the majority of AEs leading to withdrawal were within the SOC gastrointestinal disorders.
- ECG monitoring and evaluations of vital signs and clinical laboratory parameters showed no findings of concern.

Conclusions
Oral administration of LEO 32731 30 mg twice daily for 16 weeks was superior to placebo for the primary efficacy endpoint, PASI score at Week 16, and for the secondary efficacy endpoint PGA treatment success at Week 16. The types of AEs related to treatment with LEO 32731 were as expected. There was a high frequency of gastrointestinal-related AEs in the LEO 32731 group, particularly nausea and diarrhoea. Many of these AEs resulted in subjects withdrawing from the trial, but none of the withdrawals were due to concern for the subjects’ wellbeing. No safety concerns were identified during the conduct of the trial.

Approximately half of the subjects in both treatment groups were withdrawn from the trial, mainly owing to tolerability issues in the LEO 32731 group and lack of efficacy in the placebo group. Although the bias introduced by this attrition had an impact on the estimated efficacy, it was not considered to disqualify the clear difference observed between 2 treatments. This study has demonstrated that subjects with moderate to severe psoriasis vulgaris treated with LEO 32731 achieved significant effect at the expense of a high level of intolerance.
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