Clinical Trial Report Synopsis

A phase 2a, proof of concept trial, testing twice daily application of LEO 124249 ointment 30 mg/g in the treatment of mild to moderate inverse psoriasis

Design of trial:

Multi-centre, prospective, randomised, double-blind, 2-arm, parallel-group, vehicle-controlled, 6-weeks phase 2a trial in subjects with mild to moderate inverse psoriasis

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).

LEO Pharma A/S  Trial ID:  LP0133-1182
Date:  15-Sep-2017
Version:  1.0
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, M.Sc.
Biostatistics Lead
Global Clinical Operations

PPD, M.D.
Senior Director
Translational Medicine

Approval Statement, International Coordinating Investigator

The international coordinating investigator approves the clinical trial report synopsis by manually signing the International Coordinating Investigator Clinical Trial Report Approval Form, which is a separate document adjoined to the clinical trial report.

The following person has approved this clinical trial report synopsis:

Prof. Dr. med. Dr. h.c. Thomas A. Luger
International coordinating investigator
**Trial Registration Number**
NCT02695940

**EudraCT number**
2015-002098-40

**Title of Trial**
A phase 2a, proof of concept trial, testing twice daily application of LEO 124249 ointment 30 mg/g in the treatment of mild to moderate inverse psoriasis

**Investigators**
Professor Dr. med. Dr. h.c. Thomas A. Luger, University Medical Center Münster, Germany was appointed as signatory investigator.

**Trial Centres**
This trial was conducted at 11 centres in Germany and coordinated at LEO Pharma A/S, Ballerup.

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

**Clinical Trial Period**
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**Development Phase**
Phase 2a

**Objectives**

**Primary objective:**
To compare the efficacy of twice daily application of LEO 124249 ointment 30 mg/g and LEO 124249 ointment vehicle for 6 weeks in the treatment of subjects with mild to moderate inverse psoriasis.

**Secondary objective:**
To compare the safety and tolerability of twice daily application of LEO 124249 ointment 30 mg/g and LEO 124249 ointment vehicle for 6 weeks in the treatment of subjects with mild to moderate inverse psoriasis.

**Methodology**
This was a multi-centre, prospective, randomised, double-blind, 2-arm, parallel-group, vehicle-controlled phase 2a trial designed to compare the efficacy, and safety of twice daily application of LEO 124249 ointment 30 mg/g and LEO 124249 ointment vehicle for 6 weeks in subjects with mild to moderate inverse psoriasis.

Randomisation was in a 2:1 ratio for the active ingredient and stratified for site. The trial consisted of 3 periods: a 4-week screening phase, a 6-week treatment phase, and a 2-week follow-up phase. The subjects were screened up to 28 days prior to baseline (Day 1). Efficacy and safety were assessed at baseline and Weeks 1, 2, 4, and 6 (end of treatment). A blood sample for PK analysis was taken at Week 1. During the treatment period, subjects returned to trial site on Week 1, Week 2, Week 4 and Week 6. Clinical assessments (Physician’s Global Assessment (PGA) and total and individual sign score) were assessed on all visits. Determination of size of treatment area, Patient’s global assessment (PaGA), and subject’s assessment of itching were assessed from baseline to Week 6. A Quality of Life questionnaire (DLQI) was completed by subjects at baseline and Week 6, and a treatment satisfaction questionnaire (TSQM II) and an overall cosmetic acceptability questionnaire were completed by subjects at Week 6. If there was an adverse event (AE) or serious AE (SAE) ongoing at Week 6 that was possibly/probably to IMP, subjects were seen and assessed at follow-up.

Safety and tolerability were assessed by AE recording, electrocardiogram (ECG), clinical laboratory assessments, vital signs and physical examination. At one selected site, photographic documentation of the affected treatment areas were made at baseline and Week 6.

**Number of Subjects Planned and Analysed**
A total of 66 subjects were planned for randomisation in a 2:1 ratio, i.e. 44 to treatment with LEO 124249 ointment 30 mg/g and 22 to treatment with the ointment vehicle. In the trial, 69 subjects were allocated to treatment as follows: 45 subjects to LEO 124249 ointment 30 mg/g and 24 subjects to LEO 124249 ointment vehicle.

**Diagnosis and Main Criteria for Inclusion and Exclusion**

**Diagnosis:** inverse psoriasis

**Main criteria for inclusion:**
- Men or women between 18 and 75 years of age.
- A diagnosis of stable mild to moderate inverse psoriasis (i.e. axillae, the infra- and intermammary, genital, abdominal and retroauricular folds; the scrotum, the intergluteal cleft and perianal skin, in addition to neck or other skin folds) at screening. Mild to moderate was defined as having at least score 1 for each individual sign redness and thickness, and TSS of at least 5.
- The total treatment area could be up to 4% BSA (720 cm²).
- Subjects had to have a history of psoriasis, or have psoriasis, or present with characteristic psoriasis lesions elsewhere on the body (including the scalp) at screening.
- Stable inverse psoriasis based on TSS evaluated at screening and start of treatment, which must not differ more than 1
point in any single clinical sign score (redness, scaling and thickness).
- Except for inverse psoriasis, overall good health including well-controlled diseases (e.g. hypertension, diabetes, and thyroid disease) as determined by medical history, physical examination, electrocardiogram (ECG), vital signs (blood pressure, heart rate and body temperature), and clinical laboratory evaluation.

**Main criteria for exclusion:**
- Severe chronic inverse psoriasis, or psoriasis on the body (>30% of BSA).
- Current diagnosis of acute guttate, erythrodermic, exfoliative or pustular psoriasis.
- Use of biological therapies (marketed/not marketed) with a possible effect on inverse psoriasis within 4 weeks (etanercept), 8 weeks (adalimumab, alefacept, infliximab), 16 weeks (ustekinumab, secukinumab) or 4 weeks/5 half-lives (whichever is longer) for experimental biological products prior to Visit 2.
- Use of systemic treatments (marketed/non-marketed), other than biologics, with a potential effect on inverse psoriasis (e.g., corticosteroids, retinoids, dimethylfumarate, cyclosporine, azathioprine methotrexate, immunosuppressants) within 6 weeks prior to Visit 2.
- Use of very potent topical corticosteroids (WHO group IV) for the treatment of psoriasis on the body and/or scalp within 4 weeks prior to Visit 2.
- Use of topical medication for the treatment of inverse psoriasis: WHO group I-III corticosteroids, retinoids, vitamin D analogues, immunomodulators (e.g. macrolides, calcineurin), anthracen derivatives, tar, or salicylic acid within 2 weeks prior to Visit 2.
- Exposure to phototherapy (PUVA, UVA, UVB, Grenz Ray therapy) within 4 weeks prior to Visit 2.
- Any current dermatological disorder (e.g. serborrhic dermatitis, contact dermatitis, cutaneous mycoses) which may confound the evaluation of inverse psoriasis.

### Test Product, Dose and Mode of Administration, Batch Number

| LEO 124249 ointment 30 mg/g, topical administration twice daily. Batch number: P15020/04-2017 |

### Duration of Treatment

Wash-out up to 4 weeks, treatment for 6 weeks, follow-up 2 weeks after end of treatment (Week 6, Visit 6) for subjects with ongoing related AEs or SAEs.

### Reference Product, Dose and Mode of Administration, Batch Number

| LEO 124249 ointment vehicle, topical administration twice daily. Batch number: P15005/04-2017 |

### Criteria for Evaluation

**Primary endpoint:**

- Total Sign Score (TSS; sum of scores for redness, thickness, and scaliness of inverse psoriasis, each scored from 0 to 4, total sum from 0 to 12) at Week 6 compared for LEO 124249 ointment 30 mg/g and LEO 124249 ointment vehicle.

**Secondary endpoints:**

- The following endpoints were evaluated at Week 6 and compared for LEO 124249 ointment 30 mg/g and LEO 124249 ointment vehicle:
  - For PGA, the number of subjects reaching controlled disease defined as follows:
    - Subjects classified as having at least ‘moderate’ disease at baseline who achieved ‘clear’ or ‘almost clear’ disease severity were considered to have controlled disease.
    - Subjects classified at baseline as having ‘mild’ disease had to achieve ‘clear’ to be considered having controlled disease.
  - Clinical sign score for redness for inverse psoriasis: (score 0 to 4).
  - Clinical sign score for thickness for inverse psoriasis: (score 0 to 4).
  - Clinical sign score for scaliness for inverse psoriasis: (score 0 to 4).
  - Size of treatment area of inverse psoriasis.
  - For PaGA, the number of subjects reaching controlled disease defined as follows:
    - Subjects classified as having at least ‘moderate’ disease at baseline who achieved ‘clear’ or ‘very mild’ disease severity were considered to have controlled disease.
    - Subjects classified at baseline as having ‘mild’ disease had to achieve ‘clear’ to be considered having controlled disease.
  - Dermatology Life Quality Index (DLQI) questionnaire.
  - Treatment Satisfaction Questionnaire for Medication (TSQM II).

**Exploratory endpoints:**

- Subject’s Assessment of Itching (daily assessment in diary the first 14 days of treatment (from start of treatment to Week 2, followed by assessments at Week 2, Week 4, and end of treatment (Week 6)).
- Subject’s Assessment of Cosmetic Acceptability at end of treatment (Week 6).
Evaluation of population steady state pharmacokinetics of LEO 124249 at Week 1.

### Statistical Methods

Descriptive statistics were used to present the demographics and other baseline characteristics. The primary endpoint was analysed for the full analysis set (FAS) and the per protocol (PP) set. The analysis for the FAS was regarded as primary. The primary endpoint analysis was done by means of an analysis of covariance (ANCOVA) with treatment and pooled site as factors and baseline TSS as covariate. Missing values were imputed using last observation carried forward (LOCF) and compared to the observed data and to imputed data using baseline observation carried forward (BOCF) in a sensitivity analysis.

For the secondary endpoints, the PGA and PaGA for the two treatment groups were compared at Week 6 by calculating the Cochran-Mantel-Haenszel (CMH) odds ratios and corresponding 95% confidence intervals adjusting for pooled site. Differences between treatment in terms of clinical sign scores, size of treatment area, DLQI score were analysed using the ANCOVA model with treatment and pooled site as factors and baseline value as covariate. TSQM II derived scores were analysed using the ANCOVA model with treatment and pooled site as factors. The safety endpoint was evaluated for the safety analysis set by tabulating AEs based on Common Terminology Criteria for adverse events system organ class (SOC) or preferred term, by severity and relatedness. AEs and other safety measurements were summarised and presented using descriptive statistics.

### Summary of Results

#### Trial Population

**Disposition of Subjects**

69 subjects were treated (45 with LEO 124249 and 24 with Vehicle) with at least one application of IMP, and 60 subjects completed the trial.

9 subjects (6 subjects in the LEO 124249 group and 3 subjects in the ointment vehicle group) withdrew from the trial. The most common reason for withdrawal was voluntary withdrawal (5 subjects). 2 subjects withdrew from the trial due to lack of treatment efficacy. In addition, 2 subjects withdrew due to unacceptable AEs (severe application site burning in 1 subject in the LEO 124249 group and severe eyelid oedema combined with mild application site erythema in 1 subject in the ointment vehicle group).

**Protocol Deviations**

33 subjects (22 subjects in the LEO 124249 group and 11 subjects in the ointment vehicle group) were noted with major protocol deviations and showed a comparable distribution of the deviation categories in both treatment groups. The most frequent category of protocol deviations were ‘use of prohibited medication’, ‘IMP stopped more than two days prior to Week 6 assessment’, ‘failure to maintain sequential randomization’, and ‘overdosing of IMP’. The overdosing of IMP was judged to be a result of a faulty dosing instruction of the required amount of IMP, leading to reports of overdose based on IMP weight data, and thus not considered as overuse per se. The overdosing of IMP was not considered a safety risk, and no signs of systemic AEs were observed during the trial.

Not all major protocol deviations led to exclusion form the per protocol analysis set.

#### Treatment Compliance

A majority of subjects (86% in the LEO 124249 group and 75% in the ointment vehicle group) missed <=10% applications of IMP during the total treatment period. A total of 7 subjects (10.44%) showed less than 80% treatment compliance during the course of the trial.

The trial population comprised of 42 men (62.7%) and 25 women (37.3%). The majority of subjects were white (97.0%) with Fitzpatrick skin type II (68.7%) or III (26.9%). 66 subjects (98.5%) reported their ethnicity as ‘not Hispanic or Latino’.

In general, LEO 124249 group consisted of higher number of subjects with severe inverse psoriasis at baseline compared to the Vehicle group.

#### Efficacy Results

In the present trial, treatment with LEO 124249 did not demonstrate to be efficacious compared to treatment with Vehicle. As a preliminary observation differences in baseline values for TSS, PGA, PaGA, the clinical scores for redness, thickness and scaliness and subject’s assessments for itching and cosmetic acceptability between the two treatment groups are to be considered. None of these differences were regarded as major, however it is a fact that more severe subjects were included in the LEO 124249 30 mg/g group.

The estimated difference in adjusted mean TSS between the LEO 124249 group and Vehicle group for the FAS (p=0.89) and PP analysis set (p=0.55), did not show any statistical significance at Week 6.

The individual clinical sign scores for redness, thickness, and scaliness when compared between the two treatment groups at Week 6 showed no statistically significant differences in both the FAS and PP analysis sets.

Analysis of controlled disease using PGA showed that 4 subjects (10.3%) in LEO 124249 group and 3 subjects (14.3%) in Vehicle reached controlled disease at Week 6. This observation was not statistically significant.

Analysis of controlled disease using PaGA showed that 5 subjects (12.8%) in LEO 124249 group and 1 subject (4.8%) in Vehicle group reached controlled disease at Week 6. The observation showed no statistically significant differences between the two treatment groups.
The estimated difference in adjusted mean size of treatment area of inverse psoriasis showed no significant difference at Week 6 between the two treatment groups for both the FAS and PP analysis set. No significant differences were observed in the DLQI at Week 6 across the two treatment groups. Subject’s assessment of treatment satisfaction using TSQM did not reveal statistically significant differences across the parameters ‘effectiveness’, ‘side effects’, ‘convenience’ and ‘global satisfaction’ between the treatment groups. No noteworthy differences were observed in the Subject’s assessment of itching at Week 6 between the two treatment groups. Subject’s overall assessment of cosmetic acceptability was comparable between the two treatment groups for the scores concerning ‘pleasantness of use of ointment’, ‘ease of application’ and ‘smell’ and higher for score concerning ‘greasiness’ in the LEO 124249 group. Low systemic exposure of LEO 124249 was assessed after 1 week treatment at steady state.

Safety Results
LEO 124249 had an acceptable safety profile and was well tolerated in subjects with inverse psoriasis treated for 6 weeks. Less than half of the randomised subjects in the LEO 124249 group and Vehicle group reported AEs (46.6% and 33.3% respectively). The AEs most commonly reported were ‘nasopharyngitis’ and ‘drug overdose’. Approximately one fourth of the randomised subjects experienced AEs related to treatment (26.7 %), the most common being ‘overdose of IMP’ followed by ‘application site pain’ and ‘application site pruritus’. 4.4% of the subjects reported severe AEs. 2 SAEs (worsening of coronary heart disease and pancreatic cancer) were reported in the trial, both of which were assessed as unrelated to the IMP.

Conclusion
The trial showed no statistically significant difference between LEO 124249 and its ointment vehicle in terms of efficacy at Week 6 in subjects with mild to moderate inverse psoriasis. LEO 124249 had an acceptable safety profile and was well tolerated as twice daily treatment for up to 6 weeks in subjects with inverse psoriasis. The observed systemic exposure in inverse psoriasis patients was low.
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