Clinical Study Report Synopsis

Safety and efficacy of escalating doses of LEO 43204 applied once daily for two consecutive days on full balding scalp in subjects with actinic keratosis

Part 1: A phase 1, multicentre, open-label, dose escalation, 2-week trial

Part 2: A phase 2, multicentre, randomised, double-blind, parallel group, vehicle-controlled, 8-week trial

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: LP0084-1014
Date: 21-Sep-2015
Version: Final
Clinical Trial Report Synopsis Statement

Approval Statement, LEO Pharma A/S

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

- Biostatistics
- Medical Department

Approval Statement, International Coordinating Investigator

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

The following person has approved this clinical study report synopsis:

- , MD
  International coordinating investigator
**Trial Registration Number**
NCT02100813

**EudraCT Number**
2014-000037-23

**Title of Trial**
Safety and efficacy of escalating doses of LEO 43204 applied once daily for two consecutive days on full balding scalp in subjects with actinic keratosis

**Investigators**
Dr. MD, Gwinnett Clinical Research Center, USA was appointed as signatory investigator

**Trial Centres**
Part 1 of this trial was conducted at 7 centres in 1 country (USA), Part 2 at 16 centres in 2 countries (USA and Germany) and the trial was coordinated at the Gwinnett Clinical Research Center, USA.

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

**Clinical Trial Period**
Date of First Subject First Visit: 14-May-2014 (Part 1), 03-Sep-2014 (Part 2)
Date of Last Subject Last Visit: 12-Aug-2014 (Part 1), 02-Mar-2015 (Part 2)

**Development Phase**
Phase 1/2

**Objectives**

**Primary Objectives**
Part 1:
- To identify the maximum tolerated dose (MTD) of LEO 43204 after once daily treatment for 2 consecutive days
Part 2:
- To evaluate efficacy of two doses of LEO 43204 given as once daily treatment for two consecutive days

**Secondary Objectives**
Part 1:
- To evaluate safety of LEO 43204 in escalating doses after once daily treatment for two consecutive days
Part 2:
- To evaluate safety of two doses of LEO 43204 given as once daily treatment for two consecutive days

**Methodology**
Part 1 was a phase 1, multicentre, open-label, dose escalation, 2-week trial with LEO 43204 gel applied as field treatment in subjects with AK on the balding scalp. The objective was to find the MTD for LEO 43204, after once daily treatment for 2 consecutive days. Trial medication was to be applied to full balding scalp once daily for 2 consecutive days until the MTD had been reached. Subjects were followed for 2 weeks after first application of investigational product. Up to 6 different doses of LEO 43204 gel could be investigated in cohorts of 12 subjects. Pre-defined grades of local skin responses (LSRs) constituted dose limiting toxicities (DLTs). The MTD was defined as the highest dose level with less than 4 out of 12 subjects experiencing a DLT.

Part 2 was a phase 2, multicentre, randomised, double-blind, parallel group, vehicle-controlled, 8-week trial. Subjects were randomised in a 2:2:1 ratio to LEO 43204 gel 0.037%, LEO 43204 gel 0.05% or vehicle gel. The randomisation was stratified by trial site. The treatment area was full balding scalp. Subjects were followed for 8 weeks after first application and reduction in number of clinically visible AKs and complete and partial AK clearance were assessed. Efficacy of LEO 43204 gel was to be evaluated at the MTD level identified in Part 1 and at the dose level just below the identified MTD level and compared to vehicle gel, following once daily application for 2 consecutive days. Lower dose levels could, however, be chosen instead for Part 2 if exposure at the MTD level was associated with unexpected high LSR scores or high frequency of adverse events. No formal MTD was identified in Part 1 and Part 2 continued with 0.037%, 0.05%, and vehicle.

**Number of Subjects Planned and Analysed**
Part 1: Up to 6 different cohorts, each comprising 12 subjects were planned. A total of 57 subjects were allocated to treatment.
Part 2: 62 subjects each in 2 active treatment groups and 31 subjects in 1 vehicle group were planned. A total of 163 subjects were allocated to treatment (64 in the 0.037% group, 67 in the 0.05% group, and 32 in the vehicle group, respectively).

**Diagnosis and Main Criteria for Inclusion**
Diagnosis: actinic keratosis (AK)

Main criteria for inclusion:
Part 1: Subjects with 5 to 20 clinically typical, visible and discrete AKs on the full balding scalp. The balding part of the scalp should be at least 125 cm² and no more than 250 cm².
Part 2: Subjects with 5 to 20 clinically typical, visible and discrete AKs on the full balding scalp. The balding part of the scalp should be at least 25 cm² and no more than 250 cm².
Subject at least 18 years of age
Female patients must be of non-childbearing potential or if of childbearing potential must provide negative urine pregnancy test prior to trial treatment and use effective contraception.

**Test Product, Dose and Mode of Administration, Batch Number**
Part 1: administration on full balding scalp once daily for 2 consecutive days of LEO 43204 gel at escalating doses: 0.018%, 0.025%, 0.037%, 0.05%, and 0.075%.
Part 2: administration on balding scalp once daily for 2 consecutive days of LEO 43204 gel, 0.037%, or 0.05%.
Batch numbers:
LEO 43204 gel: 0.018%: 132717101; 0.025%: 130447601; 0.037%: 132827101 (Part 1), P14007 (Part 2); 0.05%: 130447701; and 0.075%: 130447801. LEO 43204 gel 0.1% was not used in the trial.

**Duration of Treatment**
Part 1 and 2: 2 consecutive days of treatment

**Reference Product, Dose and Mode of Administration, Batch Number**
Part 1: none
Part 2: vehicle gel administered once daily for 2 consecutive days on full balding scalp. Batch number: 130447101

**Criteria for Evaluation**

**Primary Endpoint**
Part 1: DLT based on LSRs up to and including Day 8
Part 2: Percent reduction in AK count from baseline to Week 8

**Secondary Endpoints**
Part 2:
Complete clearance of AKs at Week 8
Partial clearance of AKs at Week 8, defined as at least 75% reduction from baseline in AK count

**Statistical Methods**
Data from Part 1 and Part 2 were evaluated separately.

**Analysis Populations**
Part 1:
An evaluable subjects analysis set was defined as all subjects who received at least one dose of trial medication, and had LSRs recorded at all visits up to and including Day 8 or had experienced a DLT at one or more visits up to and including Day 8. Safety analyses were based on the safety analysis set, which was defined as all subjects who received at least one application of trial medication and had safety information available post treatment.
Part 2:
Efficacy analyses were based on the full analysis set (FAS), which was defined as all randomised subjects. Per protocol analysis set was used as an efficacy subset and was defined as subjects in the FAS who completed the trial without major protocol deviations. Safety analyses were based on the safety analysis set, which was defined as all subjects who received at least one application of trial medication and had safety information available post treatment.

**Analysis of the Primary Endpoint**
Part 1:
The number of subjects experiencing DLTs was tabulated by treatment group.
Part 2:
Percent reduction in AK count from Baseline to Week 8 was analysed by the following method. The ratio of AK count at Week 8 relative to the AK count at baseline was analysed using a negative binomial regression on AK count at Week 8 with the log baseline count as an offset variable and treatment group and analysis site as factors. The rate ratios and the corresponding 95% confidence intervals were estimated from this model comparing the treatment groups pairwise.

**Analysis of secondary endpoints**
Part 2:
Complete clearance of AKs at Week 8 was analysed by log binomial regression with treatment group as factor and baseline AK count included as continuous variable. The rate ratios of pairwise treatment groups were presented together with their 95% confidence intervals.
Partial clearance, defined as 75% or greater reduction in AK count was analysed in the same way as complete clearance.

**Safety analyses**
Part 1 and 2:
Safety analyses were descriptive and based on the safety analysis set.
Summary of Results

Trial Population
Part 1:
All 57 included subjects were treated with at least one application of investigational product and completed the trial (10 subjects in the 0.018% cohort, 11 subjects in the 0.025% cohort, and 12 subjects each in the 0.037%, 0.05%, and 0.075% cohorts.).
Median age at baseline was 69.0 years (range 45 to 86). All subjects were white men and the most common Fitzpatrick skin type was type II or III. The median duration of AK was 6.0 years (range 0 to 44) and the median AK count at baseline was 8.0. Treatment compliance was high with only 2 subjects not receiving both planned applications of trial medication.

Part 2:
A total of 163 subjects were treated with at least one application of investigational product (64 were randomised to LEO 43204 gel, 0.037%, 67 to LEO 43204 gel, 0.05%, and 32 subjects to vehicle gel). All but one subject completed the trial.
Median age at baseline was 72.0 years (range 47 to 89). All subjects were white men, and the majority had Fitzpatrick skin type II or III. The median duration of AK was 9.0 years (range 0-45) and the median AK count in the treatment area at baseline was 13.5, 25-74 cm$^2$ in 1.2% of the subjects, respectively. Treatment compliance was high with only 4 subjects not receiving both planned applications of medication.

Efficacy Results
Part 2:
• The percent reduction in AK count from baseline to Week 8 was 78.5% in the 0.05% treatment group, 72.7% in the 0.037% treatment group and 12.6% in the vehicle group. The difference between active treatment and vehicle was statistically significant for both 0.037% and 0.05% (p <0.001). There was no statistically significant difference between the 2 active treatment groups (p=0.096).
• Complete clearance of AKs at Week 8 was 29.9% in the 0.05% treatment group, 21.9% in the 0.037% treatment group, and 3.1% in the vehicle group. The difference between active treatment and vehicle was statically significant for both 0.037% (p=0.007) and 0.05% (p<0.001). There was no statistically significant difference between the 2 active treatment groups (p=0.43).
• Partial clearance of AKs at Week 8 (defined as at least 75% reduction from baseline) was 59.7% in the 0.05% treatment group, 54.7% in the 0.037% treatment group, and 6.3% in the vehicle group. The difference between active treatment and vehicle was statically significant for both 0.037% and 0.05% (p<0.001). There was no statistically significant difference between the 2 active treatment groups (p=0.55).

Safety Results
Part 1:
• No formal MTD was identified as no subjects met the predefined criteria. Based on the general tolerability profile observed in the 0.075% cohort, dose escalation was stopped at this dose level and 0.075% was appointed as the MTD of LEO 43204 gel on scalp.
• Due to the intensity of application site AEs experienced by some subjects in the 0.075% dose cohort, the doses 0.05% and 0.037% were taken forward into Part 2 of the trial.
• All dose cohorts had subjects with AEs, most AEs were related to treatment, and relatively few AEs were of severe intensity. The number and intensity of administration site reactions (MedDRA high level group term) tended to increase with increasing dose and all severe administration site reactions were observed in the 0.05% and 0.075% cohorts.
• There were no deaths and no SAEs. Two subjects discontinued treatment due to AEs.
• Vital signs and laboratory monitoring showed no evidence of safety concern.
• ECG monitoring showed no association between LEO 43204 gel treatment and evidence of cardiac effects.

Part 2:
• There were no deaths. Six non-related SAEs, distributed in the active treatment groups, were reported for 5 subjects. One subject in the 0.05% group was withdrawn from the trial due to brain neoplasm and convulsion.
• Three subjects had AEs (application site pain and/or pruritus) leading to discontinuation of treatment; 1 in the 0.037% group and 2 in the 0.05% group.
• More than half of the subjects in the active treatment groups had AEs assessed as related to treatment and the frequency was higher with increasing dose of active treatment (54.7% and 71.6%, respectively). The most common AEs related to investigational product in all treatment groups were application site pain and application site pruritus. Breakdown of the MedDRA high level group term administration site reactions by LLT showed that application site burning was the most commonly reported event at this level.
• The mean composite LSR score peaked at Day 3 in both active treatment groups (8.6 and 8.7, respectively), thereafter quickly decreasing, reaching mild levels at Week 2, and approaching baseline values at Week 4.
Vital signs and laboratory evaluations showed no findings of concern.
ECG monitoring showed no association between LEO 43204 treatment and evidence of cardiac effects.

In summary, both doses studied in Part 2 of the trial had acceptable tolerability.

**Conclusion**

No formal MTD of LEO 43204 gel applied as field treatment on balding scalp was identified as no subjects met the predefined criteria. Two doses of LEO 43204 gel (0.037% and 0.05%) were selected for efficacy evaluation based on clinically acceptable skin reactions through assessment of LSRs and AEs. Both LEO 43204 gel, 0.037% and LEO 43204 gel, 0.05% had statistically significantly higher reduction in AK count from baseline to Week 8 as well as AK clearance (complete and partial) compared to vehicle, when applied as field treatment once daily for 2 consecutive days to subjects with AKs on balding scalp. Both doses were considered well-tolerated based on AEs and LSRs.
**ELECTRONIC SIGNATURES**

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