Clinical Study Report Synopsis

Safety and efficacy of escalating doses of LEO 43204 applied once daily for two consecutive days on approximately 250 cm² on trunk and extremities in subjects with actinic keratosis

Design of trial:

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:    LP0084-1015
Date:       09-Nov-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:

[Blank], MSc
[Blank] Biostatistics

[Blank], MD
[Blank] 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:

[Blank], MD
International coordinating investigator
### Title of Trial
Safety and efficacy of escalating doses of LEO 43204 applied once daily for two consecutive days on approximately 250 cm$^2$ on trunk and extremities in subjects with actinic keratosis

### Investigators
[Name redacted], MD, Mount Sinai School of Medicine, USA was appointed as signatory investigator.

### Trial Centres
Part 1 of this trial was conducted at 6 centres in 1 country (USA), Part 2 at 21 centres in 2 countries (USA and Canada) and the trial was coordinated at Mount Sinai School of Medicine, USA.

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

### Clinical Trial Period
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### Development Phase
Phase 1/2

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

#### Secondary Objectives
- **Part 1:**
  - To evaluate safety of LEO 43204 in escalating doses after once daily treatment for 2 consecutive days
- **Part 2:**
  - To evaluate safety of 2 doses of LEO 43204 given as once daily treatment for 2 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 a contiguous, sun exposed area of 250 cm$^2$ on the arm between wrist and shoulder. 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 approximately 250 cm$^2$ on the arm between wrist and shoulder once daily for 2 consecutive days. 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 until the MTD had been reached. 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, 0.075%, LEO 43204 gel, 0.1% or vehicle gel. The randomisation was stratified by trial site. The treatment area was a contiguous, sun exposed area of 250 cm$^2$ on the extremities or trunk (except chest). 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 at Week 8. 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. No formal MTD was identified in Part 1 as no subjects met the pre-defined DLT-criteria. The MTD was defined to be the highest dose of 0.1% and Part 2 continued with 0.075%, 0.1%, and vehicle.

### Number of Subjects Planned and Analysed
**Part 1:** Up to 6 different cohorts, each comprising 12 subjects were planned. A total of 69 subjects were allocated to treatment; 12 subjects each in the 0.018%, 0.025%, 0.037%, 0.05%, and 0.075% cohorts, and 9 subjects in the 0.1% cohort. The total number of subjects randomised to the 0.1% cohort was 11, but 2 subjects allocated to 0.1% treatment but receiving
Part 2: 62 subjects each in 2 active treatment groups and 31 subjects in 1 vehicle group were planned. A total of 155 subjects were allocated to treatment (60 in the 0.075% group, 63 in the 0.1% 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 a contiguous, sun exposed area of 250 cm² on the arm between wrist and shoulder.

**Part 2:** Subjects with 5 to 20 clinically typical, visible and discrete AKs on a contiguous, sun exposed area of 250 cm² on the extremities or trunk (except chest).

Subject at least 18 years of age

Female subjects 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 approximately 250 cm² on the arm between wrist and shoulder once daily for 2 consecutive days of LEO 43204 gel at escalating doses: 0.018%, 0.025%, 0.037%, 0.05%, 0.075%, and 0.1%.

**Part 2:** administration on approximately 250 cm² on the extremities or trunk (except chest) once daily for 2 consecutive days of LEO 43204 gel, 0.075%, or 0.1%.

**Batch numbers:**

LEO 43204 gel: 0.018%: 132717101; 0.025%: 130447601; 0.037%: 132827101; 0.05%: 130447701; 0.075%: 130447801 (Part 1), P14011 (Part 2); and 0.1%: P14013.

### 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 approximately 250 cm² on the extremities or trunk (except chest). Batch number: 130447101.

### Criteria for Evaluation

**Primary Endpoint**

Part 1: DLT 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 and number of doses actually received. Two subjects were treated with the wrong investigational product according to allocation. These 2 subjects were allocated to LEO 43204 gel, 0.1% but the actual treatment was 0.018%. The subjects were presented according to the actual treatment in all tables, figures, and listings.

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.

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 69 included subjects were treated with at least one application of investigational product and completed the trial (12 subjects each in the 0.018%, 0.025%, 0.037%, 0.05%, and 0.075% cohorts, and 9 subjects in the 0.1% cohort). Median age at baseline was 70.0 years (range 42 to 90 years). All subjects were white and slightly more subjects were men than women. The most common Fitzpatrick skin type was type II. The median duration of AK was 2.5 years (range 0 to 34.6 years) and the median AK count at baseline was 9.0 (range 5 to 20). All subjects received both planned applications of trial medication.

Part 2:
A total of 155 subjects were treated with at least one application of investigational product (60 were randomised to LEO 43204 gel, 0.075%, 63 to LEO 43204 gel, 0.1%, and 32 subjects to vehicle gel). All but 3 subjects completed the trial. Median age at baseline was 68.0 years (range 38 to 93 years). All subjects were white, 58.1% were men, and the majority had Fitzpatrick skin type II or III. The median duration of AK was 6.9 years (range 0 to 38 years) and the median AK count in the treatment area at baseline was 11.0 (range 5 to 20). The treatment area was trunk and extremities, including arms, hands, and legs but excluding chest. Approximately half of the subjects were treated on the ‘arm including back of hand’ (49.7%), followed by ‘arm not including back of hand’ (38.7%), trunk (7.1%), and leg (4.5%). Treatment compliance was high with only 1 subject not receiving both planned applications of medication.

Efficacy Results

Part 2:
• The mean percent reduction in AK count from baseline to Week 8 was 70.0% in the 0.075% treatment group, 62.2% in the 0.1% treatment group and 32.7% in the vehicle group. The difference between active treatment and vehicle was statistically significant for both 0.075% and 0.1% (p<0.001). There was no statistically significant difference between the 2 active treatment groups (p=0.058).
• Complete clearance of AKs at Week 8 was 10.0% in the 0.075% treatment group, 9.5% in the 0.1% treatment group, and 9.4% in the vehicle group. There was no statistically significant difference between any of the active treatment groups compared with the vehicle group, or between the active treatment groups.
• Partial clearance of AKs at Week 8 (defined as at least 75% reduction from baseline) was 45.0% in the 0.075% treatment group, 44.4% in the 0.1% treatment group, and 15.6% in the vehicle group. The difference between active treatment and vehicle was statistically significant for both 0.075% and 0.1% (p=0.003 and p=0.004, respectively). There was no statistically significant difference between the 2 active treatment groups (p=0.95).
Safety Results

Part 1:
- The maximum post-baseline composite LSR score was slightly lower for the 2 lowest dose cohorts compared with the other cohorts that were comparable.
- No formal MTD was identified as no subjects met the pre-defined criteria for DLT. The MTD of LEO 43204 gel in the 2-day treatment regimen was defined to be the highest dose of 0.1%.
- No deaths, SAEs, or other significant AEs were reported.
- All cohorts had subjects with AEs, most AEs were related to treatment, and only 1 AE was of severe intensity. Except for the 0.025% cohort the number of subjects with administration site reactions (MedDRA high level group term) tended to increase with increasing dose of LEO 43204.
- 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:
- Approximately 60% of the subjects in the active treatment groups had AEs compared with approximately 20% in the vehicle group.
- Most AEs were mild or moderate and only 4 AEs in 2 subjects were severe.
- Approximately 50% of the subjects in the active treatment groups had AEs assessed as related to treatment (i.e. considered possibly or probably related by the investigator) with similar frequency in the 0.075% and 0.1% groups. The most common AEs related to investigational product were application site pruritus and application site pain. Breakdown of the MedDRA high level group term ‘administration site reactions’ by LLT showed that most of the application site pain events were coded as application site burning at this level.
- Three treatment emergent SAEs, distributed in the active treatment groups, were reported for 3 subjects. The SAEs keratoacanthoma and SCC of skin were both inside the treatment area and assessed as possibly related to treatment while the event of urinary tract infection was assessed as not related.
- No AEs led to withdrawal from the trial, but 2 AEs (application site pain and application site vesicles) in 1 subject led to discontinuation of treatment.
- The mean composite LSR score peaked at Day 8 in both active treatment groups (7.4 and 8.0, respectively), thereafter quickly decreasing, reaching mild levels at Week 2, and approaching baseline at Week 4. At Week 8 values had returned to baseline.
- Vital signs and laboratory evaluations showed no evidence of safety concern.
- ECG monitoring showed no association between LEO 43204 treatment and evidence of cardiac effects.

Conclusion
No formal MTD of LEO 43204 gel applied as field treatment on arm was identified as no subjects met the pre-defined criteria. Two doses of LEO 43204 gel (0.075% and 0.1%) were selected for efficacy evaluation based on clinically acceptable skin reactions through assessment of LSRs and AEs. Both LEO 43204 gel, 0.075% and LEO 43204 gel, 0.1% had statistically significantly higher percent reduction in AK count from baseline to Week 8 and a higher partial clearance at Week 8 compared with vehicle but this did not translate to increased complete clearance of AKs in the active treatment groups compared to the vehicle group. Both LEO 43204 gel, 0.075% and LEO 43204 gel, 0.1% were considered well-tolerated based on AEs and LSRs in this trial.
**ELECTRONIC SIGNATURES**

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