Clinical Study Report Synopsis

Safety and efficacy of escalating doses of two LEO 43204 formulations applied once daily for two consecutive days on full face or approximately 250 cm² (40 in²) on the chest in subjects with actinic keratosis

Part 1: A phase 1, multicentre, randomised, open-label, parallel group, dose escalation, 8-week trial

Part 2: A phase 2, multicentre, randomised, double-blind, parallel group, vehicle-controlled, 8-week trial
Clinical Study Report Synopsis Approval/Acknowledge

Approval Statement, LEO Pharma A/S

The following persons have approved this clinical trial report synopsis on behalf of LEO Pharma A/S using electronic signatures:

PPD
PPD Biostatistics

PPD
PPD Medical Department

Approval Statement, 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:

Dr. Gary Goldenberg
International Coordinating Investigator
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<th><strong>SYNOPSIS</strong></th>
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<td><strong>Trial Registration Number</strong></td>
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**Title of Trial**
Safety and efficacy of escalating doses of two LEO 43204 formulations applied once daily for two consecutive days on full face or approximately 250 cm² (40 in²) on the chest in subjects with actinic keratosis

**Investigators**
This was a multi centre trial. Dr. Gary Goldenberg, Mount Sinai School of Medicine, USA was signatory investigator.

**Trial Centres**
This trial was conducted at 12 centres in 1 country (USA) in Part 1, 23 centres in 2 countries (USA and Canada) in Part 2 and coordinated at the Mount Sinai School of Medicine, USA.

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

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<th><strong>Trial Period</strong></th>
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<td><strong>Date of first enrolment (informed consent signed and CRF started):</strong> 09-Oct-2013 (Part 1), 14-May-2014 (Part 2)</td>
<td><strong>Date of last completed:</strong> 23-May-2014 (Part 1), 01-Dec-2014 (Part 2)</td>
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**Objectives**

**Primary Objectives**

**Part 1:**
- To identify maximum tolerated dose (MTD) levels of LEO 43204 gel and cream, respectively, after once daily treatment for 2 consecutive days.
- Dose escalation beyond cohort 4 continued with gel formulation only due to CMC development issues with the cream formulation, which did not affect the quality of the investigational medicinal product in this trial and therefore have no consequences for the analysis and interpretation of the collected data. Consequently, the MTD of LEO 43204 cream could not be identified.

**Part 2:**
- To evaluate efficacy of LEO 43204 gel in a maximum of 4 doses after once daily treatment for 2 consecutive days compared to vehicle gel.

**Secondary Objectives**

**Part 1:**
- To evaluate safety of LEO 43204 gel and cream, respectively, after once daily treatment for 2 consecutive days.
- Dose escalation beyond cohort 4 continued with gel formulation only.

**Part 2:**
- To evaluate safety of LEO 43204 gel, in a maximum of 4 doses after once daily treatment for 2 consecutive days compared to vehicle gel.

**Methodology**
Part 1 was a phase 1, multicentre, randomised, open-label, parallel group, dose escalation, 8-week trial of 2 different formulations of LEO 43204 (gel and cream) in subjects with AK. The objective was to find the maximum tolerated dose (MTD) for LEO 43204 gel and cream, respectively, after once daily treatment for 2 consecutive days.
Dose escalation of LEO 43204 cream was discontinued at the dose of 0.012% at cohort 4 (for details see primary objective) and for the following dose escalation subjects were only allocated LEO 43204 gel. Trial medication was to be applied to full face once daily for 2 consecutive days until the MTD had been reached for each formulation. Subjects were followed for 8 weeks after first application of investigational product. Up to 9 different doses of LEO 43204 gel and 4 different doses of cream could be investigated in cohorts of 3 to 18 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 (cohorts 1 to 4) or less than 6 out of 18 subjects (cohorts 5 and 6) experiencing a DLT.

Part 2 was a phase 2, multicentre, randomised, double-blind, parallel group, vehicle-controlled, 8-week trial. Subjects were allocated to LEO 43204 gel or vehicle (gel) in a randomised manner, stratified by trial site. The treatment area was full face or a contiguous area of approximately 250 cm² (40 in²) on the 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. Efficacy of LEO 43204 gel was evaluated at the MTD level identified in Part 1 and at up to 3 dose levels below the identified MTD level and compared to vehicle gel, following once daily application for 2 consecutive days. After completion of Part 1, the MTD for gel was identified as 0.018% and therefore Part 2 continued with 0.018%, 0.012%, 0.006%, and vehicle.
Number of Subjects Planned and Analysed
Part 1: Up to 9 different cohorts of LEO 43204 gel and 4 different cohorts of cream, each comprising 3 to 18 subjects. A total of 77 subjects were evaluated. 
Part 2: 62 subjects each in 3 active treatment groups and 1 vehicle group were planned. A total of 242 subjects were included in the full analysis set (FAS) and safety analysis set.

Diagnosis and Main Criteria for Inclusion
Diagnosis: actinic keratosis (AK)
Main criteria for inclusion:
Subjects with 5 to 20 clinically typical, visible and discrete AKs on the face (Part 1) or on either the face or within a contiguous area of approximately 250 cm$^2$ (40 in$^2$) on the chest (Part 2)
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 and use effective contraception.
Ability to provide informed consent

Investigational Product, Dose and Mode of Administration, Batch Number
Part 1: administration on full face once daily for 2 consecutive days of LEO 43204 gel at escalating doses: 0.0015%, 0.003%, 0.006%, 0.012%, 0.018%, 0.025%, 0.037%, 0.05%, and 0.075%, and LEO 43204 cream at escalating doses: 0.0015%, 0.003%, 0.006%, 0.012%
Part 2: administration on full face or within a contiguous area of approximately 250 cm$^2$ (40 in$^2$) on the chest of LEO 43204 gel, 0.006%, 0.012%, 0.018%
Batch numbers:
LEO 43204 gel: 0.0015%: 130447201; 0.003%: 130447301; 0.006%: 130447401; 0.012%: 130447501; 0.018%: 132717101; and 0.025%, 0.037%, 0.05%, and 0.075% were not used in the trial.
LEO 43204 cream: 0.0015%: 130457201; 0.003%: 130457301; 0.006%: 130457401; 0.012%: 130457501.

Duration of Treatment
Part 1 and 2: 2 consecutive days of treatment and 8 weeks follow-up.

Reference Therapy, Dose and Mode of Administration, Batch Number
Part 1: none
Part 2: vehicle gel administered once daily for 2 consecutive days on full face or within a contiguous area of approximately 250 cm$^2$ (40 in$^2$) on the chest. 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, 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, 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 FAS defined as all randomised subjects who received treatment with investigational product. Per protocol (PP) analysis set was used as an efficacy subset defined as subjects in the FAS who completed the trial without major protocol deviations. Safety analyses were based on the safety analysis set, 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.
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 value as 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

Trial Population

Part 1:

All 77 included subjects were treated with at least one application of investigational product and completed the trial (3 subjects in the 0.0015% gel cohort, 3 subjects in the 0.003% gel cohort, 6 in the 0.006% gel cohort, 6 in the 0.012% gel cohort, 7 in the 0.018% gel cohort, 18 in the 0.025% gel cohort, 3 in the 0.0015% cream cohort, 3 in the 0.003% cream cohort, 6 in the 0.006% cream cohort, and 12 in the 0.012% cream cohort).

Median age at baseline was 69.0 years for both treatment formulations (range 48 to 91 [gel] and 40 to 82 [cream]). All subjects in both treatment groups were white, most subjects were men (33 out of 53 [gel] and 18 out of 24 [cream]), and the most common Fitzpatrick skin type was type II (37 out of 53 [gel] and 11 out of 24 [cream]). The median duration of AK was 6.0 years for the group treated with gel and 5.0 years in the group treated with cream. Median AK count at baseline was 10.0 (gel) and 12.0 (cream). More than 90% of the subjects received both planned applications of medication.

Part 2:

243 subjects were randomised to treatment, but 1 subject in the vehicle group discontinued before applying investigational product and was excluded from the FAS. Of the remaining 242 randomised subjects, 237 attended the last visit: 3 withdrew voluntarily and 1 had another reason (hip fracture). One subject attended the Week 8 visit and then withdrew from the trial before clinical assessments were performed. The FAS consisted of 242 subjects: 58 in the vehicle group, 62 in the 0.006% group, 60 in the 0.012% group, and 62 in the 0.018% group. All subjects in the FAS were included in the safety analysis set.

Median age at baseline was 69.0 years (range 42 to 91). All subjects were white, 68.6% were men, and 73.9% had Fitzpatrick skin type I or II. The median duration of AK was 8.0 years and the median AK count in the treatment area at baseline was 11.0. The location of the treatment area was on full face (90.5% of the subjects) or chest (9.5% of the subjects). More than 95% of the subjects received both planned applications of medication.

Efficacy Results

Part 2:

• The percent reduction in AK count from baseline to Week 8 was 79.0% in the group receiving LEO 43204 gel, 0.018%, followed by the groups receiving LEO 43204 gel, 0.012% (73.4%), LEO 43204 gel, 0.006% (69.7%), and vehicle (42.3%). All active treatment groups had statistically significantly higher reduction in AK count compared with vehicle (p=0.001).
• Complete clearance of AKs at Week 8 was 24.2% in the 0.018% group, 18.8% in the 0.012% group, 9.9% in the 0.006% group, and 12.2% in the vehicle group. No active treatment group was statistically significantly different in complete clearance compared with vehicle treatment in pairwise comparisons.
• Partial clearance of AKs at Week 8 was 62.9% in the 0.018% group, 54.5% in the 0.012% group, 52.4% in the 0.006% group, and 29.9% in the vehicle group. All active treatment groups had statistically significantly higher partial clearance compared with vehicle treatment in pairwise comparisons (p=0.026 [0.006%], p=0.013 [0.012%], and p=0.001 [0.018%]).

Safety Results

Part 1:

• Based on pre-defined MTD criteria, the MTD was 0.018%. This dose and 2 doses below (0.012% and 0.006%) were taken forward to Part 2.
• There were no deaths, 2 subjects had non-related SAEs (squamous cell carcinoma of skin in the treatment area and breast cancer, both had gel treatment), and 5 subjects had discontinued treatment due to AEs (all subjects had AEs related to treatment).
• All cohorts for both gel and cream had subjects with AEs and most AEs were related to treatment (i.e. considered possibly or probably related by the investigator). Approximately half of the subjects had administration site reactions (MedDRA high level group term), and relatively few AEs were of severe intensity.
• Vital signs and laboratory monitoring showed no evidence of safety concern.
• ECG monitoring showed no association between LEO 43204 treatment and evidence of cardiac effects.

Part 2:

• There were no deaths. Eight non-related SAEs, distributed in the 0.006% and 0.012% groups, were reported for 7 subjects. One subject in the 0.012% group was withdrawn from the trial due to hip fracture, and 2 subjects had AEs leading to
discontinuation from treatment: 1 in the 0.012% group due to application site dermatitis and 1 in the 0.018% group due to application site pain.

- Most subjects in the active treatment groups had AEs (>60%) compared with about one fifth in the vehicle group. Most AEs were mild or moderate and 5 AEs were severe. AEs assessed as related to investigational product were reported for ≥50% of the subjects in the active treatment groups and the frequency was higher with increasing dose of active treatment. The most common AEs related to investigational product in all treatment groups were application site pain and application site pruritus.

- The composite LSR score was higher for active treatments than vehicle treatment. It attained its maximum at Day 3 for all active treatments, approaching close to baseline at Week 2 and returned to baseline values at Week 8. There was a tendency towards an increase in maximum post-baseline composite LSR score with increasing dose.

- 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, all 3 treatment doses studied in Part 2 of the trial had acceptable tolerability.

**Conclusion**

The MTD level of LEO 43204 gel after once daily treatment for 2 consecutive days was identified as 0.018%. LEO 43204 gel at doses of 0.006%, 0.012%, and 0.018% administered once daily for 2 consecutive days had a statistically significant higher percent reduction in AK count from baseline to Week 8 compared with vehicle, when administered for treatment of full face or approximately 250 cm² (40 in²) on the chest in subjects with AK. In addition, there was a dose response trend in percent reduction in AK count in the sense that the 0.018% group was statistically significantly higher compared with the 0.006% group. No statistically significant difference was seen in complete clearance of AKs between the active treatment groups and vehicle. Note that the sample size in this trial was chosen to give estimates of percent reduction in AK count and not to detect a difference in complete clearance of AKs between the treatment groups.

All doses of LEO 43204 in gel formulation up to 0.018% were considered well-tolerated based on AE profile and LSRs.

The clinical trial was conducted in compliance with the clinical trial protocol, ICH Good Clinical Practice and the Declaration of Helsinki as adopted by the 18th World Medical Association General Assembly 1964, and subsequent amendments.
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