Clinical Study Report Synopsis

Safety of LEO 43204 0.018%, 0.037% and 0.1% for actinic keratosis applied once daily for three consecutive days on face/chest, scalp and trunk/extremities, respectively

Design of trial:
A phase 2, multicentre, open-label, 8-week trial in three groups, face/chest, scalp, and trunk/extremities

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 study report synopsis using electronic signatures as presented on the last page of this document:

[Signature]
MSc
Biostatistics

[Signature]
MD
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:

[Signature]
MD MSc
International coordinating investigator
**Title of Trial**
Safety of LEO 43204 0.018%, 0.037% and 0.1% for actinic keratosis applied once daily for three consecutive days on face/chest, scalp and trunk/extremities, respectively

**Investigators**
[Name redacted], MD MSc, [Name redacted], US, was appointed as signatory investigator.

**Trial Centres**
This trial was conducted at 20 centres in the US and coordinated at [Name redacted].

**Objectives**
**Primary Objective:**
- To evaluate safety of LEO 43204 (0.018%, 0.037% and 0.1% for face/chest, scalp and trunk/extremities, respectively) after once daily field treatment for three consecutive days.

**Secondary Objective:**
- To evaluate efficacy of LEO 43204 (0.018%, 0.037% and 0.1% for face/chest, scalp and trunk/extremities, respectively) after once daily field treatment for three consecutive days.

**Methodology**
This was a phase 2, multicentre, open-label, 8-week trial in subjects with actinic keratosis lesions (AKs) evaluating the safety and efficacy of LEO 43204 in a once daily regimen for three consecutive days, when applied to treatment areas up to approximately 250 cm² on one of the anatomical locations face/chest, scalp, or trunk/extremities. An early data review was performed in each treatment group, as a safety precaution, following completion of Day 8 visit by 18 subjects (see trial design figure).

**Number of Subjects Planned and Analysed**
186 subjects were planned and 189 subjects were allocated to treatment (63 in each treatment group).
Diagnosis and Main Criteria for Inclusion

All of the following criteria needed to be met for a subject to be enrolled in the trial:

1. Signed and dated informed consent has been obtained.
2. Subjects with 5 to 20 clinically typical, visible, discrete, non-hyperkeratotic and non-hypertrophic AKs within a selected treatment area of sun-damaged skin on either:
   - The full face or a contiguous area of approximately 250 cm² on chest
   - The full balding scalp (the balding part of the scalp should be greater than 25 cm² and up to approximately 250 cm²)
   - A contiguous area of approximately 250 cm² on trunk or extremities (except chest)

Note: In addition to the requirement of 5-20 clinically typical, visible, discrete, non-hyperkeratotic and non-hypertrophic AKs within a selected treatment area, subjects may also have visible and discrete hyperkeratotic/hypertrophic lesions in this area.

3. Subjects at least 18 years of age
4. Female subjects of childbearing potential must be confirmed not to be pregnant by a negative urine pregnancy test prior to trial treatment
5. Female subjects of child-bearing potential must be willing to use effective contraception at trial entry and until completion.

Test Product, Dose and Mode of Administration, Batch Number

- LEO 43204 0.018% gel applied topical on face/chest; Batch number: P14040
- LEO 43204 0.037% gel applied topical on scalp; Batch number: P14007
- LEO 43204 0.1% gel applied topical on trunk/extremities; Batch number: P14013

Duration of Treatment

3 consecutive days of once daily treatment

Reference Product, Dose and Mode of Administration, Batch Number

NA

Criteria for Evaluation

Primary Endpoint
- Dose Limiting Toxicity (DLT) based on LSRs up to and including Day 8

Secondary Endpoints
- Reduction in AK count from baseline to Week 8, excluding lesions identified at baseline as hypertrophic/hyperkeratotic
- Reduction in AK count from baseline to Week 4, excluding lesions identified at baseline as hypertrophic/hyperkeratotic
- Reduction in AK count from baseline to Week 8 in the subgroup of lesions identified at baseline as hypertrophic/hyperkeratotic
- Reduction in AK count from baseline to Week 4 in the subgroup of lesions identified at baseline as hypertrophic/hyperkeratotic
- Complete clearance of AKs at Week 8, excluding lesions identified at baseline as hypertrophic/hyperkeratotic

Statistical Methods

The primary endpoint was analysed for the safety analysis set by tabulating the number of subjects experiencing DLTs based on LSRs up to and including Day 8 by treatment group.

The secondary endpoints were analysed for the full analysis set (and for the per protocol analysis set). The ratio of number of AK lesions at Week 8 relative to baseline, excluding lesions identified at baseline as hyperkeratotic/hypertrophic lesions, were analysed separately for each treatment group, using a negative binomial regression on the AK count at Week 8 with the log baseline value as an offset variable. The estimated percent reduction in AK count and a corresponding 95% confidence interval were presented. The same analysis was performed for the subgroup of lesions identified as hyperkeratotic/hypertrophic at baseline.

The same analyses were conducted for the number of AK lesions at Week 4.

The number and percentage of subjects with complete clearance (i.e. no clinically visible AK lesions) at Week 8, excluding lesions identified at baseline as hyperkeratotic/hypertrophic lesions, were tabulated by treatment group with an exact 95% CI.

Summary of Results

Trial Population

189 subjects were treated (63 in each group) with at least one application/dose of investigational medicinal product and 187 subjects completed the trial (97% of subjects completed the full regimen of 3 doses). The trial population reflected the general population treated for AK, mostly consisting of elderly men with fair skin and a long duration of AK. Most subjects had previously been treated for AK and approximately half of trial population had a history of other skin disease. By treatment group at baseline, the median age ranged from 64 to 68 years, the median duration of AK ranged from 7 to 10 years, and the median number of non-hyperkeratotic and non-hypertrophic AKs ranged from 10 to 11.
Summary of Results – Continued

Efficacy Results

Secondary Endpoints:

- A larger mean percent reduction in AK count, excluding baseline hyperkeratotic/hypertrophic lesions, from baseline to Week 8 was indicated in the face/chest and the scalp groups than in the trunk/extremities group (78.9%, 76.3%, and 69.1%, respectively).
- Similar results were seen for the mean percent reduction in AK count, excluding baseline hyperkeratotic/hypertrophic lesions, from baseline to Week 4 (81.2%, 78.8%, and 59.0%), indicating that the effect on AK reduction was achieved already at Week 4 (especially in the face/chest and the scalp groups).
- A larger mean percent reduction in AK count of baseline hypertrophic/hyperkeratotic lesions was indicated at Week 8 in the face/chest and the scalp groups than in the trunk/extremities group (68.5%, 62.5%, and 39.2%, respectively). The confidence intervals for the estimated mean percent reduction were wide owing to the small number of subjects with hypertrophic/hyperkeratotic AKs at baseline and the low number of lesions per subject.
- Similar results were seen for the mean percent reduction in AK count of baseline hypertrophic/hyperkeratotic lesions from baseline to Week 4 (78.7%, 58.1%, and 36.0%).
- The proportion of subjects with complete clearance at Week 8, excluding baseline hyperkeratotic/hypertrophic lesions, was higher in the face/chest and the scalp groups than in the trunk/extremities group (36.5%, 39.7%, and 22.6%, respectively).

Safety Results

Primary Endpoint:

- DLT, predefined by LSR criteria, from baseline to Day 8 was reported for 9 (14%), 0 (0%), and 11 (18%) subjects in the face/chest, scalp, and trunk/extremities groups, respectively. The full enrolment contingency was achieved in each treatment group (identification of less than 6 DLTs in the first 18 subjects in each treatment group).

Other Safety Results:

- The compliance was high and the full treatment regimen of 3 doses, in a once daily regimen for 3 consecutive days, was administered to 182 of 188 (97%) subjects.
- There was no difference in the distribution of the most common AEs between the treatments groups. More than half of the subjects had an AE. The proportion was lower in the face/chest group (55.6%) than in the scalp and trunk/extremities groups (74.6% and 69.4%). The majority of all AEs were judged to be treatment related and, by preferred term, approximately half of the subjects had application site pain and approximately one third had application site pruritus. No other event by preferred term occurred in more than 5% of subjects in any treatment group.
- Less than 5% of subjects in each treatment group had an AE reported as severe.
- Excluding administration site reactions, 10 subjects had an AE inside the treatment area. SCC inside the treatment area was reported in 2 subjects in the trunk/extremities group (diagnosed as keratoacanthomas and SCC in situ based on central pathology review).

In both the face/chest and the scalp groups, the mean composite LSR score peaked at Day 4, thereafter quickly decreasing, reaching mild levels at Week 2 and baseline levels at Week 4. In the trunk/extremities group, the mean composite LSR score also peaked at Day 4, but remained high until Day 8, thereafter quickly decreasing, reaching mild levels at Week 2, and approaching the baseline level at Week 4.

- The mean maximum composite LSR scores were comparable in the three treatment groups (10.6, 11.0, and 10.2 in the face/chest, scalp, and trunk/extremities groups).
- One subject was treated on the chest with LEO 43204 0.1% intended for the trunk/extremities. This overdose did not entail any AEs (the subject was excluded from the full analysis set).
- No clinically significant abnormalities or changes from baseline to Day 4 in vital signs were observed during the course of trial.
- The ECG results did not indicate an effect of LEO 43204 on QTcF or other ECG intervals of interest (PR, QRS, and HR).
- Overall, there were no clinically relevant changes in the haematology- and biochemistry laboratory parameters from baseline to Day 4 in any of the treatment groups.

Conclusion

This open-label trial LP0084-1148 was designed to evaluate safety of LEO 43204 (0.018%, 0.037%, and 0.1% for face/chest, scalp and trunk/extremities, respectively) after once daily field treatment for three consecutive days. The results demonstrate that there were:

- No issues with DLTs or with severe related AEs
- No compliance issues and a tolerable LSR profile
- No indication of subject dissatisfaction towards the treatment effect
- No evidence contradicting the assumption that once daily field treatment for three consecutive days will yield a higher effect than once daily field treatment for two consecutive days.
Electronic Signatures

Electronic signature made within eDoc LEO by LEO Pharma A/S employees or employees of any LEO Pharma A/S affiliate located anywhere in the world, are to be considered to be legally binding equivalent of traditional handwritten signatures.

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