Clinical Trial Report Synopsis

Efficacy and Safety of LEO 43204 in Field Treatment of Actinic Keratosis on Balding Scalp including 12-month follow-up

Design of trial:

A phase 3, multi-centre, randomised, parallel group, double-blind, vehicle-controlled trial
  Part 1: 3-day treatment period including an 8-week follow-up period
  Part 2: extended 12-month follow-up period

The clinical trial, including the archival of essential documents, was conducted in compliance with the clinical trial protocol, Good Clinical Practice, and the applicable regulatory requirement(s).

LEO Pharma A/S  Trial ID:  LP0084-1195
Date:  27-Feb-2018
Version:  14M 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:

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[Name], M.Sc. Stat
Biostatistics Lead
Global Clinical Operations

[Name], MD, Ph.D
Medical Lead
Medical Science and Safety

Approval statement, international coordinating investigator

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

The following person has approved this clinical study report:

Daniel M. Siegel, MD MSc
International coordinating investigator
**Trial Registration Number**
NCT02547363

**EudraCT number**
2015-002451-10

### Title of Trial
Efficacy and Safety of LEO 43204 in Field Treatment of Actinic Keratosis on Balding Scalp including 12-month follow-up

### Investigators
Dr. Daniel M. Siegel was international coordinating investigator.

### Trial Sites
This trial was conducted at 23 sites in 4 countries (United States, Canada, United Kingdom, and France) and coordinated at the Long Island Skin Cancer and Dermatologic Surgery, Smithtown, New York, United States.

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

### Clinical Trial Period
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<th>Date of First Subject First Visit</th>
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### Objectives
**Primary objective**
To confirm the efficacy of ingenol disoxate gel (0.037% for scalp) in actinic keratosis (AK) when applied topically once daily for 3 consecutive days as field treatment.

**Secondary objectives**
To evaluate the safety of ingenol disoxate gel (0.037% for scalp) in AK when applied topically once daily for 3 consecutive days as field treatment.
To evaluate the long-term efficacy of ingenol disoxate gel (0.037% for scalp) in AK in an extended 12-month follow-up period after initial complete clearance (AKclear100) at Week 8.

### Methodology
This was an international, randomised, parallel-group, double-blind, vehicle-controlled trial in subjects with AK. Eligible subjects were randomised in a 2:1 ratio to receive either ingenol disoxate 0.037% gel or vehicle gel. Subjects were stratified by trial site.
The subjects applied the investigational medicinal product (IMP) to the selected treatment area for 3 consecutive days (Day 1, Day 2, and Day 3) and then attended visits at Days 4 and 8, and Weeks 2, 4, and 8 (follow-up period), and at Months 5, 8, 11, and 14 (extended 12-month follow-up period). The number of clinically typical and visible actinic keratoses (AKs) present in the treatment area was counted at Day 1 (baseline AK count) and at all visits from Week 4 until Month 14. Local skin responses (LSRs) and adverse events (AEs) were assessed at baseline and all subsequent visits until Week 8; from Week 8 until Month 14, AEs occurring in the treatment area were assessed.

### Number of Subjects Planned and Analysed
306 subjects were planned to be randomised in a 2:1 ratio to the 2 treatment groups. 316 subjects were randomised.
313 subjects were treated with IMP and analysed for efficacy and safety.

### Diagnosis and Main Criteria for Inclusion
**Diagnosis:** Actinic keratosis

**Main criteria for inclusion:**
Subjects with 5 to 20 clinically typical, visible, and discrete AKs within a treatment area of sun-damaged skin on the full balding scalp (the balding part of the scalp was to be greater than 25 cm² [4 in²] and up to approximately 250 cm² [40 in²]). Subjects at least 18 years of age.

### Test Product, Dose and Mode of Administration, Batch Number
**Ingenol disoxate (LEO 43204) 0.037% gel,** applied topically once daily on the full balding scalp (25 to 250 cm²), batch P15022

### Duration of Treatment
3 consecutive days

### Reference Product, Dose and Mode of Administration, Batch Number
Vehicle gel, applied topically once daily on the full balding scalp (25 to 250 cm²), batch P14075
Criteria for Evaluation

Primary endpoint
AKclear100 at Week 8, defined as no clinically visible AKs in the treatment area.

Secondary endpoints
AKclear75 at Week 8, defined as at least 75% reduction in the number of clinically visible AKs in the treatment area.
AKclear75 at Week 4.
Percent reduction in AK count in the treatment area at Week 8 compared to baseline.
Safety and Efficacy of ingenol disoxate gel

Safety:
Incidence of AEs and serious AEs (SAEs).
Incidence and severity of LSRs following treatment.
Scarring.
Clinical laboratory evaluations.
Physical examination and vital signs.
12-lead electrocardiograms.

Statistical Methods

Efficacy:
The primary efficacy analyses were performed on the full analysis set. The analysis of AKclear100 at Week 8 was a comparison between the 2 treatment groups at a significance level of 5% using Fisher’s exact test. The secondary endpoints AKclear75 at Week 8 and AKclear75 at Week 4 were analysed using a Cochran-Mantel-Haenszel test adjusting for pooled site. Percent reduction in AK count at Week 8 was analysed using a negative binomial regression for the AK count at Week 8 including the log baseline AK count as offset and treatment group and pooled site as factors. The Holm-Bonferroni method was used to account for multiplicity in the analyses of the secondary endpoints. Last observation carried forward was used to handle missing data.

Safety:
Safety evaluations were based on the safety analysis set and were descriptive only.

Summary of Results

Trial Population
313 subjects were treated (209 subjects randomised to ingenol disoxate gel; 104 subjects randomised to vehicle) with at least 1 application/dose of IMP, and 301 subjects (ingenol disoxate gel: 207 subjects; vehicle: 94 subjects) completed the 8-week follow-up period. 275 subjects (ingenol disoxate gel: 194 subjects; vehicle: 81 subjects) completed the extended 12-month follow-up period. Over 90% of subjects in each group (ingenol disoxate gel: 90.9%; vehicle: 94.2%) received 3 days of treatment with the IMP according to the protocol.

Efficacy Results

Primary endpoint:
The AKclear100 rate at Week 8 was 25.8% in the ingenol disoxate gel group, whereas no subjects in the vehicle group achieved AKclear100. The difference between the treatment groups was statistically significant (p<0.001). Similar results were seen in the pre-protocol analysis and in sensitivity analyses varying the imputation method.

Secondary endpoints:
The AKclear75 rate at Week 8 was higher in the ingenol disoxate gel group compared with the vehicle group (58.9% versus 1.0%). The difference in AKclear75 rates at Week 8 between the treatment groups was statistically significant (Mantel-Haenszel adjusted relative risk (RR) 62.59, 95% confidence interval [CI]: 8.68–451.08, p<0.001).
The AKclear75 rate at Week 4 was higher in the ingenol disoxate gel group compared with the vehicle group (57.4% versus 1.0%), and the difference between the treatment groups was statistically significant (Mantel-Haenszel adjusted RR 59.21, 95% CI: 8.44–415.35, p<0.001).
The percent reduction from baseline in AK count at Week 8 was greater in the ingenol disoxate gel group compared with the vehicle group (72.3% versus -2.0%). The rate ratio for AK count at Week 8 was 0.27 (95% CI: 0.23–0.32), and the difference between the treatment groups was statistically significant (p<0.001).

Safety Results

During the treatment period and 8-week follow-up period, 378 AEs were reported by 164 subjects (78.5%) in the ingenol disoxate gel group and 52 AEs were reported by 38 subjects (36.5%) in the vehicle group. Most of the AEs reported in subjects treated with ingenol disoxate gel (302 AEs in 156 subjects [74.6%]) were assessed as related to the IMP. The majority of related AEs in this group were administration site reactions inside the treatment area, reported by 67.0% of subjects; by lowest-level term, these were most commonly application site pain (36.8%), application site burning (31.1%), and application site pruritus (30.1%). Severe AEs were reported by 17 subjects (8.1%) in the ingenol disoxate gel group and 2 subjects (1.9%) in the vehicle group. By preferred term, the severe AEs in the ingenol disoxate gel group were 11 events
of application site pain, and 1 event each of application site pruritus, face oedema, chills, pyrexia, headache, conjunctivitis, appendicitis perforated, neoplasm of appendix, pain in extremity, and epistaxis.

Only 1 subject, in the vehicle group, withdrew from the trial due to an AE. 3 subjects, all in the ingenol disoxate gel group, discontinued treatment due to AEs (2 subjects due to application site pain and 1 subject due to conjunctivitis). No deaths were reported; SAEs were reported in 4 subjects in the ingenol disoxate gel group and 2 subjects in the vehicle group; all were assessed as not related to the IMP. No AEs of special interest (squamous cell carcinoma) were reported.

Most subjects in the ingenol disoxate gel group experienced a post baseline increase in LSR score for 1 or more components (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, erosion/ulceration). The 6 individual LSR components were evaluated by the LSR grading scale and a composite LSR score (0–24) was calculated. The maximum composite LSR score (mean value) was 11.3 in the ingenol disoxate gel group and 1.8 in the vehicle group. The composite LSR score peaked at Day 4 for approximately 70% of subjects treated with ingenol disoxate gel. The mean composite LSR score in this group was 10.5 at Day 4, declining to reach mild levels (3.8) by Week 2, 1.5 at Week 4, and 1.0 at Week 8.

After Week 8, when only AEs in the treatment area were to be collected, 36 AEs were reported for 29 subjects (14.2%) in the ingenol disoxate gel group, compared with 18 AEs for 14 subjects (16.3%) in the vehicle group. The most frequent AEs by preferred term were application site scar (ingenol disoxate gel: 10 subjects [4.9%] versus vehicle: 7 subjects [8.1%]), post-inflammatory pigmentation change (5 subjects [2.5%] versus 5 subjects [5.8%]), and squamous cell carcinoma of skin (5 subjects [2.5%] versus 1 subject [1.2%]). 3 of 204 subjects in the ingenol disoxate gel group and 1 of 86 subjects in the vehicle group had a diagnosis of squamous cell carcinoma on the scalp as evaluated by the Independent Adjudication Committee (consisting of 3 specialists in dermatology); the subject in the vehicle group had 2 such events. 2 investigator-reported events of squamous cell carcinoma in the ingenol disoxate gel group were downgraded by the committee to Bowen’s disease. 1 severe AE of application site scab and 1 severe AE of malignant melanoma were reported, both in subjects in the ingenol disoxate gel group. The malignant melanoma was classified as serious and was assessed by the investigator as possibly related to IMP. Based on possible alternative causality, the sponsor considered the event not related to IMP. No other SAEs were reported. No subjects in either treatment group withdrew from the trial due to an AE.

Conclusion

In this trial, ingenol disoxate gel 0.037% was applied once daily for 3 consecutive days on the scalp in adults. Ingenol disoxate gel was superior to vehicle for the primary and all secondary efficacy endpoints at 8 weeks.

The local skin response was transient and typically peaked the day after the last treatment. On average, LSRs declined to reach mild levels within 2 weeks of treatment initiation and resolved within 4 weeks. The types and frequency of AEs were as expected, with the most common events being application site pain and pruritus. During the 12-month extended follow-up period a higher frequency of Bowen’s disease was observed in subjects treated with ingenol disoxate gel than in subjects treated with vehicle. A possible explanation for the difference in frequencies is detection bias.
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