Clinical Trial Report Synopsis

Efficacy and Safety of LEO 43204 in Field Treatment of Actinic Keratosis on Face or Chest 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).
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:

PPD, M.Sc. Stat
Biostatistics Lead
Global Clinical Operations

PPD, 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:

Michael Bukhalo, MD
International coordinating investigator
Trial Registration Number  
NCT02549339

EudraCT number  
2015-002450-12

Title of Trial  
Efficacy and Safety of LEO 43204 in Field Treatment of Actinic Keratosis on Face or Chest including 12-month follow-up

Investigators  
Dr. Michael Bukhalo was the international coordinating investigator.

Trial Sites  
This trial was conducted at 23 sites (21 of which randomised subjects) in 4 countries (United States, United Kingdom, France, and Spain) and coordinated at Altman Dermatology Associates, Arlington Heights, Illinois, United States.

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

Clinical Trial Period  
Date of First Subject First Visit: 24-Nov-2015  
Date of Last Subject Last Visit: 14-Nov-2017  
Development Phase  
Phase 3

Objectives  
Primary objective  
To confirm the efficacy of ingenol disoxate gel (0.018% for face or chest) 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 (0.018% for face or chest) in AK when applied topically once daily for 3 consecutive days as field treatment.

To evaluate the long-term efficacy of ingenol disoxate gel (0.018% for face or chest) 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 0.018% gel or vehicle gel. Subjects were stratified by trial site. Enrolment was controlled so that between 15% and 25% of all enrolled subjects were treated on the chest.

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. 307 subjects were randomised. 305 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 face or chest (a contiguous area of 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) 0.018% gel, applied topically once daily on the face or chest (a contiguous area of approximately 250 cm²), batch P14083

Duration of Treatment  
3 consecutive days

Reference Product, Dose and Mode of Administration, Batch Number  
Vehicle gel, applied topically once daily on the face or chest (a contiguous area of approximately 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.

Safety and tolerability of ingenol disoxate gel.

Percent reduction in AK count in the treatment area at Week 8 compared to baseline.

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 a Cochran-Mantel-Haenszel test adjusting for pooled site. The secondary endpoints AKclear75 at Week 8 and AKclear75 at Week 4 were analysed in the same manner as the primary endpoint. Percent reduction in AK count at Week 8 was analysed using a negative binomial regression model 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. A multiple imputation method 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
305 subjects were treated (205 subjects randomised to ingenol disoxate gel; 100 subjects randomised to vehicle) with at least 1 application/dose of IMP, and 295 subjects (ingenol disoxate gel: 203 subjects; vehicle: 92 subjects) completed the 8-week follow-up period. 252 subjects (ingenol disoxate gel: 185 subjects; vehicle: 67 subjects) completed the extended 12-month follow-up period. 91.5% of subjects (ingenol disoxate gel: 88.3%; vehicle: 98.0%) received 3 days of treatment with the IMP in accordance with the protocol.

Efficacy Results

Primary endpoint:
The AKclear100 rate at Week 8 was higher in the ingenol disoxate gel group compared with the vehicle group (31.3% versus 1.0%), and the difference between the treatment groups was statistically significant (Mantel-Haenszel adjusted relative risk [RR] 30.55, 95% confidence interval [CI]: 4.28–218.0, p<0.001). Similar results were seen in the per-protocol analysis, in sensitivity analyses varying the imputation method, and in the sensitivity analysis without pooling sites.

Secondary endpoints:
The AKclear75 rate at Week 8 was higher in the ingenol disoxate gel group compared with the vehicle group (55.8% versus 4.6%). The difference in AKclear75 rates at Week 8 between the treatment groups was statistically significant (Mantel-Haenszel adjusted RR 12.26, 95% CI: 4.73–31.78, p<0.001).

The AKclear75 rate at Week 4 was higher in the ingenol disoxate gel group compared with the vehicle group (56.6% versus 5.5%), and the difference between the treatment groups was statistically significant (Mantel-Haenszel adjusted RR 10.31, 95% CI: 4.43–23.97, 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 (72.1% versus 7.3%). The rate ratio for AK count at Week 8 was 0.30 (95% CI: 0.25–0.37, p<0.001).

Safety Results

During the treatment period and 8-week follow-up period, 333 AEs were reported for 150 subjects (73.2%) in the ingenol disoxate gel group compared with 22 AEs for 16 subjects (16.0%) in the vehicle group. Most of the AEs reported in subjects treated with ingenol disoxate gel (271 AEs in 136 subjects [66.3%]) 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 63.9% of subjects; by lowest-level term, these were most commonly application site burning (42.9%), followed by application site pruritus (34.6%) and application site pain (26.8%). Severe AEs were reported by 14 subjects (6.8%) in the ingenol disoxate gel group and no subjects in the vehicle group. By preferred term, the severe AEs in the ingenol disoxate gel group were
9 events of application site pain, and application site discomfort, application site pruritus, jaundice, liver function test abnormal, pyrexia, renal pain, rib fracture, and squamous cell carcinoma of skin (1 event for each).

1 subject (0.5%) in the ingenol disoxate gel group withdrew from the trial due to an AE (lethargy). 7 subjects (3.4%, with 12 events) in the ingenol disoxate gel group, compared with no subjects in the vehicle group, discontinued IMP due to an AE. By preferred term, the most frequent events leading to discontinuation were application site pain (5 subjects [2.4%]) and application site pruritus (2 subjects [1.0%]). No deaths were reported; 7 SAEs were reported for 2 subjects (1.0%) in the ingenol disoxate gel group compared with no subjects in the vehicle group. 1 event (rib fracture) was assessed as not related to IMP. Of the 6 SAEs occurred in 1 subject in connection with 1 hospitalisation and were assessed by the investigator as possibly related to the IMP (severe pyrexia, dehydration, hyponatraemia, jaundice, liver function test abnormal, and pancytopenia, all with an onset on the same day). No diagnosis of squamous cell carcinoma or keratoacanthoma was reported by the Independent Adjudication Committee (consisting of 3 specialists in dermatology). 1 investigator-reported event of squamous cell carcinoma in a subject in the ingenol disoxate gel group was downgraded by the committee to Bowen’s disease.

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 post-baseline composite LSR score (mean value) was 12.0 in the ingenol disoxate gel group and 1.9 in the vehicle group. In the ingenol disoxate gel group, the composite LSR score peaked at Day 4 for 87.3% of the subjects. The mean composite LSR score in this group was 11.6 at Day 4, declining to reach mild levels (2.6) at Week 2, 1.2 at Week 4, and 1.0 at Week 8.

After Week 8, when only AEs in the treatment area were to be collected, 45 AEs were reported for 35 subjects (17.6%) in the ingenol disoxate gel group, compared with 9 AEs for 8 subjects (9.5%) in the vehicle group. The most frequent AEs by preferred term were squamous cell carcinoma of skin (ingenol disoxate gel: 10 subjects [5.0%] versus vehicle: 1 subject [1.2%]) and basal cell carcinoma (9 subjects [4.5%] versus 1 subject [1.2%]). 9 of the 199 subjects in the ingenol disoxate gel group and 1 of the 84 subjects in the vehicle group had a diagnosis of squamous cell carcinoma in the treatment area, as evaluated by the Independent Adjudication Committee. In the ingenol disoxate gel group, 1 further investigator-reported event of squamous cell carcinoma was reclassified as keratoacanthoma and 2 investigator-reported events of squamous cell carcinoma (both in the same subject) were downgraded to AK by the committee. No severe AEs were reported. No subjects in either treatment group withdrew from the trial due to an AE, and no SAEs in the treatment area were reported.

**Conclusion**

In this trial, ingenol disoxate gel 0.018% was applied once daily for 3 consecutive days on the face or chest 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 squamous cell carcinoma and basal cell carcinoma 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.
<table>
<thead>
<tr>
<th>Reason for signing: Approved</th>
<th>Management / Lead Approver Verdict(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Name: PPD</td>
</tr>
<tr>
<td></td>
<td>Capacity: Medical</td>
</tr>
<tr>
<td></td>
<td>Date of signature: 19-Mar-2018 08:30:07 GMT+0000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for signing: Approved</th>
<th>Management / Lead Approver Verdict(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Name: PPD</td>
</tr>
<tr>
<td></td>
<td>Capacity: Biostatistics</td>
</tr>
<tr>
<td></td>
<td>Date of signature: 21-Mar-2018 15:22:50 GMT+0000</td>
</tr>
</tbody>
</table>