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).

LEO Pharma A/S

Trial ID: LP0084-1194
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:

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:

C. William Hanke, MD
International coordinating investigator
**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. C. William Hanke was international coordinating investigator.

**Trial Sites**
This trial was conducted at 22 sites in 5 countries (United States, Canada, Germany, Spain, and Italy) and coordinated at the Laser & Skin Surgery Center of Indiana, Carmel, Indiana, United States.

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

**Clinical Trial Period**
| Date of First Subject First Visit: 20-Nov-2015 | Development Phase |
| Date of Last Subject Last Visit: 10-Aug-2017 | 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 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. 309 subjects were randomised. 306 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**
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 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**
306 subjects were treated (202 subjects randomised to ingenol disoxate gel; 104 subjects randomised to vehicle) with at least 1 application/dose of IMP, and 300 subjects (ingenol disoxate gel: 201 subjects; vehicle: 99 subjects) completed the 8-week follow-up period. 279 subjects (ingenol disoxate gel: 192 subjects; vehicle: 87 subjects) completed the extended 12-month follow-up period. Over 90% of subjects in each group (ingenol disoxate gel: 90.1%; vehicle: 98.1%) 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 (20.4% versus 2.9%), and the difference between the treatment groups was statistically significant (Mantel-Haenszel adjusted relative risk [RR] 7.57, 95% confidence interval [CI]: 2.26–25.31, 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 (60.3% versus 10.7%). The difference in AKclear75 rates at Week 8 between the treatment groups was statistically significant (Mantel-Haenszel adjusted RR 5.90, 95% CI: 3.30–10.54, p<0.001).

The AKclear75 rate at Week 4 was higher in the ingenol disoxate gel group compared with the vehicle group (61.1% versus 10.8%), and the difference between the treatment groups was statistically significant (Mantel-Haenszel adjusted RR 5.75, 95% CI: 3.24–10.20, 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 (74.8% versus 15.0%). The rate ratio for AK count at Week 8 was 0.30 (95% CI: 0.25–0.35, p<0.001).

**Safety Results**
During the treatment period and 8-week follow-up period, 300 AEs were reported by 136 subjects (67.3%) in the ingenol disoxate gel group and 52 AEs were reported by 32 subjects (30.8%) in the vehicle group. Most of the AEs reported in subjects treated with ingenol disoxate gel (236 AEs in 124 subjects [61.4%]) 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 56.9% of subjects; by lowest-level term, these were most commonly application site burning (46.0%), followed by application site pruritus (31.2%) and application site pain (24.3%). Severe AEs were reported by 20 subjects (9.9%) 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...
16 events of application site pain, 9 events of application site pruritus, 2 events of application site discomfort, and 1 event each of application site paraesthesia and laceration.

8 subjects (with 16 events) in the ingenol disoxate gel group, and 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 (8 subjects [4.0%]) and application site pruritus (4 subjects [2.0%]). No SAEs were reported. No diagnosis of squamous cell carcinoma or keratoacanthoma was reported by the Independent Adjudication Committee (consisting of 3 specialists in dermatology). 2 investigator-reported events of squamous cell carcinoma (both in the same subject) in the ingenol disoxate gel group were downgraded to AK by the committee, and 1 investigator-reported event of squamous cell carcinoma in another subject in this group was downgraded 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 11.5 in the ingenol disoxate gel group and 2.0 in the vehicle group. In the ingenol disoxate gel group, the composite LSR score peaked at Day 4 for 86.6% of the subjects. The mean composite LSR score in this group was 11.1 at Day 4, 7.4 at Day 8, 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 (17.4%) in the ingenol disoxate gel group, compared with 17 AEs for 14 subjects (14.3%) in the vehicle group. The most frequent AEs by preferred term were Bowen’s disease (ingenol disoxate gel: 10 subjects [5.0%] versus vehicle: 2 subjects [2.0%]), basal cell carcinoma (9 subjects [4.5%] versus 1 subject [1.0%]), and squamous cell carcinoma of skin (7 subjects [3.5%] versus 3 subjects [3.1%]). 5 of the 201 subjects in the ingenol disoxate gel group and 3 of the 98 subjects in the vehicle group had a diagnosis of squamous cell carcinoma on the face or chest as evaluated by the Independent Adjudication Committee. 2 investigator-reported events of squamous cell carcinoma in the ingenol disoxate gel group were downgraded by the committee to Bowen’s disease and AK, respectively. No severe AEs were reported. No subjects in either treatment group withdrew from the trial due to an AE. 1 SAE (squamous cell carcinoma of skin) was reported in the ingenol disoxate gel group; the event, assessed as not related to IMP, was classified as an SAE because the subject was hospitalised. No deaths 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 basal cell carcinoma and 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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