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 requiremen(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, MSc Stat
Biostatistics Lead
Biometrics

PPD, MD PhD
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:

Rolf-Markus Szeimies, MD
International coordinating investigator


**Trial Registration Number**  
NCT02549352  

**EudraCT number**  
2015-002452-27  

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

**Investigators**  
Prof. Dr. med. Rolf-Markus Szeimies was international coordinating investigator.  

**Trial Sites**  
This trial was conducted at 23 sites in 3 countries (United States, Germany, and Italy) and coordinated at the Klinik für Dermatologie & Allergologie, Klinikum Vest, Recklinghausen, Germany.  

**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 (0.037% 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. 311 subjects were randomised. 310 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.
- AKcount at Week 8.
- 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 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
310 subjects were treated (209 subjects randomised to ingenol disoxate gel; 101 subjects randomised to vehicle) with at least 1 application/dose of IMP, and 303 subjects (ingenol disoxate gel: 207 subjects; vehicle: 96 subjects) completed the 8-week follow-up period. 280 subjects (ingenol disoxate gel: 199 subjects; vehicle: 81 subjects) completed the extended 12-month follow-up period. Approximately 90% of subjects in each group received 3 days of treatment with the IMP according to 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 (22.0% versus 3.0%), and the difference between the treatment groups was statistically significant (Mantel-Haenszel adjusted relative risk [RR] 7.83, 95% confidence interval [CI]: 2.58-23.71, 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 (63.1% versus 11.0%). The difference in AKclear75 rates at Week 8 between the treatment groups was statistically significant (Mantel-Haenszel adjusted RR 5.91, 95% CI: 3.32-10.51, p<0.001).

The AKclear75 rate at Week 4 was higher in the ingenol disoxate gel group compared with the vehicle group (53.4% versus 7.1%), and the difference between the treatment groups was statistically significant (Mantel-Haenszel adjusted RR 7.59, 95% CI: 3.70-15.61, 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 (74.0% versus 13.7%). The rate ratio for AK count at Week 8 was 0.30 (95% CI: 0.25-0.36), 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, 374 AEs were reported by 165 subjects (78.6%) in the ingenol disoxate gel group and 64 AEs were reported by 38 subjects (38.0%) in the vehicle group. Most of the AEs reported in subjects treated with ingenol disoxate gel (292 AEs in 151 subjects [71.9%]) 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 64.8% of subjects; by lowest-level term, these were most commonly application site burning (33.3%), application site pruritus (32.4%), and application site pain (27.1%). Severe AEs were reported by 15 subjects (7.1%) in the ingenol disoxate gel group and
3 subjects (3.0%) in the vehicle group. By preferred term, the severe AEs in the ingenol disoxate gel group were 9 events of application site pain, 3 events of application site pruritus, 2 events of insomnia, and 1 event each of eyelid oedema, headache, dizziness, swelling face, angina pectoris, and nephrolithiasis. Only 1 subject, in the vehicle group, withdrew from the trial due to an AE. In the ingenol disoxate gel group, 6 subjects (2.9%) discontinued treatment due to AEs (all application site pain); in the vehicle group, 2 subjects (2.0%) discontinued due to AEs, 1 due to a hypertensive crisis and 1 (who also withdrew from the trial) due to application site pain, ear discomfort, and asthenopia. No deaths were reported. SAEs were reported in 3 subjects in each 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 post-baseline composite LSR score (mean value) was 10.8 in the ingenol disoxate gel group and 2.7 in the vehicle group. The composite LSR score peaked at Day 4 for 70% of subjects treated with ingenol disoxate gel. The mean composite LSR score in this group was 10.0 at Day 4, declining to reach mild levels (4.0) by Week 2, 1.7 at Week 4, and 1.1 at Week 8.

After Week 8, when only AEs in the treatment area were to be collected, 19 AEs were reported for 16 subjects (7.7%) in the ingenol disoxate gel group, compared with 3 AEs for 2 subjects (2.2%) in the vehicle group. The most frequent AEs by preferred term were squamous cell carcinoma of skin (ingenol disoxate gel: 5 subjects [2.4%] versus vehicle: 1 subject [1.1%]), application site scar (1 subject [0.5%] versus 2 subjects [2.2%]), and Bowen’s disease and pemphigoid (each 2 subjects [1.0%] versus no subjects). 2 subjects in the ingenol disoxate gel group had a diagnosis of squamous cell carcinoma in the treatment area, as evaluated by the Independent Adjudication Committee (consisting of 3 specialists in dermatology); there were no confirmed cases of squamous cell carcinoma in the vehicle group. 3 investigator-reported events of SCC in the ingenol disoxate gel group and 1 event in the vehicle group were downgraded to AK or Bowen’s disease by the committee. No severe AEs were reported, no subjects withdrew from the trial due to an AE, and no SAEs in the treatment area were reported.

**Conclusion**

In this trial, ingenol disoxate gel 0.037% 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 squamous 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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