Clinical Study Report Synopsis

Efficacy and safety of ingenol mebutate gel 0.015% compared to diclofenac sodium gel 3% in subjects with actinic keratoses on the face or scalp

A phase 4 trial

A multi-centre, randomized, two group, open label, active controlled, parallel group, 17 week trial

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).

LEO Pharma A/S

Trial ID: LP0041-1120
Date: 15-Dec-2016
Version: 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:

Kim Mark Knudsen, PhD

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Biostatistics Lead, Global Clinical Operations

Torsten Skov, MD

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Medical Lead, Medical Sciences and Safety

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:

Prof. Dr. med. Eggert Stockfleth

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International coordinating investigator
Title of Trial
Efficacy and safety of ingenol mebutate gel 0.015% compared to diclofenac sodium gel 3% in subjects with actinic keratoses on the face or scalp

Investigators
Prof. Dr. med. Eggert Stockfleth, Direktor der Universitätshautklinik St. Josef-Hospital, Bochum, Germany was appointed as signatory investigator.

Trial Centres
This trial was conducted at 33 centres in 3 countries (Germany, Spain and the United Kingdom) and coordinated by the signatory investigator.

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

Clinical Trial Period
Date of First Subject First Visit: 21-Apr-2015
Date of Last Subject Last Visit: 10-Jun-2016

Development Phase
Phase 4

Objectives
Primary Objective:
To compare the efficacy of daily application for 3 consecutive days of ingenol mebutate gel 0.015% with the efficacy of diclofenac sodium gel 3% for 90 days in subjects with AK on the face or scalp.

Secondary Objective:
To compare the efficacy of up to two treatment courses of ingenol mebutate gel 0.015% (daily application for 3 consecutive days) with the efficacy of diclofenac sodium gel 3% for 90 days in subjects with AK on the face or scalp.

Methodology
This was a multi-centre, randomised, open-label, active-controlled, parallel group, 17-week trial.
The (sub)investigators were blinded for AK assessments.
The eligible subjects were randomised in a 1:1 ratio to one of 2 treatment groups.
Treatment Group A: Ingenol mebutate gel 0.015%, once daily for 3 consecutive days for the first treatment course. At 8 weeks after treatment initiation, subjects who presented with existing AKs or newly emergent AKs in the treatment area received one more treatment course of ingenol mebutate gel 0.015%, daily for 3 consecutive days.
Treatment Group B: Diclofenac sodium gel 3%, (0.5 grams), twice daily for 90 days.
Trial visits took place at Visit 1 (Day 1) for all subjects, Visit 2 (Day 57, Week 8) for subjects randomised to ingenol mebutate gel 0.015% and Visit 3 (Day 120, Week 17) for all subjects.
Investigator assessments
The treatment areas were identified. Efficacy was assessed by documenting the number of AKs in the treatment area at the treatment visits. The (sub) investigators were blinded when performing the AK assessments at Weeks 8 and 17. Safety was assessed using standard clinical methods of subject evaluations such as AE monitoring.

Subject assessments
The Treatment Satisfaction Questionnaire for Medication (TSQM) was used to capture treatment satisfaction.

Number of Subjects Planned and Analysed
500 randomised subjects were planned and 502 subjects were allocated to treatment (255 in the ingenol mebutate gel 0.015% group and 247 in the diclofenac sodium gel 3% group).

Diagnosis and Main Criteria for Inclusion
**Diagnosis**
Actinic keratosis on the face or scalp (typical, visible, and discrete AKs)

**Main Criteria for Inclusion**
Male or Female subjects had to be at least 18 years and have from 4 to 8 clinically typical, visible or discrete actinic keratoses (AKs) within a contiguous 25 cm² treatment area on the face or scalp.
Female subjects must have been of non-childbearing potential or if of childbearing potential must have provided negative urine pregnancy test and used effective contraception.
 Ability to provide informed consent.
<table>
<thead>
<tr>
<th>Test Product, Dose and Mode of Administration, Batch Numbers</th>
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<tbody>
<tr>
<td>Ingenol mebutate gel 0.015%, topical application on face or scalp, EK0639, EK0868A</td>
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<tr>
<th>Duration of Treatment</th>
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<tr>
<td>For ingenol mebutate gel 0.015% (Treatment Group A), a maximum of 2 treatment courses of once daily for 3 consecutive days, administered within a period of 17 weeks, requiring 3 visits.</td>
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<tr>
<td>For diclofenac sodium gel 3% (Treatment Group B), one treatment course, twice daily for 90 days, administered within a period of 17 weeks, requiring 2 visits.</td>
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<thead>
<tr>
<th>Reference Product, Dose and Mode of Administration, Batch Numbers</th>
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<tr>
<td>Diclofenac sodium gel 3%, topical application on face or scalp, 432861, 439901, 519351</td>
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<tr>
<th>Criteria for Evaluation</th>
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<td><strong>Primary endpoint</strong></td>
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<tr>
<td>Complete clearance of all AKs in the treatment field at Week 8 for ingenol mebutate gel 0.015% and Week 17 for diclofenac sodium gel 3%</td>
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<tr>
<td><strong>Secondary endpoints</strong></td>
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<tr>
<td>Complete clearance at Week 17 for diclofenac sodium gel 3% compared with the following three measures of complete clearance in the ingenol mebutate gel 0.015% group:</td>
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<tr>
<td>- Complete clearance of all AKs in the treatment field after one or two ingenol mebutate treatment courses. Subjects receiving only one treatment course are evaluated at Week 8 and subjects receiving two treatment courses are evaluated at Week 17.</td>
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<tr>
<td>- Complete clearance of all AKs in the treatment field at Week 17</td>
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<tr>
<td>- Complete clearance of all AKs in the treatment field at Week 17 following only one ingenol mebutate treatment course. Subjects receiving a second ingenol mebutate treatment course are considered non-cleared.</td>
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<tr>
<th>Other endpoints</th>
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<tr>
<td>The percent reduction from baseline (Day 1) of the number of AKs in the treatment field at Week 17 for diclofenac sodium gel 3% was compared with the following reductions for ingenol mebutate gel 0.015%:</td>
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<tr>
<td>- Percent reduction from baseline (Day 1) of the AK count in the treatment field at Week 8</td>
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<tr>
<td>- Percent reduction from baseline (Day 1) of the AK count in the treatment field at Week 8 for subjects receiving only one treatment course and at Week 17 for subjects receiving two treatment courses</td>
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<tr>
<td>- Percent reduction from baseline (Day 1) of the AK count in the treatment field at Week 17</td>
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<tr>
<th>Treatment Satisfaction Questionnaire for Medication</th>
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<tr>
<td>The TSQM contained questions related to effectiveness, side effects, convenience, and overall satisfaction</td>
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<tr>
<th>Statistical Methods</th>
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<tr>
<td><strong>Primary endpoint</strong></td>
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<tr>
<td>The complete clearances for ingenol mebutate (Week 8) and diclofenac sodium (Week 17) were analysed in a logistic regression model with factors treatment and anatomical location as fixed effects and site as a random effect. Subjects were considered not to have achieved complete clearance if the assessment of AK lesion count had not been performed or was missing for other reasons.</td>
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<tr>
<td><strong>Secondary endpoints</strong></td>
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<tr>
<td>The analysis of the secondary endpoints followed the method described for the primary endpoint.</td>
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<tr>
<td><strong>Other endpoints</strong></td>
</tr>
<tr>
<td>The reduction in AK count at Week 8 for ingenol mebutate and Week 17 for diclofenac sodium were analysed by negative binomial regression on the number of lesions, including the log baseline AK count as an offset and with treatment group and anatomical location as fixed effects and site as a random effect. The analysis of the remaining endpoints pertaining to reduction in AK count followed the same method.</td>
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<tr>
<td><strong>Treatment Satisfaction Questionnaire for Medication</strong></td>
</tr>
<tr>
<td>TSQM transformed scores were analysed for each domain (effectiveness, side effects, convenience, global satisfaction) using a linear mixed model with factors treatment group, anatomical location, and site as a random effect.</td>
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Summary of Results

Trial Population

Out of the 511 subjects screened, 502 subjects were randomised in the trial with 255 in the ingenol mebutate group and 247 subjects in the diclofenac sodium group. The trial population reflected the general population treated for AK, mostly consisting of men with fair skin. The treatment groups were well matched with respect to age, sex, skin type and duration of disease. Most subjects had previously been treated for AK and approximately half of trial population had a history of skin malignant tumours. The median duration of AK was 4 years, and the median number of AKs at baseline was 6.

Efficacy Results

- For the primary endpoint, complete clearance (baseline observation carried forward (BLOCF)) at the end of the first treatment course was 34.5% in the ingenol mebutate treatment group (Week 8) and 23.5% in the diclofenac sodium group (Week 17), p=0.006.
- Complete clearance following the last treatment course (BLOCF) was 53.3% for ingenol mebutate and 23.5% for diclofenac sodium (p<0.001).
- Complete clearance at Week 17 (BLOCF) was 45.1% for ingenol mebutate and 23.5% for diclofenac sodium (p<0.001).
- Complete clearance at Week 17 following a single treatment course (BLOCF) was 26.3% for ingenol mebutate and 23.5% for diclofenac sodium (p=0.51).
- The results for percent reduction in AK count were generally in accordance with the results for complete clearance where there was a larger overall effect for the 3 treatment comparisons with ingenol mebutate (Week 8, after last treatment course, and Week 17) as compared to diclofenac sodium at Week 17.
- The percent reduction in AK count (BLOCF) at Week 8 (ingenol mebutate) versus Week 17 (diclofenac sodium) was 69.5% for ingenol mebutate and 57.7% for diclofenac sodium (p<0.001).
- The percent reduction in AK count after last treatment course (BLOCF) was 80.2% for ingenol mebutate and 57.7% for diclofenac sodium (p<0.001).
- The percent reduction in AK at Week 17 was 77.2% for ingenol mebutate and 57.7% for diclofenac sodium (p<0.001).

Treatment satisfaction

- Mean global satisfaction scores (TSQM) were statistically significantly greater in ingenol mebutate versus diclofenac sodium for 2 of the 4 domains.
  - The mean global satisfaction scores were 73.7 for ingenol mebutate and 65.4 for diclofenac sodium (p<0.001).
  - The mean effectiveness scores were 71.9 for ingenol mebutate and 64.4 for diclofenac sodium (p=0.002).
  - The mean side effects scores were 93.9 for ingenol mebutate and 93.6 for diclofenac sodium (p=0.62).
  - The mean convenience scores were 80.1 for ingenol mebutate and 81.0 for diclofenac (p=0.53).

Safety Results

- There were 2 SAEs leading to death in this trial. Both events (myocardial infarction and granulomatosis with polyangiitis) occurred in the diclofenac sodium group and the events were considered not related to IMP as assessed by the investigator.
- No SAEs were considered related to treatment with IMP.
- There were 6 subjects in the ingenol mebutate group and 17 subjects in the diclofenac sodium group who withdrew from trial due to adverse events. The 2 subjects with fatal outcomes are also counted in among the subjects who withdrew due to adverse events.
- The percentage of subjects reporting adverse events was 49.4% for ingenol mebutate and 40.6% for diclofenac sodium.
- For the ingenol mebutate group, out of 246 adverse events 115 (46.7%) were rated as mild and 95 (38.6%) were rated as moderate.
- For the diclofenac sodium group, out of 176 adverse events 87 (49.4%) were rated as mild and 68 (38.6%) were rated as moderate.
- Most adverse events in both treatment groups were assessed as related to investigational medicinal product by the investigator.
Most of the adverse events considered related to the investigational medicinal product were recorded as recovered or recovering.

In both treatment groups application site erythema was the most common administration site reaction (by lowest level term): 19.0% of subjects for ingenol mebutate and 11.5% of subjects for diclofenac sodium.

Overall there was a shorter duration of AEs following treatment with ingenol mebutate as compared to diclofenac sodium.

**Conclusion**

In this trial ingenol mebutate gel 0.015% demonstrated greater efficacy as compared to diclofenac sodium gel 3% in a ‘real life’ setting. The safety profiles of both treatments were as expected.