Clinical Trial Report Synopsis

Efficacy and Safety of Ingenol Mebutate Gel in Field Treatment of Actinic Keratosis on Full Face, Balding Scalp or Approximately 250 cm² on the Chest

Design of trial:

Part 1: 3-day treatment period including an 8-week follow-up period
  Part 2: extended 12-month follow-up period

An international, phase 3, randomised, parallel group, double-blind, vehicle-controlled trial

The clinical trial, including the archival of essential documents, was conducted in compliance with the clinical trial protocol, GCP, and the applicable regulatory requirements.
Clinical Trial Report Synopsis Statement

Approval Statement, LEO Pharma A/S

The following persons have approved this clinical trial report synopsis using electronic signatures as presented on the last page of this document:

PPD, MSc Stat
PPD, Biometrics

PPD, MD, PhD
PPD, Medical Science and Safety

Approval Statement, International Coordinating Investigator

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

The following person has approved this clinical trial report synopsis:

C. William Hanke, MD, MPH
International coordinating investigator
**Trial Registration Number**
NCT02361216

**EudraCT number**
Not applicable

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<tr>
<th><strong>Title of Trial</strong></th>
<th>Efficacy and Safety of Ingenol Mebutate Gel in Field Treatment of Actinic Keratosis on Full Face, Balding Scalp or Approximately 250 cm² on the Chest.</th>
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<th><strong>Investigators</strong></th>
<th>C. William Hanke, MD, MPH, Laser &amp; Skin Surgery Center of Indiana, United States (US), was appointed as signatory investigator.</th>
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<th><strong>Trial Sites</strong></th>
<th>This trial was conducted at 50 sites in 3 countries (US, Canada, Australia) and coordinated at LEO Pharma A/S.</th>
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<th><strong>Publications:</strong></th>
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<th><strong>Development Phase</strong></th>
<th>Phase 3</th>
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| **Clinical Trial Period** | **Part 1:** Date of First Subject First Visit: 23-Apr-2015  
Date of Last Subject Last Visit: 02-Feb-2016  
**Part 2:** Date of Last Subject Last Visit: 22-Feb-2017 |

| **Objectives** | **Primary objective**  
To compare the short-term efficacy of ingenol mebutate gel 0.027% with vehicle gel in actinic keratosis (AK) when applied topically once daily for 3 consecutive days as field treatment.  
**Secondary objectives**  
To evaluate the long-term efficacy of ingenol mebutate gel 0.027% in AK in an extended 12-month follow-up period after initial AKclear100 at Week 8 (AKclear100 was defined as ‘complete clearance’ in the protocol),  
To evaluate the safety of ingenol mebutate gel 0.027% in AK when applied topically once daily for 3 consecutive days as field treatment. |

| **Methodology** | This was an international, phase 3, randomised, parallel group, double-blind, vehicle-controlled trial consisting of 2 parts.  
Part 1 consisted of a 3-day treatment period including an 8-week follow-up period.  
Part 2 consisted of an extended 12-month follow-up period. |

| **Number of Subjects Planned and Analysed** | A total of 720 subjects were planned and 729 subjects were randomised to treatment in a 3:1 ratio. |

| **Diagnosis and Main Criteria for Inclusion** | 1. Signed and dated informed consent has been obtained.  
2. Subjects with 5 to 20 clinically typical, visible and discrete AKs within a selected treatment area of sun-damaged skin on either: the full face, the full balding scalp (the balding part of the scalp should be greater than 25 cm² and up to approximately 250 cm²), or a contiguous area of approximately 250 cm² on the chest.  
3. Subject at least 18 years of age.  
4. Female subjects of childbearing potential* must be confirmed not pregnant by a negative urine pregnancy test prior to trial treatment.  
5. Female subjects of childbearing potential* must be willing to use effective contraception at trial entry and until Visit 7/Week 8. |

| **Test Product, Dose and Mode of Administration, Batch Number** | Ingenol mebutate gel 0.027%, applied topically on the full face/full balding scalp or within a contiguous area of approximately 250 cm² on the chest; daily maximum 2 unit dose tubes.  

| **Duration of Treatment** | Once daily for 3 consecutive days approximately at the same time of the day. |
Reference Product, Dose and Mode of Administration, Batch Number
Vehicle gel containing ingenol mebutate, applied topically on the full face/full balding scalp or within a contiguous area of approximately 250 cm² on the chest; daily maximum 2 unit dose tubes.
Batch number/expiry date: P14028/Jun-2016

Criteria for Evaluation
Primary endpoint
- AKclear100 at Week 8, defined as no clinically visible AKs in the selected treatment area

Secondary endpoints
- AKclear75 Week 8, defined as at least 75% reduction in the number of clinically visible AKs in the selected treatment area (AKclear75 was defined as ‘partial clearance’ in the protocol)
- AKclear75 at Week 4
- Percent reduction in AK count in the selected treatment area at Week 8 compared to baseline

Statistical Methods
All significance tests were two-sided using the 5% significance level with the exception of tests for treatment by analysis site interactions, which were made at the 10% level. All confidence intervals (CI) are presented with 95% degree of confidence.
An observed cases approach was used for tabulations of data by visit (i.e. involving only those subjects who attended each specific visit). Missing values of AK counts at Week 4 and/or Week 8 were imputed using multiple imputations.
To account for multiplicity, the p-values from the 3 secondary endpoint analyses were adjusted using the Holm-Bonferroni method.
A pre-specified pooling procedure was used to pool trial sites that recruited too few subjects for analysis.
In Part 1, all subjects were included in the full analysis set (FAS) and analysed for efficacy. 2 per-protocol (PP) analysis sets for Week 4 (PP4) and Week 8 (PP8) were used to support the results obtained for the FAS. In Part 2, the follow-up analysis set (FUAS) was used for safety evaluations after Week 8. The AKclear100 at Week 8 analysis set (CCW8; AKclear100 was called ‘complete clearance’ in the protocol) was used for analysis of the secondary trial objective on long-term efficacy.
Categorical data are summarised using the number and percentage of subjects in each category and treatment group. Continuous data are summarised using the mean, median, standard deviation, minimum and maximum values.

Efficacy:
Primary endpoint: AKclear100 at Week 8 was analysed for the FAS and the PP analysis set. The FAS was regarded as primary, whereas analysis based on the PP analysis set served a supportive purpose. A Cochran-Mantel-Haenszel (CMH) test adjusting for analysis site (pooled trial site) was performed, and the Mantel-Haenszel adjusted relative risk (RR) of AKclear100, its 95% CI, and p-value were calculated. The Mantel-Haenszel adjusted RR, its 95% CI, and p-value were calculated (FAS only). AKclear100 is summarised (including a normal approximation confidence interval) by anatomical location (face, chest or scalp), by baseline AK count in two categories (more than 10 AKs, 10 AKs or less), and by trial site and country based on observed cases (no formal hypotheses were tested in these subgroups).

Secondary endpoints: 1) AKclear75 at Week 8 was analysed by a CMH test adjusting for analysis site. The Mantel-Haenszel adjusted RR of AKclear75, its 95% CI, and p-value were calculated. To combine results for multiple imputed data sets in the event of missing data, Rubin’s pooling methodology was used on the log transformed RRs and CIs. As a supportive analysis, the CMH test adjusting for analysis site was performed within each anatomical location, i.e., for subjects treated on face/chest and for subjects treated on the scalp, respectively (FAS only). 2) AKclear75 at Week 4 was analysed in a similar fashion to AKclear75 at Week 8. 3) Percent reduction in AK count at Week 8 was analysed by negative binomial regression (of AK lesions at Week 8) including the log baseline AK count as offset and with factors of treatment group, anatomical location (face/chest or scalp) and analysis site. Percent reduction in AK count at Week 8 was estimated by treatment group from the model and is presented by mean and 95% CI.

Safety:
Adverse events: An overall summary of the number (percentage) of subjects with any treatment emergent adverse events (AEs), serious adverse events (SAEs), premature discontinuations from the trial due to AEs, treatment related AEs, and AEs leading to withdrawal of investigational medicinal product (IMP) are presented. The number of subjects experiencing each type of AE was tabulated by treatment group regardless of the number of times each AE was reported by each subject.
Within the given trial period, AEs were collected both inside and outside of the treatment area. In Part 2, AEs were collected inside the treatment area only.

**Local skin responses:** The incidence and grade of LSRs are summarised by treatment group overall at each visit (Day 1 to Week 8) and by anatomical location (face, chest, or scalp). LSR grades are summarised by frequency counts and descriptive statistics by treatment group for each of the six individual LSRs: erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration. LSRs leading to withdrawal from trial and/or withdrawal of IMP were tabulated.

### Summary of Results

#### Trial Population

**Part 1:** Of the 857 subjects screened in the trial, there were 128 screening failures, and the remaining 729 subjects were randomised in the trial. Overall, there were 460 (63.1%), 123 (16.9%), and 146 (20.0%) subjects randomised to treatment on the face, chest, and scalp, respectively, with similar percentages in both treatment groups. Of the 729 subjects randomised to treatment, 4 did not receive treatment with IMP. These 4 subjects (3 subjects from the active treatment group and 1 from the corresponding vehicle group) were excluded from the FAS, which consisted of 725 subjects (549 subjects in the active treatment group and 176 in the corresponding vehicle group). A total of 30 subjects were withdrawn from the trial. The percentage of premature discontinuation was higher among vehicle group subjects (10.7%) compared with active treatment group subjects (2.0%). Withdrawal by subject (corresponding to voluntary withdrawal) was higher in vehicle group subjects (6.2% versus 1.1%) and appeared to have the greatest influence on premature discontinuation. The percentages of AEs and LSRs were relatively low in the 2 treatment groups. Overall, 98.0% of active treatment group subjects (n=541) completed Part 1 of the trial compared with 89.3% of subjects (n=158) in the corresponding vehicle group.

**Part 2:** Of the 725 subjects treated with IMP in the FAS, there were 27 subjects (8 in the active treatment group and 19 in the corresponding vehicle group) excluded from the FUAS, as efficacy/safety data were not provided at and after Week 8. The FUAS thus comprised 698 subjects: 541 in the active treatment group and 157 in the vehicle group. One subject missed the Visit 7 (Week 8) window in Part 1, but was still considered to be in the trial; this subject was later excluded from the CCW8. The percentage of premature discontinuation was higher among vehicle group subjects (17.2%) compared with active treatment group subjects (9.6%). Voluntary withdrawal (corresponding to withdrawal by subject) was higher in the vehicle group (8.9% versus 5.0%). Similarly, a higher percentage of subjects in the vehicle group withdrew due to lack of efficacy (3.2% versus 0.0%). Overall, 90.4% of active treatment group subjects in the FUAS (n=489) completed Part 2 of the trial compared with 82.8% of subjects in the corresponding vehicle group (n=130).

Of the 698 subjects in the FUAS, 575 subjects (424 in the active treatment group and 151 in the vehicle group) were excluded from the CCW8, as these subjects did not achieve AKclear100 at Week 8. Furthermore, 1 subject in the active treatment group did not attend Visit 7 and was excluded from the CCW8. The CCW8 thus comprised 122 subjects: 116 subjects in the active treatment group and 6 subjects in the corresponding vehicle group.

**Part 1:** The median age in subjects constituting the FAS at baseline was 68 (range 38-91) years. All subjects were white; 535 (73.4%) were men, 194 (26.6%) were women, and 497 of the 729 subjects (68.1%) had Fitzpatrick skin type I to II. The median duration of AK was 8 years for both treatment groups; however, the median duration of AK was higher in randomised subjects from Australia (11 years) compared to the US and Canada (each 7 years). The mean number of AKs in the treatment area at baseline was the same for both groups on the face (12.7) and scalp (12.5). The mean number of AKs at baseline on the chest was slightly lower in active treatment group subjects (10.1) compared with those subjects in the corresponding vehicle group (11.1). The location of the treatment area was on the face, chest, and scalp in 63.1%, 16.9%, and 20.0% of subjects, respectively, for all randomised subjects and treatment groups were generally similar regarding location of treatment.

**Part 2:** The median age for subjects in the CCW8 at baseline was 66.5 (range 42-87) years. All subjects were white; 77 (63.1%) were men, 45 (36.9%) were women, and 83 of the 122 subjects (68.0%) had Fitzpatrick skin type I to II. Because the CCW8 included only 6 vehicle group subjects, comparisons cannot be made between treatment groups. The median duration of AK was slightly higher in active treatment group subjects from Australia (10.0 years) compared to active treatment group subjects from the US (9.0 years) and Canada (7.0 years). The mean number of AKs at baseline was similar across anatomical locations in active treatment group subjects (10.8, 9.9, and 10.7 on the face, chest, and scalp, respectively). Most subjects in the active treatment group were treated on the face (62.9%) and chest (25.0%) compared to scalp (12.1%).

### Efficacy Results

**Primary endpoint and secondary endpoints:**

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<th>Description</th>
<th>Data</th>
<th>Notes</th>
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<td><strong>Within the given trial period.</strong> In Part 1 of the trial, AEs were collected both inside and outside of the treatment area. In Part 2, AEs were collected inside the treatment area only.</td>
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Part 1: the 3-day treatment period including an 8-week follow-up period

- Subjects treated with ingenol mebutate gel 0.027% for 3 days exhibited statistically significantly higher rates of AKclear100 of AKs at Week 8 (21.4% of subjects) compared with those subjects treated with the vehicle gel (3.4%). Rates of AKclear100 at Week 8 were 23.8% (95% CI: 19.7, 27.8) for the face/chest compared with 12.5% (95% CI: 6.4, 18.6) for the scalp in active treatment group subjects. Rates of AKclear100 at Week 8 were higher in active treatment group subjects with <10 AKs at baseline.
- The rates of AKclear75 observed at Week 4 and Week 8 and the percent reduction in AKs at Week 8 were generally in accordance with the findings for AKclear100 at Week 8; subjects in the active treatment group experienced significantly higher rates of AKclear75 and percent reduction compared with subjects in the vehicle group. The 3 secondary endpoints depended less on baseline AK count, in contrast to what was observed for AKclear100 at Week 8.
- Subjects in the active treatment group exhibited higher rates of AKclear100 at Week 4 (23.8%) compared with subjects treated with vehicle gel (2.5%), similar to what was observed for AKclear100 at Week 8. Thus, the full effect of treatment was demonstrated after 4 weeks.
- Patient-reported outcomes (PROs) were statistically significantly higher in subjects in the active treatment group with respect to subject satisfaction, as measured by the TSQM. Similarly, the treatment difference mean score for Week 8 change from baseline in both symptoms and emotions was statistically significantly lower in active treatment group subjects compared to vehicle group subjects, as measured by the Skindex-16.
- Self-reported improvement ('much improved' or 'somewhat improved') in both overall appearance and feel in the treatment area at Week 8 was higher in subjects in the active treatment group (93.8% and 92.2% of subjects, respectively) compared with subjects in the vehicle group (19% and 17.7%).
- Subjects in the active treatment group had higher mean improvement scores in the treatment area, as measured by global photo-damage outcome, compared with subjects treated with the vehicle gel at Week 8.

**Safety Results**

**Part 1: the 3-day treatment period including an 8-week follow-up period**

- There were no deaths reported. In the active treatment group, there was 1 AE leading to withdrawal from the trial and 9 SAEs reported in 8 subjects; none of these AEs were suspected to be related to treatment by the investigator.
- Most subjects in the active treatment group (79.8%) reported AEs and the majority of these events were determined to be related to treatment (741/934). Less than 10% of the AEs reported were of severe intensity (71/934).
- The majority of AEs were due to reactions at the administration site, with application site pain and application site pruritus as the most frequently reported AEs. Most of the reports of application site pain (as PT) were due to application site burning at the LLI level. There were 27 subjects with AEs leading to discontinued treatment, mostly due to application site pain.
- A total of 2 of 549 (0.4%) assessed subjects in the active treatment group and 1 of 176 (0.6%) subjects in the vehicle group had confirmed AESI diagnoses (i.e., SCC).
- The mean composite LSR score change from baseline was highest at Day 4 and higher in active treatment group subjects. Mean composite LSR scores generally returned to baseline by Day 15. Similarly, LSR component scores increased after application of treatment and were higher in the active treatment group, generally peaking at Day 4 before returning to baseline levels.
- The findings from ECG monitoring, vital signs, and clinical laboratory evaluation showed no evidence of safety concern.

**Part 2: the extended 12-month follow-up period**

- There was 1 death that was determined not to be related to treatment and no SAEs reported. There were 2 severe AEs (BCC and laceration), each in different subjects, that were determined not to be related to treatment with ingenol mebutate gel 0.027% gel.
- Most subjects (88.7%) did not report AEs and less than 20% of the AEs reported were considered to be related to treatment. Most of the AEs were of mild or moderate intensity. The most frequently reported AEs were BCC and Bowen’s disease with similar rates observed in both groups.
- Administration site reactions accounted for similar percentage of the total AEs reported in both groups (0.06% in active treatment group versus 0.04%).
- A total of 8 of 541 (1.5%) assessed subjects in the active treatment group and 3 of 157 (1.9%) subjects in the vehicle group had an AESI (SCC) as assessed by the investigator, which was also assessed as an AESI (SCC or KA) during central review. There were 3 local AESI diagnoses assessed as possibly related to treatment by the investigator, 2 of which were confirmed by the IAC.
- The percentage of skin malignancies inside the treatment area did not differ between the treatment groups across the trial period (i.e., 7.3% versus 5.1% observed in the active treatment and corresponding vehicle group, respectively).
**Conclusions**

Ingenol mebutate gel at a dose of 0.027% administered once daily for 3 consecutive days resulted in statistically significantly higher rates of AK clearance (AKclear100 and AKclear75) and reduction in the number of AKs from baseline compared with vehicle gel at the end of 8 weeks. Moreover, the efficacy of 3 days of treatment demonstrated at Week 8 was already present at Week 4. At the end of 1 year, the probability of sustained AKclear100 in active treatment group subjects was 22.9%. There were no safety concerns identified in this trial. Treatment with ingenol mebutate gel 0.027% showed an acceptable tolerability with 27 (4.9%) subjects in the active treatment group discontinuing treatment mainly due to AEs of application site pain.
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