Clinical Study Report Synopsis

Ingenol Mebutate Gel, 0.015% Repeat Use for Multiple Actinic Keratoses on Face and Scalp

A phase 3 trial evaluating the repeat use of ingenol mebutate gel, 0.015% in the treatment of actinic keratosis on the face and scalp

A multi-centre, randomised, stratified, double-blind, vehicle-controlled, parallel group, 12-month trial

LEO Pharma A/S
Clinical Development and Safety

LP0041-22
01-Jul-2014
EudraCT Number: 2011-005018-13
Clinical Study Report Synopsis Statement

Approval Statement, Sponsor

The following persons have approved this Clinical Study Report Synopsis on behalf of LEO Pharma A/S using electronic signatures:

Biostatistics

Medical Department

Approval Statement, Investigator

The International Co-ordinating Investigator approves the Clinical Study Report Synopsis by manually signing the International Co-ordinating Investigator Clinical Study Report Approval Form, which is a separate document adjoined to this report.

The following person has approved this Clinical Study Report Synopsis:

Professor, MD

International Co-ordinating Investigator
**SYNOPSIS**

Name of Sponsor/Company: LEO Pharma A/S

Name of Finished Product: Ingenol Mebutate Gel, 0.015%

Name of Active Ingredient: Ingenol Mebutate

Title of Trial:
Ingenol Mebutate Gel, 0.015% Repeat Use for Multiple Actinic Keratoses on Face and Scalp

Investigators:
This was a multi centre trial. Professor [Redacted], MD was international coordinating investigator.

Trial Centres: The trial was conducted in Australia - 6 sites, Canada - 9 sites, France - 12 sites, Germany - 9 sites, and UK - 9 sites

Publication(s) based on the trial: None at the time of this clinical study report.

Trial Period:
date of first enrolment (informed consent signed and CRF started): 04-Jun-2012
date of last completed: 05-Feb-2014

Phase of Development: 3

Objectives:
Primary objective:
- To demonstrate that ingenol mebutate gel is efficacious in treating actinic keratoses (AKs) present 8 weeks after initial field treatment (field recalcitrant) or emerging in a previously cleared field (field recurrent).

Efficacy was evaluated separately for the two sub-groups of field recalcitrant and field recurrent AKs.

Secondary objectives:
- To demonstrate that ingenol mebutate gel repeat use shows a higher complete clearance rate at Month 12 compared with single use of ingenol mebutate gel plus vehicle gel use in patients with multiple AKs on face or scalp.
- To evaluate the safety profile of ingenol mebutate gel second use compared with ingenol mebutate gel first use in patients with multiple AKs on face or scalp.

Methodology:
This was a phase 3, multi-centre, randomised, stratified, double-blind, vehicle-controlled, parallel group, 12-month trial evaluating the repeat use of ingenol mebutate gel in the treatment of AKs on the face and scalp.
The trial population included subjects at least 18 years of age with 4 to 8 clinically typical, visible, and discrete AK lesions within a contiguous 25 cm² treatment area on either the face or scalp. This area of skin was referred to as the selected treatment area (STA).
The trial consisted of 4 periods: a first treatment cycle, an observation period, a second treatment cycle, and a follow-up period.

First Treatment Cycle (Day 1 to Week 8):
In the first treatment cycle, all eligible subjects were to be treated with ingenol mebutate gel, 0.015% in the STA for 3 consecutive days (Day 1-3). At Day 4, the STA was assessed for local skin responses (LSRs). At 8 weeks following first application with ingenol mebutate gel (Day 57), an assessment of the STA, including LSRs and AK lesion count, was performed. Subjects not completely cleared in the STA were randomised 2:1 to ingenol mebutate gel or vehicle gel. The first unit dose of trial medication was applied on the same day, corresponding to Day 1 in the second treatment cycle (see below). Subjects completely cleared in the STA continued in the observation period until trial completion at Week 52.

Observation Period (Week 8 to Week 52)
The observation period was only applicable for subjects completely cleared at Week 8. Visits were performed at Weeks 26, 44, and 52 at which assessments of the STA, including LSRs and AK lesion count, were performed. Subjects with AKs emerging in the previously cleared STA at Week 26 or Week 44 were randomised on the same day to ingenol mebutate gel or vehicle gel, corresponding to Day 1 in the second treatment cycle.
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Second Treatment Cycle (Period of 8 weeks)
At Day 1 in the second treatment cycle, subjects who were not completely cleared in the STA were randomised 2:1 to treatment with ingenol mebutate gel or vehicle gel. Applications were performed for 3 consecutive days in the STA and subjects subsequently attended visits at Day 4, Day 15, Day 29, and Day 57 after randomisation for assessments of LSRs. AK lesion count was assessed at Day 57

Follow-up Period (Week 16 to Week 52)
The follow-up period was only applicable for subjects who had completed the second treatment cycle (8 weeks after randomisation), and the period continued until trial completion at Week 52. At each visit (Week 34 and Week 52), an assessment of the STA, including LSRs and AK lesion count, was performed.

Safety assessments included recordings of vital signs and adverse events (AEs). The presence/absence and grade (0 to 4) of the individual LSR components (erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration) was evaluated for each visit and summarised in a composite LSR score (range 0 to 24), reflecting the sum of the individual LSR components.

Number of Subjects (Planned and Analysed):
454 subjects were planned to be enrolled to ensure a sufficient number of subjects in each of the two subgroups to be randomised (141 subjects to the field recalcitrant subgroup and 63 subjects to the field recurrent subgroup).
In total, 450 subjects were analysed.

Diagnosis and Main Criteria for Inclusion:
The trial population was chosen to include subjects ≥ 18 years of age with 4 to 8 clinically typical, visible and discrete AKs within a contiguous 25 cm² treatment area on the face or scalp. The eligibility criteria prevented confounding issues with diagnosis and eliminated any possible effect of concurrent diseases or concomitant medications on clinical assessment.

Investigational Product, Dose and Mode of Administration, Batch Number:
Ingenol mebutate gel 0.015%; batch numbers 112377201/Sep-2012 and 120617101/Feb-2014.
The investigational product was applied once daily for 3 consecutive days in the STA.

Duration of Treatment:
- Two cycles for patients with recalcitrant or recurrent disease on the face or scalp (first cycle: Ingenol mebutate gel 0.015%; second cycle: Ingenol mebutate gel 0.015% or Vehicle gel according to randomisation).
- One cycle (Ingenol mebutate gel 0.015%) for patients with an AK count of 0 at Week 8 and throughout the trial.

Reference Therapy, Dose and Mode of Administration, Batch Number:
Vehicle gel; batch numbers 112377101/Sep-2013 and 112377102/Sep-2013.
The investigational product was applied once daily for 3 consecutive days in the STA in patients with recalcitrant or recurrent disease on the face or scalp.

Criteria for Evaluation:
Efficacy:
Primary endpoint:
- Complete clearance of AKs, defined as no clinically visible AKs in the STA, 8 weeks after randomisation

Secondary endpoints:
- Complete clearance through to Month 12, defined as no clinically visible AKs and no lesions treated in the STA at any time from last treatment cycle through to Month 12
- Change in AK count in the STA from randomisation to 8 weeks after randomisation

Safety:
- Adverse events
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- Local skin responses (LSRs): erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, and erosion/ulceration

Statistical Methods:

Efficacy:
Efficacy analyses were based on the Full Analysis Set (FAS), which was defined as all subjects who received an initial ingenol mebutate gel treatment. Endpoints were analysed separately for the two subgroups of the FAS who were in the:

- Field recalcitrant subgroup, i.e. those randomised at Week 8 with AKs present 8 weeks after initial field treatment
- Field recurrent subgroup, i.e. those randomised at Week 26 or 44 with AKs emerging in a previously cleared field.

The primary endpoint (complete clearance 8 weeks after randomisation) was analysed separately for the two subgroups (field recalcitrant and field recurrent). No adjustment for multiple tests was needed, due to the analyses were based on distinct subject groups. In this manner, superiority could be assessed with regards to either of the subgroups. The complete clearance rates 8 weeks after randomisation were compared between the two treatment arms using a Cochran-Mantel-Haenszel chi-square test for stratified data with a significance level of 5%. The ratio of rates was estimated together with its 95% confidence interval. 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.

The order of the secondary endpoints (see previous page) designates the hierarchical order of evaluating the endpoints. A closed test procedure was chosen where the evaluation process stopped when the first non-significant results were observed thus securing that the overall significance level did not exceed 5% for multiple testing.

The analysis of complete clearance through to Month 12 followed the method described for complete clearance 8 weeks after randomisation and compared the two treatment arms in the two subgroups separately.

Summary – Conclusions

Study Population:
In total, 450 subjects received ingenol mebutate gel in the first treatment cycle and comprised the FAS. All 450 subjects in the FAS have available safety information; hence the safety analysis set is identical to the FAS.

Following the first treatment cycle 141 subjects had an AK count >0 within the selected treatment area and were randomised in a 2:1 ratio to a second treatment cycle with either ingenol mebutate gel (92 subjects) or vehicle gel (49 subjects) at Visit 2.1/Week 8. These subjects comprise the field recalcitrant subgroup. Of these, 119 (84.4%) completed the trial up to and including the Week 52 visit.

Following the first treatment cycle 277 subjects were clear of AKs within the selected treatment area. Of these subjects, 62 were randomised to a second treatment cycle with either ingenol mebutate gel or vehicle gel at Visit 3.1/Week 26 (40 subjects; 28 in the ingenol mebutate group and 12 in the vehicle group) or Visit 4.1 (22 subjects; 14 in the ingenol mebutate group and 8 in the vehicle group) and thus comprise the field recurrent subgroup. Of the 62 subjects (95.2%) completed the trial up to and including the Week 52 visit.

In the first treatment cycle, the majority of subjects (97.3%) applied trial medication 3 times. In the second treatment cycle,
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All but two subjects (both in the ingenol mebutate group) applied trial medication 3 times.

Summary of efficacy results:
Repeat use of ingenol mebutate gel in field treatment of AKs on the face and scalp is efficacious.

- For the field recalcitrant subgroup, a second 8-week treatment cycle with ingenol mebutate gel was superior to vehicle gel in treating AKs present after initial field treatment with ingenol mebutate gel
  - The complete clearance rate was statistically significantly higher in the ingenol mebutate group (46.7%) compared to the vehicle group (18.4%) (p=0.001)
  - There was a statistically significant difference in the adjusted mean AK count from randomisation to Week 8 between the ingenol mebutate and vehicle groups of -0.88 (p<0.001)
- For the field recurrent subgroup, a second 8-week treatment cycle with ingenol mebutate gel was superior to vehicle gel in treating AKs emerging in a field previously cleared with ingenol mebutate gel
  - The complete clearance rate was statistically significantly higher in the ingenol mebutate group (59.5%) compared to the vehicle group (25.0%) (p=0.013)
  - The difference in the adjusted mean AK count from randomisation to Week 8 between the ingenol mebutate and vehicle groups was -0.69 (p=0.008). Formal statistical significance could not be established because of the closed test procedure where the first secondary endpoint tested (12 months clearance) did not reach statistical significance in the recurrent subgroup.
- Long-term efficacy data suggests a benefit of retreatment with ingenol mebutate gel
  - The complete clearance rate through to Month 12 in the field recalcitrant subgroup was statistically significantly higher in the ingenol mebutate group (18.5%) compared to the vehicle group (4.1%) (p=0.016)
  - The complete clearance rate through to Month 12 in the field recurrent subgroup was higher in the ingenol mebutate group (31.0%) compared to the vehicle group (15.0%), but this difference was not statistically significant (p=0.10)
- There was very little change over the time period of the trial in the subject-reported outcomes (EQ-5D-3L and EQ VAS) in both the field recalcitrant and field recurrent subgroups

Summary of safety results:
Repeat use of ingenol mebutate gel in field treatment of AKs on the face and scalp is safe and tolerable

- There were similar rates of related AEs during the second treatment cycle compared to the first treatment cycle
- There were similar to lower LSRs during the second treatment cycle compared to the first treatment cycle (mean paired difference in composite LSR score was -1.22 [p<0.001])

Conclusion:
Ingenol mebutate gel 0.015% is efficacious in the treatment of AKs that are present 8 weeks after initial treatment (field recalcitrant) or that arise in a previously cleared field (field recurrent). In the field recalcitrant subgroup, this superior efficacy was maintained through to Month 12. Repeat use of ingenol mebutate gel was generally well tolerated and no safety concerns were identified. Overall, the nature and frequency of adverse events was similar during the second treatment cycle compared to the first treatment cycle
**ELECTRONIC SIGNATURES**

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