Clinical Study Report Synopsis

A Sequential Treatment Regimen of Cryotherapy and Picato® (Ingenol Mebutate) gel, 0.015% Field Therapy Compared to Cryotherapy Alone for the Treatment of Actinic Keratosis on the Face and Scalp

“FIELD STUDY 1”

A Phase 3, multi-centre, randomised, two-arm, parallel group, double-blind, vehicle controlled, 12-month trial

LEO Pharma A/S
Clinical Development and Safety

LP0041-21
FINAL 17-Dec-2013
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 and Data Management

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:

International Co-ordinating Investigator
SYNOPSIS

Name of Sponsor/Company: LEO Pharma A/S
Name of Finished Product: PEP005 Gel, 0.015% (Picato® gel)
Name of Active Ingredient: Ingenol mebutate

Title of Trial: A Sequential Treatment Regimen of Cryotherapy and Picato® (Ingenol Mebutate) gel, 0.015% Field Therapy Compared to Cryotherapy Alone for the Treatment of Actinic Keratosis on the Face and Scalp

Investigators: There were 35 principal investigators. [Redacted], [Redacted], MD, PhD, [Redacted]. Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine.

Trial Centre(s): A total of 35 trial centres in the US.

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): 13-Mar-2012
date of last completed: 20-Jun-2013

Objectives:
Primary Objective: To determine the 11-week rate of complete clearance of actinic keratosis (AKs) using sequential cryotherapy and field treatment with ingenol mebutate gel compared to cryotherapy alone.
Secondary Objective: To evaluate the safety and additional efficacy of the sequential cryotherapy and field treatment using ingenol mebutate gel compared to cryotherapy alone.

Methodology: A Phase 3, multi-centre, randomised, two-arm, parallel group, double-blind, vehicle controlled, 12-month trial in adults with AK lesions on the face or scalp. Eligible subjects were randomised in a 1:1 ratio to receive one of two treatments (Arm A: cryotherapy followed by field treatment with ingenol mebutate gel or Arm B: cryotherapy followed by field treatment with vehicle gel). Subjects were stratified by trial site and by location of the selected treatment area (face or scalp). Enrollment was controlled so approximately 20% of subjects were to be treated on the scalp and approximately 80% were to be treated on the face. Eligible subjects received cryotherapy at Visit 1 to treat 4-8 "baseline" AKs in the selected treatment area (a contiguous 25 cm² treatment area on the face or scalp). After 2-4 weeks' healing time (Visit 2) subjects administered field treatment with ingenol mebutate gel, 0.015% or vehicle gel once daily for 3 consecutive days. Subsequent follow-up visits were conducted the day after the last application of trial medication (Visit 3) and at Weeks 5, 7 and 11 (Visits 4, 5, and 6) to evaluate the efficacy and safety of the sequential treatment. Local skin responses (LSRs) were assessed at Visit 1 and Visits 3, 4, 5, 6, and 11 whereas adverse events (AEs) were assessed at baseline and all subsequent visits. At Week 11 (56 days after the start of trial medication), subjects were assessed for complete clearance. All subjects were followed up in the Extended Follow-up Phase which consisted of visits at Months 6, 9, and 12 post treatment (Visits 7, 8, and 9). Health economic questionnaires were administered throughout the trial at Visits 1, 2, 3, 4, 6, 7 and 9 and at Visit 1 the Dermatology Life Quality Index (DLQI) was completed before cryotherapy and the EQ-5D was completed twice (once before cryotherapy and once after cryotherapy).

Number of Subjects (Planned and Analysed): A total of 326 subjects randomised (i.e., 163 in each treatment arm) was planned in the protocol and 329 subjects were randomised and received cryotherapy (167 to the ingenol mebutate group and 162 in the vehicle group).

Diagnosis and Main Criteria for Inclusion: Adults (aged at least 18 years) with 4 to 8 clinically typical, visible and discrete AKs within a contiguous 25 cm² treatment area on the face or scalp (the selected treatment area). The selected treatment area must not be within 5 cm of an incompletely healed wound or within 10 cm of a suspected basal cell carcinoma (BCC) or Squamous cell carcinoma (SCC). Prior treatment with ingenol mebutate gel on face or scalp, selected treatment area lesions that had atypical clinical appearance (e.g., hypertrophic, hyperkeratotic, cutaneous horns) and/or recalcitrant disease (had cryotherapy on two previous occasions) were excluded. Any skin conditions (e.g., eczema, unstable psoriasis, xeroderma pigmentosum) or any treatments received prior to enrollment that would interfere with evaluation of the trial medication were also excluded. Informed consent was given.

Investigational Product, Dose and Mode of Administration. Batch Number: Ingenol mebutate gel, 0.015%, topical application (batch 112377201/PLD0001).

Duration of Treatment: Applied once daily for 3 consecutive days.

Reference Therapy, Dose and Mode of Administration. Batch Number: Vehicle gel, topical application (batch 112377101/PLC0001).
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<th>Criteria for Evaluation:</th>
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<td><strong>Efficacy:</strong></td>
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<td>Primary: Complete clearance of AKs in the selected treatment area, defined as no clinically visible AKs, at Week 11.</td>
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<td>Secondary endpoints:</td>
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<td>• Complete clearance of AKs in the selected treatment area, defined as no clinically visible AKs at any time through 12 months</td>
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<td>• Percent reduction from baseline in number of AKs at Week 11</td>
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<td>• Percent reduction from baseline in total number of all AKs seen at Week 11 through to Month 12</td>
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<td>• Partial clearance of AKs at Week 11, defined as 75% or greater reduction from baseline in the number of clinically visible AKs in the selected treatment area at Week 11</td>
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<tr>
<td>• Partial clearance of AKs through Month 12, defined as 75% or greater reduction from baseline in the total number of all AKs seen at Week 11 through to Month 12</td>
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<td><strong>Safety:</strong></td>
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<td>• Incidence of AEs and Serious adverse events (SAEs).</td>
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<td>• Incidence of AEs and LSRs leading to discontinuation of trial medication.</td>
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<td>• Incidence and severity of LSRs following treatment.</td>
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**Statistical Methods:** Efficacy analyses of the endpoints pertaining to AKs were performed on the Full Analysis Set (FAS) defined as all randomised subjects who received cryotherapy. The Week 11 and Month 12 PP analysis sets and the applied trial mediation analysis set were also used as appropriate. Complete clearance at Week 11 was the comparison of the two treatment arms using a Cochran–Mantel-Haenszel (CMH) chi-square test stratified by anatomical location and study site with significance level of 5%. The secondary endpoints complete clearance through 12 months and partial clearance were analysed in the same manner as the primary endpoint. Percent reduction from baseline in number of all AKs at Week 11 and through to Month 12 was analysed using an analysis of variance (ANOVA) with anatomic location and study site as factors and number of baseline lesions as covariate. Safety analyses of AEs were based on the safety analysis set defined as all subjects who received cryotherapy (i.e. the FAS) who had available safety information. Safety analysis of LSRs was based on the LSR Safety Set (all subjects in the FAS who receive at least one ingenol mebutate gel/vehicle gel administration and had available LSR assessments). The number and percent of subjects with AEs were tabulated by body system and preferred term and summarised using descriptive statistics for the above summaries. Listings were provided for all subjects with SAEs and study or treatment discontinuations due to adverse events. The overall incidence and grade of LSRs in the LSR safety set were summarised by treatment arm and at each visit by anatomical location. A composite (sum) score was obtained by summing the six individual LSR scores at each visit. The composite score and change from baseline were summarised by treatment arm at each visit using descriptive statistics.

**Summary – Conclusions**

**Study Population:** A total of 329 subjects were randomised in the trial (167 subjects to cryotherapy followed by ingenol mebutate gel and 162 subjects to cryotherapy followed by vehicle) and 289 (87.8%) subjects completed the trial; 149 (89.2%) in the ingenol mebutate group and 140 (86.4%) in the vehicle group. The majority of subjects (92.8% in ingenol mebutate group and 92.6% in vehicle group) received all 3 applications of trial medication.

**Efficacy Summary:**

Primary endpoint: The complete clearance rate at Week 11 in the FAS was statistically significantly higher in the ingenol mebutate group (60.5%) compared to the vehicle group (49.4%) (p=0.04). A sensitivity analysis, including only subjects who applied trial medication, showed similar results (63.9% vs. 53.3%; p=0.05) and the same trend was seen for the PP analysis set (63.6% vs. 55.0%) but the difference between the groups was smaller and not statistically significant (p=0.15). The clearance rates were similar for face and scalp (59.5% and 63.9%, respectively), in the ingenol mebutate group. After adjusting for all three factors of cryotherapy (duration, number of cycles and distance between tip and AK) in an exploratory regression analysis, clearance rates were still similar for face and scalp.

Secondary endpoints: Similar to the Week 11 analysis, the complete clearance rate in the FAS was statistically significantly higher in the ingenol mebutate group (30.5%) compared to the vehicle group (18.5%) (p=0.01). A sensitivity analysis, including only subjects who applied trial medication, showed similar results (32.3% vs. 20.0%; p=0.01). The PP analysis set also showed similar results (35.3% vs. 22.0%) which were statistically significant (p=0.01) in contrast to the Week 11 PP analysis where statistical significance was not observed. The clearance rates were higher for the face than for the scalp (33.6% and 19.4%, respectively) in the ingenol mebutate group which also differs from the Week 11
analysis where similar results were observed on both locations. There was a statistically significant difference between the two treatment groups for the face but not for the scalp. On the face clearance rates were 33.6% versus 18.7% in the ingenol mebutate and vehicle groups, respectively ($p=0.01$) and on the scalp they were 19.4% and 17.9% ($p=0.84$).

- Percent reduction from baseline in number of AKs at Week 11: The mean percent reduction was higher in the ingenol mebutate group (83.4%) compared to the vehicle group (77.5%). The difference was smaller for the PP analysis set (86.2% and 82.9%, respectively). These results were not statistically significant ($p=0.10$ and $p=0.27$, respectively). Similar results were seen for face; 80.7% in the ingenol mebutate group and 74.0% in the vehicle group, while for scalp almost no difference was seen between the ingenol mebutate group and the vehicle group (84.2% and 82.5%, respectively).

- Percent reduction from baseline in total number of all AKs seen at Week 11 through to Month 12: Similar to the Week 11 analysis, the Month 12 percent reduction from baseline was higher in the ingenol mebutate group (57.2%) compared to the vehicle group (42.3%). The difference was smaller for the PP analysis set (63.4% and 47.8%, respectively). Unlike the Week11 results, these results were statistically significant ($p=0.004$ and $p=0.01$, respectively). Similar results were seen for face; 59.9% in the ingenol mebutate group and 40.6% in the vehicle group ($p=0.002$), while for scalp the percent reduction in number of AKs was slightly higher in the vehicle group (54.1%) compared to the ingenol mebutate group (49.7%) ($p=0.64$).

- Partial clearance of AKs at Week 11: Similar to the complete clearance rate, the partial clearance rate (75% or greater reduction from baseline) was also higher in the ingenol mebutate group compared to the vehicle group (77.8% vs. 67.3%; $p=0.05$) and the same trend was seen for the PP analysis set (82.5% vs. 75.0%) but statistical significance was not observed ($p=0.17$). Similar results were seen for face (77.9% vs. 64.2%) but for scalp the partial clearance rate was slightly higher in the vehicle group (82.1%) compared to the ingenol mebutate group (77.8%).

- Partial clearance of AKs through Month 12: Similar to the Week 11 analysis, the partial clearance rate was statistically significantly higher in the ingenol mebutate group compared to the vehicle group (50.9% vs. 37.0%; $p=0.01$). The PP analysis showed similar results (58.6% vs.48.2%) which were statistically significant ($p=0.01$) in contrast to the Week 11 PP analysis where statistical significance was not observed. Similar results were seen for face (55.7% vs. 36.6%), but for scalp, the partial clearance rate was slightly higher in the vehicle group (39.3%) compared to the ingenol mebutate group (33.3%).

### Quality of Life Questionnaires:
- The only notable differences between treatments in DLQI score and EQ-5D index were at 3 days after treatment when the DLQI score increased and the EQ-5D index decreased with ingenol mebutate gel compared with vehicle gel, possibly reflecting the immediate application site effects of ingenol mebutate gel.

### Safety Summary:
- In the first 11 weeks a total of 73 AEs were reported by 41 subjects (24.6%) in the ingenol mebutate group compared with the vehicle group where 46 AEs were reported by 35 subjects (21.6%). Twenty seven of the AEs were judged as related to trial medication. Of these, 26 were reported by 19 subjects (11.4%) in the ingenol mebutate group and 1 AE was reported by 1 subject (0.6%) in the vehicle group. The most common AE related to trial medication was application site pain for 7 subjects (4.2%) all in the ingenol mebutate group. Of the AEs related to trial medication, 4 events of application site pain and 1 event of eye swelling were considered severe (all in the ingenol mebutate group), all the remaining AEs were mild to moderate. All the AEs related to trial medication in the first 11 weeks were recovered/resolved at Week 11. In the ingenol mebutate group, 2 subjects reported 4 AEs (eye swelling, application site pain and headache in 1 subject and application site pruritus in 1 subject) that were judged as related to cryotherapy compared to 1 subject in the vehicle group reporting 1 AE (application site discolouration). There was 1 AE leading to discontinuation from the trial before application of trial medication (BCC) and 1 AE leading to discontinuation from trial medication (application site pain, reported as burning at treatment site), both in the ingenol mebutate group. After Week 11, only AEs and SAEs related to the treatment or inside the selected treatment area were to be reported and only 8 AEs were reported for 7 subjects (3 in the ingenol mebutate group and 4 in the vehicle group). All were judged as not-related to application of trial treatment (one was judged probably related to cryotherapy). One of the AEs in the ingenol mebutate group (BCC) and 3 AEs in the vehicle group (one BCC and two SCC) were SAEs.

### Conclusion:
The short-term clearance rate of AKs is higher when treating with ingenol mebutate gel after cryotherapy compared to cryotherapy alone. This superior efficacy overall and for AK on the face was maintained for up to 12 months. Ingenol mebutate field treatment after cryotherapy is safe and tolerable on face and scalp.
Electronic Signatures

Electronic signature made within eDoc LEO by LEO Pharma A/S employees or employees of any LEO Pharma A/S affiliate located anywhere in the world, are to be considered to be legally binding equivalent of traditional handwritten signatures.

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