Consolidated Clinical Study Report Synopsis

Histological Confirmation of Clinical Clearance of Actinic Keratoses
Following Treatment with Ingenol Mebutate Gel, 0.05%

A phase 1 trial

A multi-centre, single arm, open-label, 8-week trial

LEO Pharma A/S
Clinical Development and Safety

Final: 27-Nov-2014
EudraCT Number: 2012-004191-20
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:

Dr. International Co-ordinating Investigator
SYNOPSIS

Name of Sponsor/Company: LEO Pharma A/S

Name of Finished Product:
Picato® Ingenol mebutate gel, 0.5%

Name of Active Ingredient:
Ingenol mebutate 0.05% w/w

Title of Trial:
Histological Confirmation of Clinical Clearance of Actinic Keratoses Following Treatment with Ingenol Mebutate Gel, 0.05%

Investigators: There were 10 principal investigators. Dr. MD, Germany was international coordinating investigator.

Trial Centres: 10 trial centres: 6 in Australia and 4 in Germany.

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

Phase of Development:
1

Objectives:

Primary objective:
To demonstrate an adequate predictive value of the clinical diagnosis of clearance of AK after the treatment with ingenol mebutate using histopathological examination as the standard.

Secondary objective
To determine the efficacy in terms of complete clearance of AKs in the selected treatment area and histological clearance of the pre-identified lesion.

Methodology:

This was a phase 1, multi-centre, single-arm, open-label, 8-week trial. All subjects attended 4 visits (Screening, Baseline, Day 3 and Week 8). At the screening visit a biopsy was taken of one of the actinic keratoses (AKs) to confirm AK by histopathology. The first unit-dose of investigational product (IP) was applied at Baseline under the supervision of trial site personnel and the second treatment was applied by the subject at home. Local skin responses (LSRs) and adverse events (AEs) were assessed at Baseline and all subsequent visits. AK count was assessed at Screening, Baseline, and Week 8. A pre-identified randomised AK lesion was evaluated clinically (present/absent) at Week 8, thereafter biopsied and evaluated histologically for presence or absence of AK by 2 independent pathologists.

Number of Subjects (Planned and Analysed):
A total of 100 subjects were planned for and 108 subjects were enrolled in the trial to account for withdrawals and ensure that the target 100 subjects completed the trial.

Diagnosis and Main Criteria for Inclusion:

Diagnosis:
Actinic keratosis on trunk and extremities

Main Criteria for Inclusion:
- Subjects with 5-9 clinically typical, visible and discrete AKs within a contiguous 25 cm² treatment areas on the trunk and extremities except the back of the hand
- Must be male or female and at least 18 years of age
- Female patients must be of non-childbearing potential or if of childbearing potential must provide negative urine pregnancy test and use effective contraception
- Ability to provide informed consent

Investigational Product, Dose and Mode of Administration, Batch Number:
Ingenol mebutate gel 0.05%, once daily topical administration, batch number EG5302A.

Duration of Treatment:
The duration of the trial was 8 weeks (excluding screening).

Reference Therapy, Dose and Mode of Administration, Batch Number:
Not applicable.
### SYNOPSIS

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#### Criteria for Evaluation:

**Efficacy:**
- **Primary endpoint:** Clinical and histological clearance of AK at Day 57.
- **Secondary endpoint:** Composite 8-week complete clearance rate, defined as complete clinical clearance of all AKs in the selected treatment area and histological confirmation of clinical clearance of the Day 57 biopsy of the previously identified AK lesion.

#### Statistical Methods:

- Analyses were based on the Full Analysis Set (FAS), which was defined as all subjects who received an initial study treatment. Safety analyses were based on the Safety Analysis Set, which was defined as all subjects who received an initial study treatment and had safety data available. A per protocol (PP) analysis set was used as subset and was defined as subjects in the FAS who completed the trial without major protocol deviations.
- **Efficacy analyses:**
  - The primary endpoint was analysed by comparing both the clinical lesion-specific clearance with the histopathological clearance and, as supportive, complete clearance with the histopathological clearance. A generalised kappa coefficient was calculated for the clinical- and the two histological assessments of clearance taking the inter-histological agreement into account.
  - The secondary endpoint was analysed by calculating the composite 8-week complete AK clearance rates for each pathologist and the common composite 8-week complete clearance rate was estimated by the mean value of the two pathologist-specific composite 8-week complete clearance rates. In addition, the pathologist-specific positive predictive values of the clinical diagnosis, i.e. from each pathologist, were calculated with exact 95% confidence interval (CI) and the common positive predictive value was estimated by the mean value of the two pathologist-specific positive predictive values of the clinical diagnosis with approximate 95% CI.

All other efficacy results and all safety results were summarised using descriptive statistics.

### Summary – Conclusions

#### Study Population:

All enrolled 108 subjects were treated with at least one application/dose of investigational product (FAS) and completed the trial. All subjects in the FAS had available safety information; hence the safety analysis set was identical to the FAS. Out of these 68.5% were men, 74.5% of the 47 subjects in Australia were men, and 63.9% of the 61 subjects in Germany were men. The mean age was 71.5 years, the most common Fitzpatrick skin type was type II (69.4%), mean duration of AK was 12.2 years (range 0 to 46), and most subjects (97.2%) had previously been treated for AK. Overall, the baseline demographic characteristics were similar between the countries and similar to the pivotal clinical trials.

#### Efficacy Summary:

- **Primary Endpoint:** The observed agreement between the clinical and the two histological assessments of clearance of single AK was 81.9% with generalised kappa coefficient $\kappa = 0.46$ with 95% CI [0.20; 0.71].
- **Secondary Endpoint:** The common composite 8-week clinical clearance rate was 0.41 (95% CI [0.32; 0.50]) and the common PPV of the clinical diagnosis was 0.87 (95% CI [0.81; 0.93]).

#### Other Relevant Results:

- The pathologists had an 88.0% agreement rate and $\kappa=0.61$ (95% CI [0.42; 0.80]).
- The clearance rate for single AK lesion was 75.0% for both pathologists’ assessments combined, 81.5% for pathologist I, 80.6% for pathologist II, and 85.2% for the clinical assessment.

#### Safety Summary:

A total of 30 subjects (27.8%) had 38 AEs, whereof 10 AEs where inside the selected treatment area. Eight subjects (7.4%) had 9 AEs related to IP, the majority of these were mild (6 out of 9 AEs), and 1 subject had a severe AE (application site inflammation). Most AEs inside the selected treatment area were related to IP (8 out of 10) and the most common related AE inside the selected treatment area was application site pain (4 subjects). All AEs related to IP were recovered or resolved.

The mean composite LSR score was highest at Day 3 and the baseline score (Day 1) was slightly higher than at Week 8 (Day 57). The same trend was seen for each anatomical location.

Four subjects had 1 SAE each: melanocytic hyperplasia and superficial basal cell carcinoma (inside the selected treatment area).
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area), and cerebrovascular accident and nephrolithiasis. Out of these, melanocytic hyperplasia was the only SAE related to the IP.

Conclusion:
The observed agreement between the clinical- and the two pathologists' histological assessment in clearance of single AK was 81.9%. Most AK lesions treated with ingenol mebutate had clearance of single AK at Week 8: 85.2% according to the clinical assessment, 81.5% and 80.6% according to the pathologists' histology assessments. Ingenol mebutate treatment was generally well tolerated and no safety concerns were identified.
**Electronics Signatures**

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