Clinical Trial Report Synopsis

Pharmacokinetics of ingenol mebutate gel in actinic keratosis under maximum use conditions

A phase 1, multi-centre, open-label, uncontrolled, non-randomised study to evaluate the systemic exposure and safety of ingenol mebutate when applied to full face, balding scalp or an area of approximately 250 cm² on the arm in subjects with actinic keratosis
Clinical Trial Report Synopsis Statements

Approval Statement, LEO Pharma A/S

The following persons have approved this clinical trial report synopsis on behalf of LEO Pharma A/S using electronic signatures:

[Name], MSc
Biostatistics

[Name], MD
Medical Department

Approval Statement, 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:

[Name], DO, JD
International Coordinating Investigator
**SYNOPSIS**

<table>
<thead>
<tr>
<th>Trial Registration Number</th>
<th>EudraCT Number</th>
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<tr>
<td>NCT02124239</td>
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**Title of Trial**
Pharmacokinetics of ingenol mebutate gel in actinic keratosis under maximum use conditions

**Investigators**
This was a multi-centre trial. DO, CPI, JD, United States was signatory investigator

**Trial Centres**
This trial was conducted at 3 centres in US and coordinated by...

**Publications**
None at the time of the final clinical study report

**Trial Period**

| date of first enrolment (informed consent signed and CRF started): 09-Jun-2014 |
| date of last completed: 16-Oct-2014  |

**Development Phase**
Phase 1

**Objectives**

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<th>Primary objective</th>
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<tr>
<td>To evaluate systemic exposure of ingenol mebutate under maximum use conditions on full face, balding scalp or on a treatment area of approx. 250 cm$^2$ on the arm.</td>
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<th>Secondary objective</th>
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<tr>
<td>To evaluate safety of ingenol mebutate under maximum use conditions on full face, balding scalp or on a treatment area of approx. 250 cm$^2$ on the arm.</td>
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**Methodology**
This was an open-label, uncontrolled, non-randomised trial involving three active parallel treatment groups based on anatomical location: (1) once daily application of ingenol mebutate gel 0.027% on the full face for three consecutive days, (2) the same regimen on approximately 250 cm$^2$ on the balding scalp, and (3) once daily application of ingenol mebutate gel 0.06% on the arm on a treatment area of approximately 250 cm$^2$ for three consecutive days.

Blood was drawn once daily on all treatment days and on the day after the last application at different time points. Pharmacokinetic evaluations were based on whole blood concentration analysis of ingenol mebutate and the two metabolites PEP015 and PEP025. The trial did not include a vehicle group, since the pharmacokinetic measurements are not subject to observer bias.

**Number of Subjects Planned and Analysed**
It was planned to include 60 AK subjects with 20 subjects in each of the three aforementioned treatment groups. To conduct the planned analyses a minimum of 16 subjects should complete the study in each group.

A total of 61 subjects entered and completed the trial with a distribution of 22, 20 and 19 subjects in the face treatment group, scalp treatment group and arm treatment group, respectively.

**Diagnosis and Main Criteria for Inclusion**

<table>
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<th>Diagnosis</th>
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<td>Actinic keratosis on the face, balding scalp or arm</td>
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<th>Main Criteria for Inclusion</th>
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<td>Male or female subjects had to be at least 18 years and have at least 15 clinically typical, visible, and discrete actinic keratosis (AKs) on the face (minimum 250 cm$^2$), on approximately 250 cm$^2$ of balding scalp or on the arm (except back of the hand) within an area of approximately 250 cm$^2$ of sun-damaged skin.</td>
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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, 0.027%. Topical application on face and scalp. 132567101 |
| Ingenol mebutate gel, 0.06%. Topical application on the arm. 132607101 |

**Duration of Treatment**
Once daily treatment for three days on face, balding scalp or arm.
Criteria for Evaluation

The compounds to be assayed are ingenol mebutate and its major metabolites PEP015 and PEP025. Based on the obtained blood concentrations the pharmacokinetic variables \( AUC_{0-t} \), \( AUC_{0-\infty} \), \( C_{\text{max}} \), \( T_{\text{max}} \) and \( T_{1/2} \) were to be determined. Safety: Adverse events (AEs and SAEs) including local skin reactions, physical examination including vital signs and 12-lead electrocardiograms as well as clinical laboratory evaluations.

Statistical Methods

Pharmacokinetic (PK) evaluation was based on the PK analysis set, which was defined as all enrolled subjects receiving all applications of trial drug, who had at least 5 blood samples taken after last application. Safety evaluation was based on the safety analysis set which was defined as enrolled subjects, who applied any trial drug and for whom safety information was available post-treatment.

Summary

Trial Population

Out of the 79 subjects, 61 subjects were included in the trial in the 3 sites: 22 subjects were treated with 0.027% ingenol mebutate gel on the face, 20 subjects were treated with 0.027% ingenol mebutate gel on the scalp, and 19 subjects were treated with 0.06% ingenol mebutate gel on the arm. The majority of subjects were men (range of 68 to 100% across the 3 treatment groups). The median age in years was 71.3 (scalp treatment group), 66.3 (face treatment group) and 65.7 (arm treatment group). The majority of subjects in all 3 treatment groups were classified as Fitzpatrick Skin Type II (range of 57.9 to 65.0%).

Pharmacokinetic Results

One subject from the face treatment group was excluded from the PK analysis set due to early termination. There were 8 of the 21 subjects in the face treatment group who had quantifiable levels of ingenol mebutate and the highest value observed was 0.199 ng/mL (0.462 nM). None of the 20 subjects in the scalp treatment group had levels of ingenol mebutate above the lower limit of quantification (0.1 ng/mL). There were 2 of the 19 subjects in the arm treatment group who had quantifiable levels of ingenol mebutate and the highest observed value was 0.177 ng/ml (0.411 nM). No blood samples had metabolite levels of PEP015 and PEP025 above the lower limit of quantification (0.1 ng/mL). No other metabolites were detected in the blood samples.

Safety Results

There was one death (road traffic accident) during the trial. This subject was also tracked as an SAE leading to withdrawal due to a fatal outcome. There were no other SAEs or withdrawals due to AEs in the trial. The majority of the subjects in the scalp treatment group had AEs. More than half of the subjects in the face and arm treatment groups had AEs. Most AEs in all 3 treatment groups were assessed as related to investigational product by the investigator. The most common AEs related to investigational product in all treatment groups were application site pain and C-reactive protein increased (as measured using an hs-CRP assay). All AEs considered related to the investigational product were recovered/resolved. The most common AEs of administration site pain coded by lower level terms were events of application site pain and were mainly of moderate severity. There were no administration site pain events that were reported as severe. The mean composite LSR score was highest at Day 4 for all 3 treatment groups and declined to values close to baseline at Day 16. The mean composite LSR score decline in the arm treatment group was slower than that for the face or scalp treatment groups. ECG monitoring showed no association between ingenol mebutate treatment and evidence of any cardiac effects.

Conclusion

A total of 10 out of 61 subjects had quantifiable levels of ingenol mebutate: 8 subjects in the face treatment group and 2 subjects in the arm treatment group. The results of this trial demonstrate that following once daily administration for 3 consecutive days under maximum use systemic exposure conditions there was low (subnanomolar) systemic exposure when ingenol mebutate gel, 0.027%, was applied to at least 250 cm\(^2\) on the full face or to approximately 250 cm\(^2\) balding scalp or when ingenol mebutate gel, 0.06% was applied to approximately 250 cm\(^2\) on the arm. In the maximal use setting of this trial, treatment with ingenol mebutate gel, 0.027% or 0.06%, was safe and well tolerated.

The clinical trial was conducted in compliance with the clinical trial protocol, ICH Good Clinical Practice and the Declaration of Helsinki as adapted by the 18th World Medical Assembly 1964, and subsequent amendments.
**ELECTRONIC SIGNATURES**

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<tr>
<td></td>
<td>Department, Medical Approval</td>
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