Clinical Study Report Synopsis

Pharmacokinetics of LEO 43204 gel in actinic keratosis administered under maximum use conditions

Design of trial:

An open-label, uncontrolled study to evaluate the systemic exposure and safety of LEO 43204 when applied to full face, balding scalp or an area of approximately 250 cm² on the arm in subjects with actinic keratosis

A phase I, multi-centre, open-label, uncontrolled trial

The clinical trial, including the archival of essential documents, was conducted in compliance with the clinical trial protocol, GCP, and the applicable regulatory requirement(s).

LEO Pharma A/S

Trial ID: LP0084-1077
Date: 05-Feb-2016
Version: Final
Clinical Trial Report Synopsis Statement

Approval Statement, LEO Pharma A/S

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

[Name], MSc
Biostatistics

[Name], MD
Medical Department

Approval Statement, International Coordinating Investigator

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

The following person has approved this clinical study report synopsis:

[Name], MD
International coordinating investigator
Title of Trial
Pharmacokinetics of LEO 43204 gel in actinic keratosis administered under maximum use conditions

Investigators
[redacted] MD, United States was appointed as signatory investigator

Trial Centres
This trial was conducted at 2 centres in the United States and coordinated by the signatory investigator.

Publications
None at the time of the final clinical trial report.

Clinical Trial Period
Date of First Subject First Visit: 04-May-2015
Date of Last Subject Last Visit: 05-Aug-2015

Development Phase
Phase 1

Objectives
Primary Objective
To evaluate systemic exposure under maximum use conditions of LEO 43204 on full face, balding scalp, or on a treatment area of approximately 250 cm$^2$ on the arm.

Secondary Objectives
To evaluate safety under maximum use conditions of LEO 43204 on full face, balding scalp, or on a treatment area of approximately 250 cm$^2$ on the arm.

Methodology
This was an open-label, uncontrolled, non-randomised multi-centre trial to evaluate the systemic exposure and safety of LEO 43204 when applied to full face, balding scalp, or an area of approximately 250 cm$^2$ on the arm in subjects with actinic keratosis.

The trial included three active treatment groups: (A) once daily application of LEO 43204 gel 0.018% on the full face (minimum 250 cm$^2$), (B) once daily application of LEO 43204 gel 0.1% on the arm on a treatment area of approximately 250 cm$^2$, and (C) once daily application of LEO 43204 gel 0.037% on approximately 250 cm$^2$ on the balding scalp.

Pharmacokinetic evaluations were based on whole blood concentration analysis of LEO 43204 and its major metabolite (LEO136441A). No vehicle group was included.

Number of Subjects Planned and Analysed
It was planned to include 60 subjects in the trial in order to have 16 completers in each of the three treatment groups.

A total of 58 subjects were included in the trial with a distribution of 18, 21, and 19 subjects in the face, arm and scalp groups respectively.

Diagnosis and Main Criteria for Inclusion

Diagnosis
Actinic keratosis on the face, arm or scalp

Main Criteria for Inclusion
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 full face (at least 250 cm$^2$), or on approximately 250 cm$^2$ on the arm (between wrist and shoulder) or approximately 250 cm$^2$ of balding scalp.

Female patients must have been of non-childbearing potential or if of childbearing potential must have provided negative urine pregnancy test and used effective contraception.

Ability to provide informed consent.
Test Product, Dose and Mode of Administration, Batch Number
LEO 43204 gel 0.018%, topical application on face, 132717101
LEO 43204 gel 0.037%, topical application on scalp, P14007
LEO 43204 gel 0.1%, topical application on arm, P14013

Duration of Treatment
Once daily treatment application on face, scalp or arm.

Reference Product, Dose and Mode of Administration, Batch Number
Not applicable

Criteria for Evaluation
The compounds assayed were LEO 43204 and its major metabolite LEO136441A. Based on the obtained blood concentrations the pharmacokinetic variables AUC$_{0-t}$, AUC$_{0-\infty}$, C$_{max}$, T$_{max}$, and T$_{1/2}$ were to be determined.

Safety: Adverse events (AEs and SAEs) 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 investigational product, 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, excluding subjects who either received no treatment with investigational product and/or for whom no post-baseline safety evaluations were available.

Summary of Results
Trial Population
Out of the 71 subjects enrolled, 58 subjects were included in the trial at 2 sites: 18 subjects for the face group, 19 subjects for the scalp group, and 21 subjects for the arm group.
The majority of subjects included in the trial, across the 3 groups, were non-Hispanic Caucasians. The mean age in years was 64.4 (scalp), 65.6 (face), and 65.0 (arm). The majority of subjects were men (range of 55.6 to 100%). All subjects were classified as Fitzpatrick Skin Type II-IV with the majority of subjects in all 3 groups classified as Type II (range of 78.9 to 83.3%).

Pharmacokinetic Results
The PK analysis set included 15 subjects in the scalp group, 15 subjects in the face group and 20 subjects in the arm group.
- For the face group, 12 of 15 subjects had quantifiable LEO 43204 levels and the highest observed value was 0.044 ng/ml (0.088 nM). The highest observed AUC was 0.733 h*ng/ml and was observed in the same individual. Concerning the major metabolite, 9 of 15 subjects in the face group had quantifiable LEO136441A levels and the highest observed value was 0.033 ng/ml (0.064 nM). The highest observed AUC was 0.556 h*ng/ml and was observed in the same individual.
- For the scalp group, 10 of 15 subjects had quantifiable LEO 43204 levels and the highest observed value was 0.024 ng/ml (0.047 nM). The highest observed AUC was 0.455 h*ng/ml and was observed in the same individual. Concerning the major metabolite, 8 of 15 subjects in the scalp group had quantifiable LEO136441A levels and the highest observed value was 0.113 ng/ml (0.22 nM). The highest observed AUC was 1.98 h*ng/ml and was observed in the same individual.
- For the arm group, 10 of 20 subjects had quantifiable LEO 43204 levels and the highest observed value was 0.166 ng/ml (0.33 nM). The highest observed AUC was 1.56 h*ng/ml and was observed in the same individual. Concerning the major metabolite, 6 of 20 subjects in the arm group had quantifiable LEO136441A levels and the highest observed value was 0.036 ng/ml (0.071 nM). The highest observed AUC was 0.561 h*ng/ml and was observed in the same individual.
Safety Results
There were no deaths or SAEs in the trial.
The percentage of subjects reporting AEs was 100% in the scalp treatment group, 94.4% in the face treatment group, and 81.0% in the arm treatment group.
Most AEs in all 3 treatment groups were assessed as related to investigational product by the investigator.
The most common AE considered related to investigational product (adverse drug reactions) in all treatment groups was application site pain.
All AEs considered related to the investigational product were recorded as recovered.
In all treatment groups application site pain was the most commonly reported event (by preferred term). Most of these events were of moderate intensity.
In the face treatment group application site burning was the most commonly reported event (by lowest level term). Most of these events were of moderate intensity.
In the arm treatment group application site burning and application site itching were the most commonly reported events (by lowest level term). Most of these events were of moderate intensity.
In the scalp treatment group application site pain was the most commonly reported event (by lowest level term) by all subjects. Most of these events were of moderate intensity.
There was 1 severe event of application site pain in the arm treatment group,
There was 1 severe event each of application site pruritus and application site pain in the same subject in the face treatment group.
For all 3 treatment groups the mean composite local skin response (LSR) scores rose gradually from baseline to Day 2. The mean composite LSR score was highest at Day 4 (Visit 5) for all 3 treatment groups and approached values close to Baseline at Day 15 (Visit 6). 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 LEO 43204 treatment and evidence of any cardiac effects.
Overall, the haematology- and biochemistry laboratory parameters changes from Baseline were not clinically relevant for any of the treatment groups.

Conclusion
A total of 32 subjects out of 50 had quantifiable levels of LEO 43204: 12 subjects in the face treatment group, 10 subjects in the scalp treatment group and 10 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 (MUSE) conditions there was low (sub-nanomolar) systemic exposure when LEO 43204 gel was applied to the full face, balding scalp, or on a treatment area of approximately 250 cm$^2$ on the arm. In this maximal use setting treatment LEO 43204 gel, 0.018%, 0.037%, and 0.1%, was safe and well tolerated.
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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