Clinical Trial Report Synopsis

A Randomized, Controlled Study to Evaluate the Sensitizing Potential of LEO 43204 Gel and Vehicle Gel in Healthy Volunteers Using a Repeat Insult Patch Test Design

Design of trial:

Single-center, randomized, controlled, within-subject comparison study

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:  LP0084-1230
Date:  25-Apr-2017
Version:  Final

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Clinical Trial Report Synopsis Statement

Approval Statement, LEO Pharma A/S

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

   Kim Mark Knudsen  
   Biostatistics Lead, Biometrics

   Torsten Skov  
   Medical Lead, Medical Sciences and Safety

Approval Statement, Coordinating Investigator

The 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 (see Appendix 1.5):

   Jonathan Dosik, MD  
   Coordinating investigator
**Trial Registration Number**
NCT02650505

**EudraCT number**

**Title of Trial**
A Randomized, Controlled Study to Evaluate the Sensitizing Potential of LEO 43204 Gel and Vehicle Gel in Healthy Volunteers Using a Repeat Insult Patch Test Design

**Investigators**
Jonathan Dosik, MD, TKL Research, Inc., United States of America, was appointed as signatory investigator

**Trial Centres**
This trial was conducted at 1 centre in the United States.

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

**Clinical Trial Period**
Date of First Subject First Visit: 21-Jan-2016
Date of Last Subject Last Visit: 11-Jun-2016

**Development Phase**
Phase 1

**Objectives**
The objective of the pilot study was to determine the optimal dosing conditions for LEO 43204 gel (0.012%) to be used on a larger population by evaluating local tolerability after repeated topical applications to the healthy skin of 20 volunteers under controlled conditions.

The primary objective of the full panel study was to determine the potential of LEO 43204 gel (0.012%) to induce sensitization by repeated topical application to the healthy skin of humans under controlled conditions.

In addition, safety was assessed by evaluation of any adverse events (AEs) reported during the study.

**Methodology**
This was a randomized, single-center, controlled, within-subject comparison study of the sensitization potential of the investigational product (IP), LEO 43204 gel, under open conditions in healthy volunteers. The trial consisted of 3 phases (induction, rest phase, and challenge). Additionally, a rechallenge could be performed if a subject showed signs of contact sensitization.

**Induction Phase:** The induction phase consisted of a series of 9 applications of the investigational product (IP) and subsequent evaluations of the test sites. The IP was applied 3 times weekly for 3 consecutive weeks. The subjects returned to the trial site at 48 ± 2-hour intervals (72 ± 2 hours if IP was applied on Friday) to have the test sites evaluated. Identical product was then to be applied to the same sites.

Irritation scores, skin effect scores, and response notations were recorded.

**Rest Phase:** During the rest phase of approximately 10-14 days, subjects did not receive any application of IP.

**Challenge Phase:** At challenge, subjects who had completed the induction phase and the rest phase had the IP applied directly to naïve sites using the same methods employed during induction. Subjects returned for evaluation of test sites 48 ± 2 hours after application and then 24 ± 2 hours, 48 ± 2, and 72 ± 2 hours later. To be considered a completed case, a subject must have received 9 applications of the IP and no fewer than 8 subsequent readings during induction and one application followed by subsequent readings during challenge. Only completed cases were used to assess sensitization.

**Rechallenge:** A subject was to be rechallenged to the IP if the investigator observed any signs suggestive of contact sensitization (definite erythema with papules and/or edema) at any of the evaluations following the challenge application.

**Number of Subjects Planned and Analysed**
200 subjects were planned (20 in the pilot study; 180 in the main study) and 233 subjects (30 in the pilot study; 203 in the main study) were allocated to treatment.

**Diagnosis and Main Criteria for Inclusion**
Eligible subjects were healthy men and non-pregnant, non-breastfeeding women, 18–65 years of age, who were free of any systemic or dermatologic disorder which, in the opinion of the investigator, might have interfered with the study results or increased the risk of adverse events.

**Test Product, Dose and Mode of Administration, Batch Number**
LEO 43204 gel 0.012%, Lot P14046

In the pilot study, subjects received 10 µL and 30 µL of LEO 43204 gel applied topically under open conditions to the skin of the back 10 times over 6-8 weeks. In the main study, subjects received 30 µL of LEO 43204 gel applied topically under open conditions to the skin of the back 10 times over 6-8 weeks.

**Duration of Treatment**
Application of investigational products occurred 10 times over 6-8 weeks.
Reference Product, Dose and Mode of Administration, Batch Number
Vehicle gel for LEO 43204, Lot P1475

In the pilot study, subjects received 10 µL of vehicle gel applied topically under open conditions to the skin of the back 10 times over 6-8 weeks. In the main study, subjects received 30 µL of vehicle gel applied topically under open conditions to the skin of the back 10 times over 6-8 weeks.

Criteria for Evaluation
The primary endpoint was subjects with a reaction indicative of contact sensitization, based on the investigator’s observations of LSRs in the challenge and rechallenge phase.

The following additional endpoints were evaluated:
Response grades and irritation scores during the induction phase for the safety and PP populations.
Response grades and irritation scores during the challenge phase for the sensitization population.
Adverse events were summarized by system organ class (SOC), preferred term (PT), maximum relationship to study treatment, and maximum severity.

Statistical Methods
3 analysis populations were defined as follows:
The Safety population was defined as subjects who received at least 1 application of the IP. All safety analyses were performed on this population.
The Per Protocol (PP) population was defined as subjects who completed the induction phase of the study (that is, completed all 9 applications of study medication and no fewer than 8 subsequent readings during Induction). The evaluation of local tolerability was performed on this population.
The Sensitization population was defined as subjects who completed the challenge phase of the study (that is, had all 9 applications of the IP and no fewer than 8 subsequent readings during induction and one application followed by subsequent readings during Challenge). The evaluation of potential dermal sensitization was based on this population.

Assessment of the test sites was performed once at Baseline (Day 1) prior to application of IP and then 9 times during the induction phase, 4 times during the challenge phase, and, if applicable, 4 times during the rechallenge phase. Irritation responses observed at the time of examination were scored using the protocol-specified criteria. Symbols presented in the protocol were used to express the skin effects observed at the time of examination. The notations presented in the protocol could have been used in place of a score or in addition to a score to identify damage to the epidermis or spreading of a reaction beyond the patch site.

The irritation response scores were added to the skin effects scores to produce an irritation score for each reading. For the purpose of statistical analysis, irritation scores greater than 3 were captured in the listings but the numerical equivalents (maximum value of 3) were used for generating frequency tables. Frequency counts of each assigned numeric score, symbol score, and calculated irritation score at each reading for each IP were summarized.

The determination of dermal sensitization potential was based on the investigator’s observations of LSRs in the challenge phase of the study and confirmed in the rechallenge phase, if necessary.

A narrative description of reactions in the challenge and rechallenge phases was provided together with the opinion of the investigator as to whether such reactions were deemed indicative of contact sensitization. Frequency counts of each assigned numeric score, symbol score, and calculated irritation score at each reading for each IP were summarized.

Adverse events were summarized as an overall incidence of at least one event, incidence within body systems only, and incidence by body system and preferred term. Each subject contributed only once (for example, the first occurrence) to each of the rates, regardless of the number of occurrences (events) the subject experienced.

Treatment-emergent AEs (defined any AE with an onset date on or after the first IP administration date) were summarized and tabulated by the system organ class and preferred term, by severity (mild, moderate, severe, life-threatening), and by relationship to IP (none, unlikely, possible, probable, or definite).

Summary of Results

Trial Population
233 subjects were treated with at least one application/dose of the investigational medicinal products and 209 subjects (89.7%) completed the trial. 24 subjects (10.3%) discontinued the study prematurely; the most common reasons for discontinuation were lost to follow-up (2.6%) and withdrawal of consent (2.1%).

Most of the protocol deviations were evaluations performed out of the protocol-specified time windows. All treatments were applied by staff at the investigational site; thus, treatment compliance was not assessed.

Local Tolerability Results
211 subjects were included in the sensitization analysis. Neither 43204 gel (10 µL or 30 µL) nor vehicle gel showed any evidence of sensitization potential.
No subjects had any evidence of sensitization at any of the test sites during the Challenge phase; no subject displayed a dermal reaction graded 3 or higher. None of the subjects underwent rechallenge. In those subjects who had reactions during the Challenge phase, most of these were “minimal erythema, barely visible” and none were more severe than “definite erythema, readily visible; or minimal edema; or minimal papular response”.

For the PP population during the Induction phase, an irritation score of 1 was observed in up to 5 subjects at any assessment time point for the LEO 43204 gel 10 µL test sites, in up to 53 subjects for the LEO 43204 gel 30 µL test sites, in 1 subject for the vehicle test site, and in 1 subject for the untreated site at any assessment time point.

No irritation scores greater than 1 were observed during Induction for LEO 43204 gel 10 µL or vehicle, or at an untreated site. At LEO 43204 gel 30 µL test sites, irritation scores of 2 were observed in up to 18 subjects at any assessment time point, and irritation scores of 3 were observed in up to 3 subjects at any assessment time point.

**Safety Results**
A total of 21 subjects (9.0%) had a treatment-emergent adverse event (TEAE) during the study. Only 1 TEAE (mild dizziness) was considered possibly related to the study treatment. No serious or severe adverse events were reported.

2 subjects were withdrawn from study treatment owing to a TEAE: 1 subject for moderate contact dermatitis and 1 subject for moderate nasopharyngitis. Both of these TEAEs were considered unrelated to study treatment.

1 subject had a positive pregnancy test result at the end of study visit. She planned to terminate the unplanned pregnancy, but did not respond to the site’s attempts at follow up.

**Conclusion**
There was no evidence of sensitization to LEO 43204 gel or to the vehicle gel. Adverse events were reported in less than 10% of subjects, and only 1 event was considered treatment related. LEO 43204 gel appears to be safe under the conditions of this study and did not induce sensitization by repeated topical application.
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