Clinical trial results:
A psoriasis plaque test trial with LEO 90100 compared to Betesil® in patients with psoriasis vulgaris

Summary

EudraCT number	2015-001798-41
Trial protocol	FR
Global end of trial date	07 December 2015

Results information

Result version number	v1 (current)
This version publication date	14 December 2016
First version publication date	14 December 2016

Trial information

Trial identification

Sponsor protocol code	LP0053-1227

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02518048
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	LEO Pharma A/S
Sponsor organisation address	Industriparken 55, Ballerup, Denmark, 2750
Public contact	Clinical Trials Disclosure Manager, LEO Pharma A/S, 45 4494 5888, ctr.disclosure@leo-pharma.com
Scientific contact	Clinical Trials Disclosure Manager, LEO Pharma A/S, 45 4494 5888, ctr.disclosure@leo-pharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 December 2015
Global end of trial reached?	Yes
Global end of trial date	07 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the anti-psoriatic effect of LEO 90100 aerosol foam compared with Betesil® medicated plaster.

Protection of trial subjects:

The clinical trial was conducted to conform to the principles of the Declaration of Helsinki as adopted by the 18th World Medical Association General Assembly, 1964, and subsequent amendments.

All subjects received written and verbal information concerning the clinical trial. This information emphasised that participation in the clinical trial was voluntary and that the subject could withdraw from the clinical trial at any time and for any reason. All subjects were given an opportunity to ask questions and were given sufficient time to consider before consenting.

Background therapy: -

Evidence for comparator:

The active comparator used in this trial is Betesil® medicated plaster, a potent corticosteroid indicated for the treatment of psoriasis vulgaris and other inflammatory skin disorders. Each plaster contains 2.25 mg of betamethasone 17-valerate and may be cut to fit the shape and size of the plaque to be treated. Betesil® medicated plaster has been on the market in the US and in Europe for several years and is considered safe and effective.

The aim of this trial was to evaluate the anti-psoriatic effect of LEO 90100 compared with Betesil® medicated plaster by using a psoriasis plaque test.

Actual start date of recruitment	07 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	28
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

35 subjects from 1 centre in France were enrolled into the trial. The first subject was enrolled on 22-Sep-2015 and the last subject completed the trial (last visit, including follow-up) on 07-Dec-2015.

Pre-assignment

Screening details:

There were no screening failures.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[1]

Blinding implementation details:

All applications of trial medication were performed by designated trial personnel at the trial site.
Only they had access to the randomisation code list with the application schemes.
The investigators performing the clinical assessments were not allowed to apply trial medication or to replace the non-occlusive gauze and the medicated plaster, and subjects were instructed not to reveal any information about the trial medications to them.

Arms

Are arms mutually exclusive?	No
Arm title	LEO 90100 aerosol foam

Arm description:

Each subject had 6 test sites located within 2 or 3 psoriasis plaques on the body. Depending on the size of these plaques, 2 or 4 test sites were located within the same plaque. Treatments were allocated randomly but always pair-wise within each plaque.

Arm type	Experimental
Investigational medicinal product name	LEO 90100
Investigational medicinal product code	
Other name	Enstilar®
Pharmaceutical forms	Cutaneous foam
Routes of administration	Topical use

Dosage and administration details:

At the Screening Visit, 2 or preferably 3 lesions (“target plaques”) were identified on the arms, legs, and/or trunk of the subject. At Baseline, the investigator selected a total of 6 small sites (“test sites”; each 5 cm²) within these target plaques.
Test sites were marked with a numbered, disposable circular device attached to the skin and mapped on a drawn figure. Further, the outline of each circular device was drawn on the skin using an indelible marker.

Following randomisation, the site staff applied the 2 treatments to the test sites (each treatment to 3 designated test sites):
--LEO 90100 (calcipotriol (as monohydrate) 50 mcg/g and betamethasone (as dipropionate) 0.5 mg/g) was sprayed on the test sites and gently rubbed into the skin using a gloved finger. Each test site was treated with 50 mg of LEO 90100 (amount left after evaporation of propellants).

Investigational medicinal product name	Betesil®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicated plaster
Routes of administration	Topical use

Dosage and administration details:

At the Screening Visit, 2 or preferably 3 lesions (“target plaques”) were identified on the arms, legs, and/or trunk of the subject. At Baseline, the investigator selected a total of 6 small sites (“test sites”; each 5 cm²) within these target plaques.
Test sites were marked with a numbered, disposable circular device attached to the skin and mapped on a drawn figure. Further, the outline of each circular device was drawn on the skin using an indelible marker.

Following randomisation, the site staff applied the 2 treatments to the test sites (each treatment to 3 designated test sites):
--Betesil® (betamethasone (as valerate)) medicated plasters were cut into smaller pieces, each piece with the size of a test site. These pieces of plaster were then attached to the 3 test sites.

Arm title	Betesil®

Arm description:

Each subject had 6 test sites located within 2 or 3 psoriasis plaques on the body. Depending on the size of these plaques, 2 or 4 test sites were located within the same plaque. Treatments were allocated randomly but always pair-wise within each plaque.

Arm type	Active comparator
Investigational medicinal product name	Betesil®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicated plaster
Routes of administration	Topical use

Dosage and administration details:

At the Screening Visit, 2 or preferably 3 lesions (“target plaques”) were identified on the arms, legs, and/or trunk of the subject. At Baseline, the investigator selected a total of 6 small sites (“test sites”; each 5 cm²) within these target plaques.
Test sites were marked with a numbered, disposable circular device attached to the skin and mapped on a drawn figure. Further, the outline of each circular device was drawn on the skin using an indelible marker.

Following randomisation, the site staff applied the 2 treatments to the test sites (each treatment to 3 designated test sites):
--Betesil® (betamethasone (as valerate)) medicated plasters were cut into smaller pieces, each piece with the size of a test site. These pieces of plaster were then attached to the 3 test sites.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Due to the different formulations of the 2 IMPs (foam versus plaster), a double-blind design was not possible and the trial was performed as an investigator-blinded trial.

Number of subjects in period 1	LEO 90100 aerosol foam	Betesil®
Started	35	35
Completed	34	34
Not completed	1	1
Consent withdrawn by subject	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	35	35	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	28	28	
From 65-84 years	7	7	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	10	10	
Male	25	25	

End points

End points reporting groups

Reporting group title	LEO 90100 aerosol foam

Reporting group description:

Each subject had 6 test sites located within 2 or 3 psoriasis plaques on the body. Depending on the size of these plaques, 2 or 4 test sites were located within the same plaque. Treatments were allocated randomly but always pair-wise within each plaque.

Reporting group title	Betesil®

Reporting group description:

Each subject had 6 test sites located within 2 or 3 psoriasis plaques on the body. Depending on the size of these plaques, 2 or 4 test sites were located within the same plaque. Treatments were allocated randomly but always pair-wise within each plaque.

Primary: Absolute change in Total Clinical Score (TCS) of clinical signs (sum of erythema, scaling, and infiltration) at end of treatment compared to Baseline

End point title	Absolute change in Total Clinical Score (TCS) of clinical signs (sum of erythema, scaling, and infiltration) at end of treatment compared to Baseline

End point description:

The investigator assessed the severity of the clinical signs erythema, scaling, and infiltration for each test site by using a 7-point scale with half-mark values from 0 (no evidence) to 3.0 (severe).
TCS was calculated for each test site by summing the scores for erythema, scaling, and infiltration for that particular test site.

Each test site was assessed at Baseline and on Days 4, 8, 11, 15, 18, 22, 25, and 29 (EoT).

The mean TCS at Baseline was 6.6 for both groups.

End point type	Primary

End point timeframe:

Baseline to End of Treatment (EoT)

End point values	LEO 90100 aerosol foam	Betesil®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Units on a scale				
arithmetic mean (standard deviation)				
TCS at Baseline	6.6 (± 0.6)	6.6 (± 0.6)		
Change in TCS Baseline to EoT	-5.8 (± 1.1)	-3.6 (± 1.5)		

Statistical analyses

Statistical analysis title	Comparison

Statistical analysis description:

A last observation carried forward (LOCF) approach was used to account for drop-outs and missing values in the analysis of end of treatment values.

The number of subjects in the analysis is 35 - not 70. All 35 subjects received both treatments.

Comparison groups	LEO 90100 aerosol foam v Betesil®
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.58
upper limit	-1.76

Notes:

[1] - Least Square Means difference from ANOVA with treatment group as fixed effect and subject as random effect (105 treated sites per treatment group).

Secondary: Change in TCS at Individual Visits

End point title	Change in TCS at Individual Visits

End point description:

The investigator assessed the severity of the clinical signs erythema, scaling, and infiltration for each test site by using a 7-point scale with half-mark values from 0 (no evidence) to 3.0 (severe).
TCS was calculated for each test site by summing the scores for erythema, scaling, and infiltration for that particular test site.

Each test site was assessed at Baseline and on Days 4, 8, 11, 15, 18, 22, 25, and 29 (EoT).

End point type	Secondary

End point timeframe:

Baseline to End of Treatment

End point values	LEO 90100 aerosol foam	Betesil®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: Units on a score				
arithmetic mean (standard deviation)				
Day 4/Visit 5	-1.3 (± 0.8)	-1.3 (± 0.7)		
Day 8/Visit 8	-3.2 (± 1.2)	-2 (± 1.1)		
Day 11/Visit 11	-4.3 (± 1.1)	-2.4 (± 1.4)		
Day 15/Visit 15	-4.8 (± 1.2)	-2.8 (± 1.4)		
Day 17/Visit 18	-5.1 (± 1.2)	-3.1 (± 1.5)		
Day 22/Visit 20	-5.5 (± 1.2)	-3.2 (± 1.6)		
Day 25/Visit 23	-5.7 (± 1.1)	-3.6 (± 1.6)		
Day 29/Visit 26	-5.9 (± 1.1)	-3.7 (± 1.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Score of Erythema, Scaling, and Infiltration at Individual Visits

End point title	Change in Score of Erythema, Scaling, and Infiltration at Individual Visits

End point description:

End point type	Secondary

End point timeframe:

Baseline to End of Treatment

End point values	LEO 90100 aerosol foam	Betesil®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: units on a scale				
arithmetic mean (standard deviation)				
Erythema Day 4/Visit 5	-0.5 (± 0.4)	-0.4 (± 0.4)		
Erythema Day 8/Visit 8	-0.9 (± 0.4)	-0.6 (± 0.4)		
Erythema Day 11/Visit 11	-1.3 (± 0.5)	-0.8 (± 0.5)		
Erythema Day 15/Visit 14	-1.4 (± 0.5)	-0.9 (± 0.5)		
Erythema Day 18/Visit 17	-1.6 (± 0.6)	-1 (± 0.6)		
Erythema Day 22/Visit 20	-1.7 (± 0.6)	-1.1 (± 0.6)		
Erythema Day 25/Visit 23	-1.8 (± 0.6)	-1.3 (± 0.6)		
Erythema Day 29/Visit 26	-1.9 (± 0.5)	-1.2 (± 0.6)		
Scaling Day 4/Visit 5	-0.6 (± 0.3)	-0.6 (± 0.3)		
Scaling Day 8/Visit 8	-1.3 (± 0.5)	-0.8 (± 0.5)		
Scaling Day 11/Visit 11	-1.7 (± 0.5)	-1 (± 0.6)		
Scaling Day 15/Visit 14	-1.8 (± 0.5)	-1.1 (± 0.6)		
Scaling Day 18/Visit 17	-1.9 (± 0.5)	-1.2 (± 0.6)		
Scaling Day 22/Visit 20	-2 (± 0.5)	-1.2 (± 0.6)		
Scaling Day 25/Visit 23	-2 (± 0.4)	-1.4 (± 0.6)		
Scaling Day 29/Visit 26	-2 (± 0.4)	-1.3 (± 0.6)		
Infiltration Day 4/Visit 5	-0.3 (± 0.2)	-0.3 (± 0.2)		
Infiltration Day 8/Visit 8	-0.9 (± 0.5)	-0.5 (± 0.4)		
Infiltration Day 11/Visit 11	-1.3 (± 0.4)	-0.6 (± 0.5)		
Infiltration Day 15/Visit 14	-1.6 (± 0.4)	-0.8 (± 0.5)		
Infiltration Day 18/Visit 17	-1.7 (± 0.4)	-0.8 (± 0.6)		
Infiltration Day 22/Visit 20	-1.8 (± 0.3)	-0.9 (± 0.6)		
Infiltration Day 25/Visit 23	-1.9 (± 0.3)	-1 (± 0.6)		
Infiltration Day 29/Visit 26	-1.9 (± 0.3)	-1.1 (± 0.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in total skin thickness and echo-poor band thickness from Baseline to EoT

End point title	Change in total skin thickness and echo-poor band thickness from Baseline to EoT

End point description:

Skin thickness ultrasound measurements of the test sites were performed at Baseline and End of Treatment.

Two skin parameters were calculated using ultrasound:
--The mean total skin thickness
--The mean echo-poor band thickness

End point type	Secondary

End point timeframe:

Baseline to EoT

End point values	LEO 90100 aerosol foam	Betesil®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	35		
Units: millimeter(s)				
arithmetic mean (standard deviation)				
Change in Total Skin Thickness	-1 (± 0.3)	-0.6 (± 0.4)		
Change in Echo-Poor Band Thickness	-1.3 (± 0.5)	-0.7 (± 0.5)		

Statistical analyses

Statistical analysis title	Total Skin Thickness: LEO 90100 vs. Betesil®
Comparison groups	LEO 90100 aerosol foam v Betesil®
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	-0.32

Notes:

[2] - Least Square Means difference from ANOVA with treatment group as fixed effect and subject as random effect (105 treated sites per treatment group)

Statistical analysis title	Echo-Poor Band Thickness: LEO 90100 vs. Betesil®
Comparison groups	Betesil® v LEO 90100 aerosol foam

Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [3]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.69
upper limit	-0.41

Notes:

[3] - Least Square Means difference from ANOVA with treatment group as fixed effect and subject as random effect (105 treated sites per treatment group)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From signed Informed consent form (Day -28 to -1) to end of Follow-up (Day 43 +/-2).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	All subjects

Reporting group description: -

Serious adverse events	All subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 35 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	All subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 35 (42.86%)		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 35 (14.29%)		
occurrences (all)	8		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain subjects affected / exposed occurrences (all) Asthma subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3 1 / 35 (2.86%) 1		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 1 / 35 (2.86%) 1 1 / 35 (2.86%) 1		
Infections and infestations Influenza subjects affected / exposed occurrences (all) Hordeolum subjects affected / exposed occurrences (all)	 3 / 35 (8.57%) 3 1 / 35 (2.86%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 August 2015	One substantial amendment was made to the clinical trial protocol to include the new address of the contract manufacturing organisation responsible for the secondary packaging, labelling, and distribution of IMP. The contract manufacturing organisation was also responsible for the destruction of returned IMP. The new version of the clinical trial protocol (version 2, dated 26-Aug-2015) was approved by the regulatory authority prior to trial start.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported