



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

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 | | | |
| Gastroesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

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