



## Clinical trial results:

**LEO 32731 for the treatment of moderate to severe psoriasis vulgaris**  
**A phase 2a proof of concept study comparing an oral tablet formulation of LEO 32731 with a corresponding placebo tablet in patients with moderate to severe psoriasis vulgaris.**

**A multi-centre, prospective, randomized, double-blind, 2-arm, placebo-controlled, parallel-group study with 16 weeks twice times daily oral treatment.**

## Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-005279-25 |
| Trial protocol           | DE             |
| Global end of trial date | 06 July 2017   |

## Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 17 October 2018 |
| First version publication date | 17 October 2018 |

## Trial information

### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | LP0058-1072 |
|-----------------------|-------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02888236 |
| 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 Disclosure Specialist, LEO Pharma A/S, +45 44945888, disclosure@leo-pharma.com |
| Scientific contact           | Clinical Disclosure Specialist, LEO Pharma A/S, +45 44945888, 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:

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**Results analysis stage**

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|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 01 February 2018 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 06 July 2017     |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 06 July 2017     |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

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Main objective of the trial:

To investigate the efficacy of LEO 32731 30 mg compared with that of placebo after 16 weeks of oral treatment of psoriasis vulgaris.

Protection of trial subjects:

This 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 the amendment from Somerset West, South Africa, October 1996. All subjects received written and verbal information concerning the clinical trial. Subjects were asked to consent that their personal data were recorded, collected, processed and could be transferred to other countries in accordance with any national legislation regulating privacy and data protection.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 01 July 2016 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 36 |
| Worldwide total number of subjects   | 36          |
| EEA total number of subjects         | 36          |

Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| 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)                      | 36 |
| From 65 to 84 years                       | 0  |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

50 subjects were screened and 14 subjects were screening failures. 36 subjects were randomised: 18 to each treatment. The randomised subjects were enrolled at 7 trial sites in Germany.

### Pre-assignment

Screening details:

Key inclusion criteria:

Moderate to severe psoriasis vulgaris with or without psoriatic arthritis (maximum 4 joints with active arthritis) for  $\geq 6$  months prior to screening.

Men, or women of non-childbearing potential.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Investigator, Subject          |

Blinding implementation details:

The packaging and labelling of the IMPs contained no evidence of their identity. It was not considered possible to differentiate between the IMPs solely by sensory evaluation.

### Arms

|                              |                 |
|------------------------------|-----------------|
| Are arms mutually exclusive? | Yes             |
| <b>Arm title</b>             | LEO 32731 30 mg |

Arm description:

Subjects received twice daily treatment for 16 weeks: a 1-week dose escalation followed by 15 weeks of full dose treatment.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Placebo      |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Each dose consisted of 3 tablets, including 1 or 2 placebo tablets in combination with 1 or 2 LEO 32731 tablets, supplied at a strength of 10 mg or 30 mg.

Subjects were dosed twice daily as follows: Days 1–3: 1 tablet LEO 32731 10 mg + 2 placebo tablets; Days 4–6: 2 tablets LEO 32731 10 mg + 1 placebo tablet; Day 7–Week 16 : 1 tablet LEO 32731 30 mg + 2 placebo tablets.

|  |           |
|--|-----------|
| Investigational medicinal product name | LEO 32731 |
| Investigational medicinal product code |           |
| Other name                             |           |
| Pharmaceutical forms                   | Tablet    |
| Routes of administration               | Oral use  |

Dosage and administration details:

Each dose consisted of 3 tablets, including 1 or 2 placebo tablets in combination with 1 or 2 LEO 32731 tablets, supplied at a strength of 10 mg or 30 mg.

Subjects were dosed twice daily as follows: Days 1–3: 1 tablet LEO 32731 10 mg + 2 placebo tablets; Days 4–6: 2 tablets LEO 32731 10 mg + 1 placebo tablet; Day 7–Week 16 : 1 tablet LEO 32731 30 mg + 2 placebo tablets.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Subjects received twice daily treatment for 16 weeks.

|  |          |
|--|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

Subjects received 3 placebo tablets twice daily for 16 weeks.

| <b>Number of subjects in period 1</b> | LEO 32731 30 mg | Placebo |
|---------------------------------------|-----------------|---------|
| Started                               | 18              | 18      |
| Completed                             | 8               | 9       |
| Not completed                         | 10              | 9       |
| Consent withdrawn by subject          | 1               | -       |
| Adverse event, non-fatal              | 9               | 3       |
| Lost to follow-up                     | -               | 1       |
| Lack of efficacy                      | -               | 5       |

## Baseline characteristics

### Reporting groups

Reporting group title

Overall trial

Reporting group description: -

| Reporting group values                                | Overall trial | Total |  |
|---|---------------|-------|--|
| Number of subjects                                    | 36            | 36    |  |
| Age categorical                                       |               |       |  |
| Units: Subjects                                       |               |       |  |
| In utero  | 0             | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0             | 0     |  |
| Newborns (0-27 days)                                  | 0             | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0             | 0     |  |
| Children (2-11 years)                                 | 0             | 0     |  |
| Adolescents (12-17 years)                             | 0             | 0     |  |
| Adults (18-64 years)                                  | 36            | 36    |  |
| From 65-84 years                                      | 0             | 0     |  |
| 85 years and over                                     | 0             | 0     |  |
| Age continuous  |               |       |  |
| Units: years  |               |       |  |
| median  | 46.5          |       |  |
| full range (min-max)                                  | 20 to 61      | -     |  |
| Gender categorical                                    |               |       |  |
| Units: Subjects                                       |               |       |  |
| Female  | 3             | 3     |  |
| Male  | 33            | 33    |  |

## End points

### End points reporting groups

|   |                 |
|---|-----------------|
| Reporting group title   | LEO 32731 30 mg |
| Reporting group description:  |                 |
| Subjects received twice daily treatment for 16 weeks: a 1-week dose escalation followed by 15 weeks of full dose treatment. |                 |
| Reporting group title   | Placebo         |
| Reporting group description:  |                 |
| Subjects received twice daily treatment for 16 weeks.   |                 |

### Primary: PASI at Week 16

|   |                 |
|---|-----------------|
| End point title   | PASI at Week 16 |
| End point description:  |                 |
| The PASI score is an investigator assessment that grades the extent and severity of psoriatic involvement for each of four body regions (head and neck, upper extremities, trunk, and lower extremities) using a 7-point scale for extent of involvement in each body region and 5-point scales for severity of each of the clinical signs redness, thickness, and scaliness in each body region. |                 |
| End point type  | Primary         |
| End point timeframe:  |                 |
| At Week 16  |                 |

| End point values                             | LEO 32731 30 mg   | Placebo             |  |  |
|--|-------------------|---------------------|--|--|
| Subject group type                           | Reporting group   | Reporting group     |  |  |
| Number of subjects analysed                  | 18 <sup>[1]</sup> | 18 <sup>[2]</sup>   |  |  |
| Units: Score on a scale                      |                   |                     |  |  |
| least squares mean (confidence interval 95%) | 7.1 (4.3 to 9.9)  | 13.1 (10.3 to 15.9) |  |  |

Notes:

[1] - Based on last observation carried forward (LOCF)

[2] - Based on last observation carried forward (LOCF)

### Statistical analyses

|   |                                |
|---|--------------------------------|
| Statistical analysis title  | ANCOVA with LOCF               |
| Statistical analysis description:   |                                |
| Based on an analysis of covariance (ANCOVA) model with treatment and site as factors and baseline value as covariate. |                                |
| Comparison groups   | LEO 32731 30 mg v Placebo      |
| Number of subjects included in analysis   | 36                             |
| Analysis specification  | Pre-specified                  |
| Analysis type   | superiority                    |
| P-value   | = 0.005                        |
| Method  | ANCOVA                         |
| Parameter estimate  | Mean difference (final values) |
| Point estimate  | -6                             |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -10     |
| upper limit         | -2      |

## Secondary: PGA treatment success at Week 16

|  |                                  |
|--|----------------------------------|
| End point title  | PGA treatment success at Week 16 |
| End point description:   |                                  |
| Physician's Global Assessment of disease severity (PGA) is done on a 5-point ordinal scale and represents the average lesion severity on the trunk, limbs, and scalp. The assessment is based on the condition of the disease at the time of evaluation. Treatment success according to PGA is defined as reaching either of the 2 lowest points on the ordinal scale: 'clear' or 'almost clear' |                                  |
| End point type   | Secondary                        |
| End point timeframe:   |                                  |
| At Week 16   |                                  |

|                             |                   |                   |  |  |
|-----------------------------|-------------------|-------------------|--|--|
| <b>End point values</b>     | LEO 32731 30 mg   | Placebo           |  |  |
| Subject group type          | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed | 18 <sup>[3]</sup> | 18 <sup>[4]</sup> |  |  |
| Units: Subjects             | 7                 | 1                 |  |  |

Notes:

[3] - Based on LOCF

[4] - Based on LOCF

## Statistical analyses

|   |                               |
|---|-------------------------------|
| <b>Statistical analysis title</b>       | Logistic regression with LOCF |
| Statistical analysis description:       |                               |
| Adjusted for pooled site.               |                               |
| Comparison groups                       | LEO 32731 30 mg v Placebo     |
| Number of subjects included in analysis | 36                            |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority                   |
| P-value                                 | = 0.032 <sup>[5]</sup>        |
| Method                                  | Regression, Logistic          |
| Parameter estimate                      | Odds ratio (OR)               |
| Point estimate                          | 12.3                          |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 1.7                           |
| upper limit                             | 256.1                         |

Notes:

[5] - Wald test; test for the hypothesis of odds ratio (LEO 32731 30 mg relative to placebo) equal to 1



## Secondary: Itch NRS at Week 16

|   |                     |
|---|---------------------|
| End point title   | Itch NRS at Week 16 |
| End point description:<br>Subject assessment of the maximal intensity of itch during the previous 24 hours on a numeric rating scale (NRS) ranging from 0 (no itch at all) to 10 (worst itch imaginable). |                     |
| End point type  | Secondary           |
| End point timeframe:<br>At Week 16  |                     |

|  |                   |                   |  |  |
|--|-------------------|-------------------|--|--|
| <b>End point values</b>                      | LEO 32731 30 mg   | Placebo           |  |  |
| Subject group type                           | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed                  | 18 <sup>[6]</sup> | 18 <sup>[7]</sup> |  |  |
| Units: Score on a scale                      |                   |                   |  |  |
| least squares mean (confidence interval 95%) | 3.4 (1.8 to 5.1)  | 5.7 (4.1 to 7.3)  |  |  |

Notes:

[6] - Based on LOCF

[7] - Based on LOCF

## Statistical analyses

|   |                                |
|---|--------------------------------|
| <b>Statistical analysis title</b>   | ANCOVA with LOCF               |
| Statistical analysis description:<br>Based on an ANCOVA model with treatment and site as factors and baseline value as covariate. |                                |
| Comparison groups   | LEO 32731 30 mg v Placebo      |
| Number of subjects included in analysis   | 36                             |
| Analysis specification  | Pre-specified                  |
| Analysis type   | superiority                    |
| P-value   | = 0.053                        |
| Method  | ANCOVA                         |
| Parameter estimate  | Mean difference (final values) |
| Point estimate  | -2.3                           |
| Confidence interval   |                                |
| level   | 95 %                           |
| sides   | 2-sided                        |
| lower limit   | -4.6                           |
| upper limit   | 0                              |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the time informed consent was signed until the end of trial.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | LEO 32731 30 mg |
|-----------------------|-----------------|

Reporting group description:

All subjects who received at least 1 dose of trial medication and for whom safety data were available post-baseline.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

All subjects who received at least 1 dose of trial medication and for whom safety data were available post-baseline

| Serious adverse events                               | LEO 32731 30 mg   | Placebo        |  |
|--|---|----------------|--|
| Total subjects affected by serious adverse events    |   |                |  |
| subjects affected / exposed                          | 2 / 18 (11.11%)   | 1 / 18 (5.56%) |  |
| number of deaths (all causes)                        | 0   | 0              |  |
| number of deaths resulting from adverse events       | 0   | 0              |  |
| General disorders and administration site conditions |   |                |  |
| Condition aggravated                                 | Additional description: Relating to pre-existing Scheuermann's disease. |                |  |
| subjects affected / exposed                          | 0 / 18 (0.00%)  | 1 / 18 (5.56%) |  |
| occurrences causally related to treatment / all      | 0 / 0   | 0 / 1          |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0          |  |
| Renal and urinary disorders                          |   |                |  |
| Ureterolithiasis                                     |   |                |  |
| subjects affected / exposed                          | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1   | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0          |  |
| Infections and infestations                          |   |                |  |
| Erysipelas   |   |                |  |
| subjects affected / exposed                          | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1   | 0 / 0          |  |
| deaths causally related to treatment / all           | 0 / 0   | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                     | LEO 32731 30 mg  | Placebo          |  |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 17 / 18 (94.44%) | 16 / 18 (88.89%) |  |
| Vascular disorders                                    |                  |                  |  |
| Haematoma   |                  |                  |  |
| subjects affected / exposed                           | 0 / 18 (0.00%)   | 1 / 18 (5.56%)   |  |
| occurrences (all)                                     | 0                | 1                |  |
| Hot flush   |                  |                  |  |
| subjects affected / exposed                           | 1 / 18 (5.56%)   | 0 / 18 (0.00%)   |  |
| occurrences (all)                                     | 1                | 0                |  |
| Hypertension  |                  |                  |  |
| subjects affected / exposed                           | 0 / 18 (0.00%)   | 1 / 18 (5.56%)   |  |
| occurrences (all)                                     | 0                | 1                |  |
| General disorders and administration site conditions  |                  |                  |  |
| Fatigue   |                  |                  |  |
| subjects affected / exposed                           | 2 / 18 (11.11%)  | 0 / 18 (0.00%)   |  |
| occurrences (all)                                     | 2                | 0                |  |
| Pain  |                  |                  |  |
| subjects affected / exposed                           | 1 / 18 (5.56%)   | 1 / 18 (5.56%)   |  |
| occurrences (all)                                     | 1                | 1                |  |
| Face oedema   |                  |                  |  |
| subjects affected / exposed                           | 1 / 18 (5.56%)   | 0 / 18 (0.00%)   |  |
| occurrences (all)                                     | 1                | 0                |  |
| Feeling cold  |                  |                  |  |
| subjects affected / exposed                           | 1 / 18 (5.56%)   | 0 / 18 (0.00%)   |  |
| occurrences (all)                                     | 1                | 0                |  |
| Influenza like illness                                |                  |                  |  |
| subjects affected / exposed                           | 1 / 18 (5.56%)   | 0 / 18 (0.00%)   |  |
| occurrences (all)                                     | 1                | 0                |  |
| Peripheral swelling                                   |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                 | 0 / 18 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                           | 0               | 1               |  |
| Thirst                                      |                 |                 |  |
| subjects affected / exposed                 | 0 / 18 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                           | 0               | 1               |  |
| Psychiatric disorders                       |                 |                 |  |
| Insomnia                                    |                 |                 |  |
| subjects affected / exposed                 | 2 / 18 (11.11%) | 2 / 18 (11.11%) |  |
| occurrences (all)                           | 2               | 2               |  |
| Thinking abnormal                           |                 |                 |  |
| subjects affected / exposed                 | 2 / 18 (11.11%) | 0 / 18 (0.00%)  |  |
| occurrences (all)                           | 2               | 0               |  |
| Depressed mood                              |                 |                 |  |
| subjects affected / exposed                 | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |  |
| occurrences (all)                           | 1               | 0               |  |
| Sleep disorder                              |                 |                 |  |
| subjects affected / exposed                 | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |  |
| occurrences (all)                           | 1               | 0               |  |
| Investigations                              |                 |                 |  |
| Red blood cell sedimentation rate increased |                 |                 |  |
| subjects affected / exposed                 | 3 / 18 (16.67%) | 3 / 18 (16.67%) |  |
| occurrences (all)                           | 4               | 4               |  |
| C-reactive protein increased                |                 |                 |  |
| subjects affected / exposed                 | 2 / 18 (11.11%) | 1 / 18 (5.56%)  |  |
| occurrences (all)                           | 3               | 4               |  |
| Alanine aminotransferase increased          |                 |                 |  |
| subjects affected / exposed                 | 2 / 18 (11.11%) | 0 / 18 (0.00%)  |  |
| occurrences (all)                           | 3               | 0               |  |
| Aspartate aminotransferase increased        |                 |                 |  |
| subjects affected / exposed                 | 1 / 18 (5.56%)  | 0 / 18 (0.00%)  |  |
| occurrences (all)                           | 1               | 0               |  |
| Blood creatine phosphokinase increased      |                 |                 |  |
| subjects affected / exposed                 | 0 / 18 (0.00%)  | 1 / 18 (5.56%)  |  |
| occurrences (all)                           | 0               | 1               |  |
| Weight decreased                            |                 |                 |  |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 18 (5.56%)<br>1 | 0 / 18 (0.00%)<br>0 |  |
| Injury, poisoning and procedural complications   |                     |                     |  |
| Joint injury                                     |                     |                     |  |
| subjects affected / exposed                      | 0 / 18 (0.00%)      | 1 / 18 (5.56%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Muscle strain                                    |                     |                     |  |
| subjects affected / exposed                      | 1 / 18 (5.56%)      | 0 / 18 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Soft tissue injury                               |                     |                     |  |
| subjects affected / exposed                      | 0 / 18 (0.00%)      | 1 / 18 (5.56%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Wound  |                     |                     |  |
| subjects affected / exposed                      | 0 / 18 (0.00%)      | 1 / 18 (5.56%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Cardiac disorders                                |                     |                     |  |
| Palpitations                                     |                     |                     |  |
| subjects affected / exposed                      | 1 / 18 (5.56%)      | 0 / 18 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Tachycardia                                      |                     |                     |  |
| subjects affected / exposed                      | 1 / 18 (5.56%)      | 0 / 18 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Nervous system disorders                         |                     |                     |  |
| Headache   |                     |                     |  |
| subjects affected / exposed                      | 5 / 18 (27.78%)     | 2 / 18 (11.11%)     |  |
| occurrences (all)                                | 7                   | 2                   |  |
| Dizziness  |                     |                     |  |
| subjects affected / exposed                      | 4 / 18 (22.22%)     | 0 / 18 (0.00%)      |  |
| occurrences (all)                                | 5                   | 0                   |  |
| Dysaesthesia                                     |                     |                     |  |
| subjects affected / exposed                      | 0 / 18 (0.00%)      | 1 / 18 (5.56%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Hypoaesthesia                                    |                     |                     |  |
| subjects affected / exposed                      | 1 / 18 (5.56%)      | 0 / 18 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Migraine   |                     |                     |  |

|   |   |  |  |
|---|---|--|--|
| subjects affected / exposed<br>occurrences (all)  | 1 / 18 (5.56%)<br>1   | 0 / 18 (0.00%)<br>0  |  |
| Blood and lymphatic system disorders<br>Lymphopenia<br>subjects affected / exposed<br>occurrences (all)   | 1 / 18 (5.56%)<br>1   | 1 / 18 (5.56%)<br>1  |  |
| Ear and labyrinth disorders<br>Hypoacusis<br>subjects affected / exposed<br>occurrences (all)<br><br>Tinnitus<br>subjects affected / exposed<br>occurrences (all)<br><br>Vertigo<br>subjects affected / exposed<br>occurrences (all)  | 1 / 18 (5.56%)<br>1<br><br>0 / 18 (0.00%)<br>0<br><br>1 / 18 (5.56%)<br>1<br><br>1 / 18 (5.56%)<br>1  | 0 / 18 (0.00%)<br>0<br><br>1 / 18 (5.56%)<br>1<br><br>0 / 18 (0.00%)<br>0  |  |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)<br><br>Flatulence<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal discomfort | 11 / 18 (61.11%)<br>16<br><br>9 / 18 (50.00%)<br>12<br><br>3 / 18 (16.67%)<br>5<br><br>3 / 18 (16.67%)<br>4<br><br>2 / 18 (11.11%)<br>4<br><br>2 / 18 (11.11%)<br>3<br><br>Abdominal discomfort | 1 / 18 (5.56%)<br>1<br><br>0 / 18 (0.00%)<br>0<br><br>1 / 18 (5.56%)<br>1<br><br>1 / 18 (5.56%)<br>1<br><br>1 / 18 (5.56%)<br>1<br><br>1 / 18 (5.56%)<br>2 |  |

|  |                 |                |  |
|--|-----------------|----------------|--|
| subjects affected / exposed            | 2 / 18 (11.11%) | 0 / 18 (0.00%) |  |
| occurrences (all)                      | 3               | 0              |  |
| Toothache                              |                 |                |  |
| subjects affected / exposed            | 1 / 18 (5.56%)  | 1 / 18 (5.56%) |  |
| occurrences (all)                      | 1               | 2              |  |
| Dyspepsia                              |                 |                |  |
| subjects affected / exposed            | 1 / 18 (5.56%)  | 1 / 18 (5.56%) |  |
| occurrences (all)                      | 1               | 1              |  |
| Faeces soft                            |                 |                |  |
| subjects affected / exposed            | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |  |
| occurrences (all)                      | 1               | 0              |  |
| Frequent bowel movements               |                 |                |  |
| subjects affected / exposed            | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |  |
| occurrences (all)                      | 1               | 0              |  |
| Gastrooesophageal reflux disease       |                 |                |  |
| subjects affected / exposed            | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |  |
| occurrences (all)                      | 1               | 0              |  |
| Haemorrhoidal haemorrhage              |                 |                |  |
| subjects affected / exposed            | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |  |
| occurrences (all)                      | 1               | 0              |  |
| Paraesthesia oral                      |                 |                |  |
| subjects affected / exposed            | 1 / 18 (5.56%)  | 0 / 18 (0.00%) |  |
| occurrences (all)                      | 1               | 0              |  |
| Skin and subcutaneous tissue disorders |                 |                |  |
| Hyperhidrosis                          |                 |                |  |
| subjects affected / exposed            | 2 / 18 (11.11%) | 1 / 18 (5.56%) |  |
| occurrences (all)                      | 2               | 1              |  |
| Prurigo                                |                 |                |  |
| subjects affected / exposed            | 0 / 18 (0.00%)  | 1 / 18 (5.56%) |  |
| occurrences (all)                      | 0               | 2              |  |
| Pruritus                               |                 |                |  |
| subjects affected / exposed            | 0 / 18 (0.00%)  | 1 / 18 (5.56%) |  |
| occurrences (all)                      | 0               | 1              |  |
| Psoriasis                              |                 |                |  |
| subjects affected / exposed            | 0 / 18 (0.00%)  | 1 / 18 (5.56%) |  |
| occurrences (all)                      | 0               | 1              |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| Seborrhoeic dermatitis<br>subjects affected / exposed<br>occurrences (all) | 0 / 18 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Renal and urinary disorders  |                      |                      |  |
| Glycosuria<br>subjects affected / exposed<br>occurrences (all)             | 2 / 18 (11.11%)<br>2 | 0 / 18 (0.00%)<br>0  |  |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)             | 0 / 18 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)            | 0 / 18 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Musculoskeletal and connective tissue disorders                            |                      |                      |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)              | 2 / 18 (11.11%)<br>2 | 2 / 18 (11.11%)<br>2 |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)          | 1 / 18 (5.56%)<br>1  | 1 / 18 (5.56%)<br>1  |  |
| Joint swelling<br>subjects affected / exposed<br>occurrences (all)         | 0 / 18 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Muscle tightness<br>subjects affected / exposed<br>occurrences (all)       | 1 / 18 (5.56%)<br>1  | 0 / 18 (0.00%)<br>0  |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)                | 1 / 18 (5.56%)<br>1  | 0 / 18 (0.00%)<br>0  |  |
| Osteoarthritis<br>subjects affected / exposed<br>occurrences (all)         | 0 / 18 (0.00%)<br>0  | 1 / 18 (5.56%)<br>1  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)      | 1 / 18 (5.56%)<br>1  | 0 / 18 (0.00%)<br>0  |  |
| Tenosynovitis  |                      |                      |  |



|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 18 (0.00%)<br>0 | 1 / 18 (5.56%)<br>1 |  |
| Infections and infestations                      |                     |                     |  |
| Nasopharyngitis                                  |                     |                     |  |
| subjects affected / exposed                      | 5 / 18 (27.78%)     | 5 / 18 (27.78%)     |  |
| occurrences (all)                                | 5                   | 6                   |  |
| Gastroenteritis                                  |                     |                     |  |
| subjects affected / exposed                      | 1 / 18 (5.56%)      | 1 / 18 (5.56%)      |  |
| occurrences (all)                                | 1                   | 1                   |  |
| Bronchitis                                       |                     |                     |  |
| subjects affected / exposed                      | 1 / 18 (5.56%)      | 0 / 18 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Gastrointestinal infection                       |                     |                     |  |
| subjects affected / exposed                      | 0 / 18 (0.00%)      | 1 / 18 (5.56%)      |  |
| occurrences (all)                                | 0                   | 1                   |  |
| Gingivitis                                       |                     |                     |  |
| subjects affected / exposed                      | 1 / 18 (5.56%)      | 0 / 18 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Pulpitis dental                                  |                     |                     |  |
| subjects affected / exposed                      | 1 / 18 (5.56%)      | 0 / 18 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Rhinitis   |                     |                     |  |
| subjects affected / exposed                      | 1 / 18 (5.56%)      | 0 / 18 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Soft tissue infection                            |                     |                     |  |
| subjects affected / exposed                      | 1 / 18 (5.56%)      | 0 / 18 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Tonsillitis                                      |                     |                     |  |
| subjects affected / exposed                      | 1 / 18 (5.56%)      | 0 / 18 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Metabolism and nutrition disorders               |                     |                     |  |
| Decreased appetite                               |                     |                     |  |
| subjects affected / exposed                      | 2 / 18 (11.11%)     | 0 / 18 (0.00%)      |  |
| occurrences (all)                                | 3                   | 0                   |  |
| Hypertriglyceridaemia                            |                     |                     |  |

|                             |                |                |  |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 18 (5.56%) | 0 / 18 (0.00%) |  |
| occurrences (all)           | 1              | 0              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 06 June 2016     | Before any subjects were screened, the protocol was amended to address objections from the regulatory authority and the central IEC, and to take into account new findings on the tolerability of LEO 32731 that emerged from another phase 1 trial. The trial design was changed as follows: The maximum dose of LEO 32731 was reduced from 50 mg twice daily to 30 mg twice daily, and the number of trial arms was reduced from 4 to 2. According the original protocol, subjects were to be randomised to twice daily doses of 30 mg, 40 mg, or 50 mg LEO 32731 or placebo in a 1:1:1:1 ratio. According to the amended protocol, subjects were randomised to twice daily doses of 30 mg LEO 32731 or placebo in a 1:1 ratio. As a consequence, the number of subjects to be randomised was reduced from 72 to 36, and the percentage of subjects to be treated with LEO 32731 was reduced from 75% to 50%. |
| 21 December 2016 | During the trial conduct, the protocol was amended to allow trial sites to include more subjects. The maximum number of subjects per trial site was increased from 8 subjects to approximately one third of the total number of subjects to be randomised (that is, approximately one third of 36). This change was based on the following considerations: <ul style="list-style-type: none"><li>- Evaluation of the recruitment estimates for each trial site did not indicate that one site would be dominating the recruitment.</li><li>- The planned analysis method for the primary endpoint, PASI at Week 16, allowed for low subject numbers per trial site (should this happen as a result of some sites recruiting more than 8 subjects), as long as each treatment arm was represented at each site, which was expected to be fulfilled.</li></ul>  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported