



## Clinical trial results:

**Efficacy and Safety of LEO 43204 in Field Treatment of Actinic Keratosis on Face or Chest including 12-month follow-up**

**Part 1: 3-day treatment period including an 8-week follow-up period**

**Part 2: extended 12-month follow-up period**

**A phase 3, multi-centre, randomised, parallel group, double-blind, vehicle-controlled trial**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2015-002449-71   |
| Trial protocol           | GB               |
| Global end of trial date | 14 November 2017 |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 20 December 2018 |
| First version publication date | 20 December 2018 |

### Trial information

#### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | LP0084-1193 |
|-----------------------|-------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02547233 |
| 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:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 27 February 2018 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 14 November 2017 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To confirm the efficacy of LEO 43204 gel (0.018% for face/chest) in AK when applied topically once daily for three consecutive days as field treatment

Protection of trial subjects:

This clinical trial was conducted in accordance with the principles of the revision current at the start of the trial of the World Medical Association (WMA), Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects.

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: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 20 November 2015 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety           |
| Long term follow-up duration                              | 12 Months        |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Spain: 7           |
| Country: Number of subjects enrolled | United Kingdom: 28 |
| Country: Number of subjects enrolled | France: 26         |
| Country: Number of subjects enrolled | United States: 244 |
| Worldwide total number of subjects   | 305                |
| EEA total number of subjects         | 61                 |

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)                     | 107 |
| From 65 to 84 years                      | 193 |
| 85 years and over                        | 5   |

## Subject disposition

### Recruitment

Recruitment details:

A total of 437 subjects were enrolled across 4 countries: United States, United Kingdom, France, and Spain. 130 were screening failures, and 307 subjects were randomised to 1 of the 2 treatment groups

### Pre-assignment

Screening details:

437 subjects were enrolled, 130 were screening failures, and 307 subjects were randomised.

### Period 1

|                              |                                      |
|------------------------------|--------------------------------------|
| Period 1 title               | 3-day Treatment and 8-week Follow-up |
| Is this the baseline period? | Yes                                  |
| Allocation method            | Randomised - controlled              |
| Blinding used                | Double blind                         |
| Roles blinded                | Investigator, Subject                |

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | LEO 43204 0.018% Gel |
|------------------|----------------------|

Arm description:

Treatment once daily with LEO 43204 0.018% gel for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm<sup>2</sup> on the chest.

|  |                      |
|--|----------------------|
| Arm type                               | Experimental         |
| Investigational medicinal product name | LEO 43204 0.018% Gel |
| Investigational medicinal product code |                      |
| Other name                             | Ingenol disoxate     |
| Pharmaceutical forms                   | Gel                  |
| Routes of administration               | Topical use          |

Dosage and administration details:

Applied topically once daily for 3 consecutive days.

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | Vehicle Gel |
|------------------|-------------|

Arm description:

Treatment once daily with vehicle gel for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm<sup>2</sup> on the chest.

|  |                       |
|--|-----------------------|
| Arm type                               | Placebo               |
| Investigational medicinal product name | LEO 43204 Vehicle Gel |
| Investigational medicinal product code |                       |
| Other name                             | Placebo               |
| Pharmaceutical forms                   | Gel                   |
| Routes of administration               | Topical use           |

Dosage and administration details:

Applied topically once daily for 3 consecutive days

| Number of subjects in period 1   | LEO 43204 0.018% Gel | Vehicle Gel |
|----------------------------------|----------------------|-------------|
| Started                          | 205                  | 100         |
| Completed                        | 203                  | 92          |
| Not completed                    | 2                    | 8           |
| Unacceptable Local Skin Response | 1                    | -           |
| Consent withdrawn by subject     | -                    | 7           |
| Adverse event, non-fatal         | 1                    | -           |
| Lost to follow-up                | -                    | 1           |

## Period 2

|                              |                         |
|------------------------------|-------------------------|
| Period 2 title               | 12-month Follow-up      |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Double blind            |
| Roles blinded                | Subject, Investigator   |

## Arms

|                              |                                       |
|------------------------------|---------------------------------------|
| Are arms mutually exclusive? | Yes                                   |
| <b>Arm title</b>             | Follow-up phase: LEO 43204 0.018% Gel |

### Arm description:

Treatment once daily for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm<sup>2</sup> on the chest.

|  |                      |
|--|----------------------|
| Arm type                               | Experimental         |
| Investigational medicinal product name | LEO 43204 0.018% Gel |
| Investigational medicinal product code |                      |
| Other name                             |                      |
| Pharmaceutical forms                   | Gel                  |
| Routes of administration               | Topical use          |

### Dosage and administration details:

Applied topically once daily for 3 consecutive days.

|                  |                              |
|------------------|------------------------------|
| <b>Arm title</b> | Follow-up phase: Vehicle Gel |
|------------------|------------------------------|

### Arm description:

Treatment once daily for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm<sup>2</sup> on the chest.

|  |                       |
|--|-----------------------|
| Arm type                               | Placebo               |
| Investigational medicinal product name | LEO 43204 Vehicle Gel |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Gel                   |
| Routes of administration               | Topical use           |

### Dosage and administration details:

Applied topically once daily for 3 consecutive days

| Number of subjects in period<br>2 <sup>[1]</sup> | Follow-up phase:<br>LEO 43204 0.018%<br>Gel | Follow-up phase:<br>Vehicle Gel |
|--|---|---------------------------------|
|  |   |                                 |
| Started  | 199   | 84                              |
| Completed  | 185   | 67                              |
| Not completed                                    | 14  | 17                              |
| Consent withdrawn by subject                     | 10  | 10                              |
| Other  | -   | 1                               |
| Lost to follow-up                                | 3   | 3                               |
| Lack of efficacy                                 | 1   | 2                               |
| Protocol deviation                               | -   | 1                               |

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Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Of the 295 subjects who completed the 3-day treatment and 8-week Follow-up period, 4 subjects in the ingenol disoxate gel group and 8 subjects in the vehicle group were not included in the 12-month Follow-up because they withdrew after Week 8.

## Baseline characteristics

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | LEO 43204 0.018% Gel |
|-----------------------|----------------------|

Reporting group description:

Treatment once daily with LEO 43204 0.018% gel for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm<sup>2</sup> on the chest.

|                       |             |
|-----------------------|-------------|
| Reporting group title | Vehicle Gel |
|-----------------------|-------------|

Reporting group description:

Treatment once daily with vehicle gel for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm<sup>2</sup> on the chest.

| Reporting group values | LEO 43204 0.018% Gel | Vehicle Gel | Total |
|------------------------|----------------------|-------------|-------|
| Number of subjects     | 205                  | 100         | 305   |
| Age categorical        |                      |             |       |
| Units: Subjects        |                      |             |       |
| Adults (18-64 years)   | 73                   | 34          | 107   |
| From 65-84 years       | 129                  | 64          | 193   |
| 85 years and over      | 3                    | 2           | 5     |
| Age continuous         |                      |             |       |
| Units: years           |                      |             |       |
| arithmetic mean        | 68.2                 | 67.4        |       |
| standard deviation     | ± 8.9                | ± 9.9       | -     |
| Gender categorical     |                      |             |       |
| Units: Subjects        |                      |             |       |
| Female                 | 67                   | 38          | 105   |
| Male                   | 138                  | 62          | 200   |

## End points

### End points reporting groups

|   |                                       |
|---|---------------------------------------|
| Reporting group title   | LEO 43204 0.018% Gel                  |
| Reporting group description:<br>Treatment once daily with LEO 43204 0.018% gel for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm <sup>2</sup> on the chest. |                                       |
| Reporting group title   | Vehicle Gel                           |
| Reporting group description:<br>Treatment once daily with vehicle gel for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm <sup>2</sup> on the chest.          |                                       |
| Reporting group title   | Follow-up phase: LEO 43204 0.018% Gel |
| Reporting group description:<br>Treatment once daily for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm <sup>2</sup> on the chest.                           |                                       |
| Reporting group title   | Follow-up phase: Vehicle Gel          |
| Reporting group description:<br>Treatment once daily for 3 consecutive days applied on full face or within a contiguous area of approximately 250 cm <sup>2</sup> on the chest.                           |                                       |

### Primary: Complete Clearance of Actinic Keratosis (AK)

|   |  |
|---|--|
| End point title   | Complete Clearance of Actinic Keratosis (AK) |
| End point description:<br>Complete clearance was defined as an AK count of zero, i.e. no clinically visible AKs in the treatment area.<br>The table shows the percentage of mean number of subjects across imputations with complete clearance. |  |
| End point type  | Primary                                      |
| End point timeframe:<br>At Week 8   |  |

| End point values                 | LEO 43204 0.018% Gel | Vehicle Gel       |  |  |
|----------------------------------|----------------------|-------------------|--|--|
| Subject group type               | Reporting group      | Reporting group   |  |  |
| Number of subjects analysed      | 205                  | 100               |  |  |
| Units: percentage of subjects    |                      |                   |  |  |
| number (confidence interval 95%) | 31.3 (24.9 to 37.6)  | 1.0 (-1.0 to 3.1) |  |  |

### Statistical analyses

|  |                                    |
|--|------------------------------------|
| Statistical analysis title   | Analysis 1                         |
| Statistical analysis description:<br>Mean number of subjects across imputations. |                                    |
| Comparison groups  | LEO 43204 0.018% Gel v Vehicle Gel |



|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 305                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[1]</sup> |
| P-value                                 | < 0.001                    |
| Method                                  | Mantel-Haenszel            |
| Parameter estimate                      | Ratio of clearance rates   |
| Point estimate                          | 30.55                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 4.28                       |
| upper limit                             | 218                        |

Notes:

[1] - Mantel-Haenszel estimate (0.018% relative to vehicle), adjusted for pooled sites.

## Secondary: Partial Clearance (Multiple Imputation)

|  |   |
|--|---|
| End point title  | Partial Clearance (Multiple Imputation) |
| End point description:   |   |
| Partial clearance was defined as at least 75% reduction from baseline in the number of clinically visible AKs in the treatment area. |   |
| The table shows the percentage of mean number of subjects across imputations with partial clearance.                                 |   |
| End point type   | Secondary                               |
| End point timeframe:   |   |
| At Week 8  |   |

|                                  |                         |                  |  |  |
|----------------------------------|-------------------------|------------------|--|--|
| <b>End point values</b>          | LEO 43204<br>0.018% Gel | Vehicle Gel      |  |  |
| Subject group type               | Reporting group         | Reporting group  |  |  |
| Number of subjects analysed      | 205                     | 100              |  |  |
| Units: percentage of subjects    |                         |                  |  |  |
| number (confidence interval 95%) | 55.8 (49.0 to 62.7)     | 4.6 (0.3 to 8.9) |  |  |

## Statistical analyses

|   |                                    |
|---|------------------------------------|
| <b>Statistical analysis title</b>   | Statistical analysis 1             |
| Statistical analysis description:   |                                    |
| Mantel-Haenszel estimate (0.018% relative to vehicle), adjusted for pooled sites. The p-values for secondary endpoints have been corrected by the Holm-Bonferroni method to account for multiplicity. The prespecified multiplicity adjustment by the Holm-Bonferroni method requires the ordering of the p-values for the secondary endpoints by size. |                                    |
| Comparison groups   | Vehicle Gel v LEO 43204 0.018% Gel |

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 305                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | < 0.001                  |
| Method                                  | Mantel-Haenszel          |
| Parameter estimate                      | Ratio of clearance rates |
| Point estimate                          | 12.26                    |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 4.73                     |
| upper limit                             | 31.78                    |

## Secondary: Partial Clearance (Multiple Imputation)

|  |   |
|--|---|
| End point title  | Partial Clearance (Multiple Imputation) |
| End point description:   |   |
| Partial clearance was defined as at least 75% reduction from baseline in the number of clinically visible AKs in the treatment area. |   |
| The table shows the percentage of mean number of subjects across imputations with partial clearance.                                 |   |
| End point type   | Secondary                               |
| End point timeframe:   |   |
| At Week 4  |   |

|                                  |                         |                   |  |  |
|----------------------------------|-------------------------|-------------------|--|--|
| <b>End point values</b>          | LEO 43204<br>0.018% Gel | Vehicle Gel       |  |  |
| Subject group type               | Reporting group         | Reporting group   |  |  |
| Number of subjects analysed      | 205                     | 100               |  |  |
| Units: percentage of subjects    |                         |                   |  |  |
| number (confidence interval 95%) | 56.6 (49.7 to 63.4)     | 5.5 (0.9 to 10.2) |  |  |

## Statistical analyses

|   |                                    |
|---|------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis 1             |
| Comparison groups                       | LEO 43204 0.018% Gel v Vehicle Gel |
| Number of subjects included in analysis | 305                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | superiority <sup>[2]</sup>         |
| P-value                                 | < 0.001                            |
| Method                                  | Mantel-Haenszel                    |
| Parameter estimate                      | Ratio of clearance rates           |
| Point estimate                          | 10.31                              |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 4.43    |
| upper limit         | 23.97   |

Notes:

[2] - Mantel-Haenszel estimate (0.018% relative to vehicle), adjusted for pooled sites. The p-values for secondary endpoints have been corrected by the Holm-Bonferroni method to account for multiplicity. The prespecified multiplicity adjustment by the Holm-Bonferroni method requires the ordering of the p-values for the secondary endpoints by size.

## Secondary: Percent Reduction in AK Count in the Treatment Area Compared to Baseline

|                 |  |
|-----------------|--|
| End point title | Percent Reduction in AK Count in the Treatment Area Compared to Baseline |
|-----------------|--|

End point description:

The percent reduction at Week 8 from baseline was analysed using a negative binomial regression for the AK count at Week 8 with treatment group and pooled sites as factors and baseline count as offset variable (using multiple imputations to account for missing values). The table presents adjusted mean percent reduction at Week 8 from baseline.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Week 8

|   |                         |                    |  |  |
|---|-------------------------|--------------------|--|--|
| <b>End point values</b>                   | LEO 43204<br>0.018% Gel | Vehicle Gel        |  |  |
| Subject group type                        | Reporting group         | Reporting group    |  |  |
| Number of subjects analysed               | 205                     | 100                |  |  |
| Units: percentage of reduction            |                         |                    |  |  |
| arithmetic mean (confidence interval 95%) | 72.1 (68.3 to 75.5)     | 7.3 (-7.8 to 20.3) |  |  |

## Statistical analyses

|   |                                    |
|---|------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis 1             |
| Comparison groups                       | LEO 43204 0.018% Gel v Vehicle Gel |
| Number of subjects included in analysis | 305                                |
| Analysis specification                  | Pre-specified                      |
| Analysis type                           | superiority <sup>[3]</sup>         |
| P-value                                 | < 0.001 <sup>[4]</sup>             |
| Method                                  | Mantel-Haenszel                    |
| Parameter estimate                      | Week 8 AK count ratio              |
| Point estimate                          | 0.3                                |
| Confidence interval                     |                                    |
| level                                   | 95 %                               |
| sides                                   | 2-sided                            |
| lower limit                             | 0.25                               |
| upper limit                             | 0.37                               |

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Notes:

[3] - The p-values for secondary endpoints have been corrected by the Holm-Bonferroni method to account for multiplicity. The prespecified multiplicity adjustment by the Holm-Bonferroni method requires the ordering of the p-values for the secondary endpoints by size.

[4] - Negative binominal regression with treatment group and pooled site as factors and log baseline count as offset variable.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment period including follow-up (from Day 1 to Week 8) and extended follow-up (from Week 8 up to Month 14)

Adverse event reporting additional description:

Adverse events presented in the table are investigator-reported terms. Adverse events of special interest within system organ class (SOC) Neoplasm benign, malignant and unspecified (incl cysts and polyps), were adjudicated by an Independent Adjudication Committee based on central biopsy review.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18.1   |

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | LEO 43204 0.018% Gel - Treatment Period Including Follow-up |
|-----------------------|---|

Reporting group description:

Treatment with LEO 43204 0.018% gel once daily for 3 consecutive days.

|                       |  |
|-----------------------|--|
| Reporting group title | Vehicle Gel - Treatment Period Including Follow-up |
|-----------------------|--|

Reporting group description:

Treatment with vehicle gel once daily for 3 consecutive days.

|                       |   |
|-----------------------|---|
| Reporting group title | LEO 43204 0.018% Gel - Extended Follow-up |
|-----------------------|---|

Reporting group description:

Treatment with LEO 43204 0.018% gel once daily for 3 consecutive days.

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Vehicle Gel - Extended Follow-up |
|-----------------------|----------------------------------|

Reporting group description:

Treatment with vehicle gel once daily for 3 consecutive days.

| Serious adverse events                            | LEO 43204 0.018% Gel - Treatment Period Including Follow-up | Vehicle Gel - Treatment Period Including Follow-up | LEO 43204 0.018% Gel - Extended Follow-up |
|---|---|--|---|
| Total subjects affected by serious adverse events |   |  |   |
| subjects affected / exposed                       | 2 / 205 (0.98%)   | 0 / 100 (0.00%)                                    | 0 / 199 (0.00%)                           |
| number of deaths (all causes)                     | 0   | 0  | 0   |
| number of deaths resulting from adverse events    | 0   | 0  | 0   |
| Investigations                                    |   |  |   |
| Liver function test abnormal                      |   |  |   |
| subjects affected / exposed                       | 1 / 205 (0.49%)   | 0 / 100 (0.00%)                                    | 0 / 199 (0.00%)                           |
| occurrences causally related to treatment / all   | 1 / 1   | 0 / 0  | 0 / 0                                     |
| deaths causally related to treatment / all        | 0 / 0   | 0 / 0  | 0 / 0                                     |
| Injury, poisoning and procedural complications    |   |  |   |
| Rib fracture                                      |   |  |   |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                                 | 1 / 205 (0.49%) | 0 / 100 (0.00%) | 0 / 199 (0.00%) |
| occurrences causally related to treatment / all             | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Blood and lymphatic system disorders</b>                 |                 |                 |                 |
| Pancytopenia  |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 205 (0.49%) | 0 / 100 (0.00%) | 0 / 199 (0.00%) |
| occurrences causally related to treatment / all             | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                  | 0 / 1           | 0 / 0           | 0 / 0           |
| <b>General disorders and administration site conditions</b> |                 |                 |                 |
| Pyrexia   |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 205 (0.49%) | 0 / 100 (0.00%) | 0 / 199 (0.00%) |
| occurrences causally related to treatment / all             | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hepatobiliary disorders</b>                              |                 |                 |                 |
| Jaundice  |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 205 (0.49%) | 0 / 100 (0.00%) | 0 / 199 (0.00%) |
| occurrences causally related to treatment / all             | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Metabolism and nutrition disorders</b>                   |                 |                 |                 |
| Dehydration   |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 205 (0.49%) | 0 / 100 (0.00%) | 0 / 199 (0.00%) |
| occurrences causally related to treatment / all             | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyponatraemia   |                 |                 |                 |
| subjects affected / exposed                                 | 1 / 205 (0.49%) | 0 / 100 (0.00%) | 0 / 199 (0.00%) |
| occurrences causally related to treatment / all             | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Serious adverse events</b>                               |                 |                 |                 |
| Vehicle Gel - Extended Follow-up                            |                 |                 |                 |
| Total subjects affected by serious adverse events           |                 |                 |                 |
| subjects affected / exposed                                 | 0 / 84 (0.00%)  |                 |                 |
| number of deaths (all causes)                               | 0               |                 |                 |
| number of deaths resulting from adverse events              | 0               |                 |                 |
| <b>Investigations</b>                                       |                 |                 |                 |
| Liver function test abnormal                                |                 |                 |                 |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                          | 0 / 84 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Injury, poisoning and procedural complications       |                |  |  |
| Rib fracture   |                |  |  |
| subjects affected / exposed                          | 0 / 84 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Blood and lymphatic system disorders                 |                |  |  |
| Pancytopenia   |                |  |  |
| subjects affected / exposed                          | 0 / 84 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Pyrexia  |                |  |  |
| subjects affected / exposed                          | 0 / 84 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Hepatobiliary disorders                              |                |  |  |
| Jaundice   |                |  |  |
| subjects affected / exposed                          | 0 / 84 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Metabolism and nutrition disorders                   |                |  |  |
| Dehydration  |                |  |  |
| subjects affected / exposed                          | 0 / 84 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Hyponatraemia  |                |  |  |
| subjects affected / exposed                          | 0 / 84 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |

Frequency threshold for reporting non-serious adverse events: 2 %

| <b>Non-serious adverse events</b>                                      | LEO 43204 0.018%<br>Gel - Treatment<br>Period Including<br>Follow-up | Vehicle Gel -<br>Treatment Period<br>Including Follow-up | LEO 43204 0.018%<br>Gel - Extended<br>Follow-up |
|--|--|--|---|
| Total subjects affected by non-serious<br>adverse events               |  |  |   |
| subjects affected / exposed  | 134 / 205 (65.37%)   | 3 / 100 (3.00%)  | 23 / 199 (11.56%)                               |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps) |  |  |   |
| Basal cell carcinoma   |  |  |   |
| subjects affected / exposed  | 4 / 205 (1.95%)  | 1 / 100 (1.00%)  | 9 / 199 (4.52%)                                 |
| occurrences (all)  | 4  | 1  | 9   |
| Squamous cell carcinoma of skin  |  |  |   |
| subjects affected / exposed  | 8 / 205 (3.90%)  | 2 / 100 (2.00%)  | 10 / 199 (5.03%)                                |
| occurrences (all)  | 8  | 2  | 10  |
| Injury, poisoning and procedural<br>complications                      |  |  |   |
| Scar   |  |  |   |
| subjects affected / exposed  | 0 / 205 (0.00%)  | 0 / 100 (0.00%)  | 9 / 199 (4.52%)                                 |
| occurrences (all)  | 0  | 0  | 9   |
| Nervous system disorders   |  |  |   |
| Headache   |  |  |   |
| subjects affected / exposed  | 10 / 205 (4.88%)   | 0 / 100 (0.00%)  | 0 / 199 (0.00%)                                 |
| occurrences (all)  | 10   | 0  | 0   |
| General disorders and administration<br>site conditions                |  |  |   |
| Application site discomfort  |  |  |   |
| subjects affected / exposed  | 6 / 205 (2.93%)  | 0 / 100 (0.00%)  | 0 / 199 (0.00%)                                 |
| occurrences (all)  | 6  | 0  | 0   |
| Application site pain  |  |  |   |
| subjects affected / exposed  | 120 / 205 (58.54%)   | 1 / 100 (1.00%)  | 0 / 199 (0.00%)                                 |
| occurrences (all)  | 120  | 1  | 0   |
| Application site paraesthesia  |  |  |   |
| subjects affected / exposed  | 5 / 205 (2.44%)  | 0 / 100 (0.00%)  | 0 / 199 (0.00%)                                 |
| occurrences (all)  | 5  | 0  | 0   |
| Application site pruritus  |  |  |   |
| subjects affected / exposed  | 71 / 205 (34.63%)  | 0 / 100 (0.00%)  | 0 / 199 (0.00%)                                 |
| occurrences (all)  | 71   | 0  | 0   |
| Eye disorders  |  |  |   |



|  |                        |                      |                      |
|--|------------------------|----------------------|----------------------|
| Periorbital oedema<br>subjects affected / exposed<br>occurrences (all) | 8 / 205 (3.90%)<br>8   | 0 / 100 (0.00%)<br>0 | 0 / 199 (0.00%)<br>0 |
| Psychiatric disorders  |                        |                      |                      |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)           | 11 / 205 (5.37%)<br>11 | 0 / 100 (0.00%)<br>0 | 0 / 199 (0.00%)<br>0 |
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)     | 6 / 205 (2.93%)<br>6   | 0 / 100 (0.00%)<br>0 | 0 / 199 (0.00%)<br>0 |

|   |                                     |  |  |
|---|-------------------------------------|--|--|
| <b>Non-serious adverse events</b>   | Vehicle Gel -<br>Extended Follow-up |  |  |
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed | 3 / 84 (3.57%)                      |  |  |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps)                  |                                     |  |  |
| Basal cell carcinoma<br>subjects affected / exposed<br>occurrences (all)                | 1 / 84 (1.19%)<br>1                 |  |  |
| Squamous cell carcinoma of skin<br>subjects affected / exposed<br>occurrences (all)     | 1 / 84 (1.19%)<br>1                 |  |  |
| Injury, poisoning and procedural<br>complications                                       |                                     |  |  |
| Scar<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 84 (1.19%)<br>1                 |  |  |
| Nervous system disorders  |                                     |  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 84 (0.00%)<br>0                 |  |  |
| General disorders and administration<br>site conditions                                 |                                     |  |  |
| Application site discomfort<br>subjects affected / exposed<br>occurrences (all)         | 0 / 84 (0.00%)<br>0                 |  |  |
| Application site pain<br>subjects affected / exposed<br>occurrences (all)               | 0 / 84 (0.00%)<br>0                 |  |  |

|   |                     |  |  |
|---|---------------------|--|--|
| Application site paraesthesia<br>subjects affected / exposed<br>occurrences (all)       | 0 / 84 (0.00%)<br>0 |  |  |
| Application site pruritus<br>subjects affected / exposed<br>occurrences (all)           | 0 / 84 (0.00%)<br>0 |  |  |
| Eye disorders<br>Periorbital oedema<br>subjects affected / exposed<br>occurrences (all) | 0 / 84 (0.00%)<br>0 |  |  |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 84 (0.00%)<br>0 |  |  |
| Sleep disorder<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 84 (0.00%)<br>0 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment   |
|---------------|---|
| 04 March 2016 | The protocol was updated to specify the method (an interactive web response system) for ensuring that the trial enrolled a minimum of 15% and a maximum of 25% of chest-treated subjects. The amendment also clarified which medications were allowed and prohibited during the extended follow-up period: lesion-directed laser treatment was added to the allowed medications, and Actikerall, even as lesion-directed treatment, and laser treatment as field treatment were prohibited. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported