



Clinical trial results:

Multicenter, randomised, double-blind clinical trial on the efficacy and safety of medicinal products containing Diclofenac in patients with actinic keratosis

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-001621-33 |
| Trial protocol | DE |
| Global end of trial date | 25 June 2015 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 25 March 2017 |
| First version publication date | 20 July 2016 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data setErroneous statement regarding the primary efficacy criterion |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | 14-01/AK-Diclo |
|-----------------------|----------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Dermapharm AG |
| Sponsor organisation address | Lil-Dagover-Ring 7, Gruenwald, Germany, 82031 |
| Public contact | Head of Clinical Department, Dermapharm AG, 0049 08964186-0, |
| Scientific contact | Head of Clinical Department, Dermapharm AG, 0049 08964186-0, |

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 | 18 November 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 25 June 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 June 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Evaluation of the efficacy and safety of a new diclofenac 3% gel formulation vs. the originator Solaraze (licensed) vs. vehicle in patients with actinic keratosis.

Protection of trial subjects:

There were no specific measures necessary.

Background therapy:

There was no background therapy.

Evidence for comparator:

The trial aimed to show therapeutic equivalence with regard to the comparator in order to obtain a generic marketing authorization for the test product.

| | |
|---|-------------------|
| Actual start date of recruitment | 23 September 2014 |
| 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 | Germany: 439 |
| Worldwide total number of subjects | 439 |
| EEA total number of subjects | 439 |

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) | 66 |
| From 65 to 84 years | 355 |

| | |
|-------------------|----|
| 85 years and over | 18 |
|-------------------|----|

Subject disposition

Recruitment

Recruitment details:

all study centers in Germany; first patient first visit: 25 September 2014; last patient last visit: 25 June 2015

Pre-assignment

Screening details:

Main criteria for inclusion:

Immunocompetent women and men ≥ 18 years of age; Diagnosis of "actinic keratosis"; treatment area of approximately 50 cm² on the face or the scalp; at least 7 delimitable target lesions with the following properties: mild to moderate clinical severity, diameter ≥ 4 mm, not hypertrophic, not massively hyperkeratotic

Period 1

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

Blinding implementation details:

All study preparations were indistinguishable in terms of appearance and were filled in white tubes of identical appearance.

Arms

| | |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes |
| Arm title | DicloGel |

Arm description:

Treatment arm with test product

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Diclofenac 3% gel |
| Investigational medicinal product code | D11AX18 |
| Other name | |
| Pharmaceutical forms | Gel |
| Routes of administration | Cutaneous use |

Dosage and administration details:

To be rubbed in slightly on the observation area twice daily (in the morning, in the evening)

| | |
|------------------|----------|
| Arm title | Solaraze |
|------------------|----------|

Arm description:

Treatment arm with reference product

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Solaraze |
| Investigational medicinal product code | D11AX18 |
| Other name | |
| Pharmaceutical forms | Gel |
| Routes of administration | Cutaneous use |

Dosage and administration details:

To be rubbed in slightly on the observation area twice daily (in the morning, in the evening)

| | |
|------------------|---------|
| Arm title | Vehicle |
|------------------|---------|

Arm description:

Treatment arm with vehicle to test product

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|---------------|
| Investigational medicinal product name | Vehicle |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Gel |
| Routes of administration | Cutaneous use |

Dosage and administration details:

To be rubbed in slightly on the observation area twice daily (in the morning, in the evening)

| Number of subjects in period 1 | DicloGel | Solaraze | Vehicle |
|---------------------------------------|----------|----------|---------|
| Started | 146 | 147 | 146 |
| Completed | 141 | 133 | 143 |
| Not completed | 5 | 14 | 3 |
| Adverse event, serious fatal | - | 4 | - |
| Consent withdrawn by subject | 2 | 2 | - |
| Physician decision | - | 1 | - |
| Adverse event, non-fatal | 3 | 5 | 2 |
| Technical-logistic reasons | - | 1 | 1 |
| Lost to follow-up | - | 1 | - |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|--------------------|
| Reporting group title | Observation Period |
| Reporting group description: - | |

| Reporting group values | Observation Period | Total | |
|---|--------------------|-------|--|
| Number of subjects | 439 | 439 | |
| 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) | 66 | 66 | |
| From 65-84 years | 355 | 355 | |
| 85 years and over | 18 | 18 | |
| Gender categorical Units: Subjects | | | |
| Female | 68 | 68 | |
| Male | 371 | 371 | |

Subject analysis sets

| | |
|----------------------------|--------------------|
| Subject analysis set title | ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

includes all patients of the safety data set who comply with the study diagnosis (according to the associated inclusion criteria) and provide the baseline value and at least one post baseline value under treatment

| | |
|----------------------------|--------------|
| Subject analysis set title | PP |
| Subject analysis set type | Per protocol |

Subject analysis set description:

includes all patients of the ITT data set who do not exhibit any major protocol violations

| | |
|----------------------------|-----------------|
| Subject analysis set title | Safety |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

comprises all patients who had administered the study medication at least once

| Reporting group values | ITT | PP | Safety |
|---|-----|-----|--------|
| Number of subjects | 433 | 349 | 439 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |

| | | | |
|--|-----|-----|-----|
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 65 | 61 | 66 |
| From 65-84 years | 351 | 276 | 355 |
| 85 years and over | 17 | 12 | 18 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 67 | 56 | 68 |
| Male | 366 | 293 | 371 |

End points

End points reporting groups

| | |
|---|--------------------|
| Reporting group title | DicloGel |
| Reporting group description: | |
| Treatment arm with test product | |
| Reporting group title | Solaraze |
| Reporting group description: | |
| Treatment arm with reference product | |
| Reporting group title | Vehicle |
| Reporting group description: | |
| Treatment arm with vehicle to test product | |
| Subject analysis set title | ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| includes all patients of the safety data set who comply with the study diagnosis (according to the associated inclusion criteria) and provide the baseline value and at least one post baseline value under treatment | |
| Subject analysis set title | PP |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| includes all patients of the ITT data set who do not exhibit any major protocol violations | |
| Subject analysis set title | Safety |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| comprises all patients who had administered the study medication at least once | |

Primary: Treatment effect

| | |
|---|---------------------------------|
| End point title | Treatment effect ^[1] |
| End point description: | |
| Number (percentage) of patients with "clinical success" according to predefined criteria at end of observation period | |
| End point type | Primary |
| End point timeframe: | |
| Inclusion visit (= start of treatment) and main visit (= 30 days after end of treatment) | |

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The primary goal of this trial was to show therapeutic equivalence of test to reference product. The vehicle arm served as verification of the assay sensitivity. The three end point tests had to be done separately in order to avoid the otherwise necessary adjustment of the significance level.

| End point values | DicloGel | Solaraze | PP | |
|-----------------------------|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 112 | 111 | 223 | |
| Units: Number | 72 | 75 | 147 | |

Statistical analyses

| | |
|--|--------------------------------|
| Statistical analysis title | Analysis of efficacy |
| Statistical analysis description: equivalence test (two-sided) with 95% CI and a pre-defined equivalence interval [-0.20; 0.20] | |
| Comparison groups | DicloGel v Solaraze |
| Number of subjects included in analysis | 223 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.0328 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.1661 |
| upper limit | 0.1005 |

Other pre-specified: Superiority of Test over Vehicle

| | |
|---|---|
| End point title | Superiority of Test over Vehicle ^[2] |
| End point description: Number (percentage) of patients with "clinical success" according to predefined criteria at end of observation period | |
| End point type | Other pre-specified |
| End point timeframe: | |
| Inclusion visit (= start of treatment) and main visit (= 30 days after end of treatment) | |

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The statistical analysis for this end point served as verification of the assay sensitivity and had to be done individually for each active preparation in accordance with CPMP/EWP/908/99.

| End point values | DicloGel | Vehicle | ITT | |
|-----------------------------|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 141 | 143 | 284 | |
| Units: Number | 83 | 43 | 126 | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Superiority Test - Placebo |
| Comparison groups | DicloGel v Vehicle |
| Number of subjects included in analysis | 284 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Fisher exact |

Other pre-specified: Superiority of Reference over Vehicle

| | |
|-----------------|--|
| End point title | Superiority of Reference over Vehicle ^[3] |
|-----------------|--|

End point description:

Number (percentage) of patients with "clinical success" according to predefined criteria at end of observation period

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Inclusion visit (= start of treatment) and main visit (= 30 days after end of treatment)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The statistical analysis for this end point served as verification of the assay sensitivity and had to be done individually for each active preparation in accordance with CPMP/EWP/908/99.

| End point values | Solaraze | Vehicle | ITT | |
|-----------------------------|-----------------|-----------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 133 | 143 | 276 | |
| Units: Number | 83 | 43 | 126 | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Superiority Comparator - Placebo |
| Comparison groups | Solaraze v Vehicle |
| Number of subjects included in analysis | 276 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Fisher exact |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Inclusion visit (start of treatment) to main visit (= 30 days after end of treatment; end of observation period)

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

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

Reporting group description:

treatment arm with vehicle (to test product)

| | |
|-----------------------|----------|
| Reporting group title | Solaraze |
|-----------------------|----------|

Reporting group description:

treatment arm with reference product

| | |
|-----------------------|----------|
| Reporting group title | DicloGel |
|-----------------------|----------|

Reporting group description:

treatment arm with test product

| Serious adverse events | Vehicle | Solaraze | DicloGel |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 146 (2.05%) | 5 / 147 (3.40%) | 5 / 146 (3.42%) |
| number of deaths (all causes) | 0 | 4 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bladder transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchial carcinoma | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 0 / 146 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Colon cancer | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 0 / 147 (0.00%) | 0 / 146 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Injury, poisoning and procedural complications | | | |
| Facial bones fracture | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 0 / 146 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 2 / 146 (1.37%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 0 / 147 (0.00%) | 2 / 146 (1.37%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 0 / 146 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 0 / 147 (0.00%) | 0 / 146 (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 |
| General disorders and administration site conditions | | | |
| Sudden cardiac death | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 0 / 146 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Psychiatric disorders | | | |
| Mental disorder | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 0 / 147 (0.00%) | 0 / 146 (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 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 1 / 147 (0.68%) | 0 / 146 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 0.05 %

| Non-serious adverse events | Vehicle | Solaraze | DicloGel |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 37 / 146 (25.34%) | 52 / 147 (35.37%) | 54 / 146 (36.99%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 2 / 146 (1.37%) |
| occurrences (all) | 0 | 0 | 2 |
| Squamous cell carcinoma of the skin | | | |

| | | | |
|--|----------------------|-------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 1 / 146 (0.68%) 1 | 1 / 147 (0.68%) 1 | 0 / 146 (0.00%) 0 |
| Bowen's disease subjects affected / exposed occurrences (all) | 1 / 146 (0.68%) 1 | 0 / 147 (0.00%) 0 | 0 / 146 (0.00%) 0 |
| Basal cell carcinoma subjects affected / exposed occurrences (all) | 0 / 146 (0.00%) 0 | 0 / 147 (0.00%) 0 | 1 / 146 (0.68%) 1 |
| Keratoacanthoma subjects affected / exposed occurrences (all) | 0 / 146 (0.00%) 0 | 2 / 147 (1.36%) 2 | 0 / 146 (0.00%) 0 |
| Vascular disorders Varicose vein subjects affected / exposed occurrences (all) | 1 / 146 (0.68%) 1 | 0 / 147 (0.00%) 0 | 1 / 146 (0.68%) 1 |
| Lymphoedema subjects affected / exposed occurrences (all) | 0 / 146 (0.00%) 0 | 0 / 147 (0.00%) 0 | 1 / 146 (0.68%) 1 |
| General disorders and administration site conditions Application site pain subjects affected / exposed occurrences (all) | 6 / 146 (4.11%) 6 | 6 / 147 (4.08%) 6 | 6 / 146 (4.11%) 6 |
| Application site erythema subjects affected / exposed occurrences (all) | 5 / 146 (3.42%) 5 | 15 / 147 (10.20%) 15 | 13 / 146 (8.90%) 13 |
| Application site eczema subjects affected / exposed occurrences (all) | 1 / 146 (0.68%) 1 | 3 / 147 (2.04%) 3 | 3 / 146 (2.05%) 3 |
| Application site exfoliation subjects affected / exposed occurrences (all) | 4 / 146 (2.74%) 4 | 10 / 147 (6.80%) 10 | 7 / 146 (4.79%) 7 |
| Application site pruritus subjects affected / exposed occurrences (all) | 4 / 146 (2.74%) 4 | 7 / 147 (4.76%) 7 | 5 / 146 (3.42%) 5 |
| Application site haemorrhage | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 2 / 146 (1.37%) |
| occurrences (all) | 0 | 0 | 2 |
| Application site erosion | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 2 / 146 (1.37%) |
| occurrences (all) | 0 | 1 | 2 |
| Application site scab | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 1 | 1 |
| Application site pustules | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 0 | 1 |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 0 | 1 |
| Application site inflammation | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 0 | 1 |
| Application site discomfort | | | |
| subjects affected / exposed | 2 / 146 (1.37%) | 1 / 147 (0.68%) | 2 / 146 (1.37%) |
| occurrences (all) | 2 | 1 | 2 |
| Application site dysaesthesia | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 0 / 147 (0.00%) | 0 / 146 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 0 | 1 |
| Atopy | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 0 | 1 |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 1 | 1 |
| Prostatitis | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 146 (0.68%) 1 | 0 / 147 (0.00%) 0 | 1 / 146 (0.68%) 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 2 / 147 (1.36%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 2 | 1 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 0 | 1 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 2 / 146 (1.37%) |
| occurrences (all) | 0 | 1 | 2 |
| Asthma | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 0 / 147 (0.00%) | 0 / 146 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 0 / 147 (0.00%) | 0 / 146 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |
| Sleep disorder | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 1 | 0 | 1 |
| Depression | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 0 / 147 (0.00%) | 0 / 146 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Investigations | | | |
| Traumatic haematoma | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 0 | 1 |
| Injury, poisoning and procedural complications | | | |
| Arthropod bite | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 0 / 147 (0.00%) | 0 / 146 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tendon rupture | | | |

| | | | |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 146 (0.68%) 1 | 0 / 147 (0.00%) 0 | 0 / 146 (0.00%) 0 |
| Limb injury subjects affected / exposed occurrences (all) | 1 / 146 (0.68%) 1 | 0 / 147 (0.00%) 0 | 1 / 146 (0.68%) 1 |
| Skin wound subjects affected / exposed occurrences (all) | 0 / 146 (0.00%) 0 | 0 / 147 (0.00%) 0 | 1 / 146 (0.68%) 1 |
| Congenital, familial and genetic disorders Phimosi subjects affected / exposed occurrences (all) | 0 / 146 (0.00%) 0 | 0 / 147 (0.00%) 0 | 1 / 146 (0.68%) 1 |
| Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) | 0 / 146 (0.00%) 0 | 1 / 147 (0.68%) 1 | 0 / 146 (0.00%) 0 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 0 / 146 (0.00%) 0 | 0 / 147 (0.00%) 0 | 1 / 146 (0.68%) 1 |
| Headache subjects affected / exposed occurrences (all) | 1 / 146 (0.68%) 1 | 2 / 147 (1.36%) 2 | 1 / 146 (0.68%) 1 |
| Carpal tunnel syndrome subjects affected / exposed occurrences (all) | 0 / 146 (0.00%) 0 | 1 / 147 (0.68%) 1 | 0 / 146 (0.00%) 0 |
| Eye disorders Blepharitis subjects affected / exposed occurrences (all) | 0 / 146 (0.00%) 0 | 1 / 147 (0.68%) 1 | 0 / 146 (0.00%) 0 |
| Eye swelling subjects affected / exposed occurrences (all) | 0 / 146 (0.00%) 0 | 0 / 147 (0.00%) 0 | 1 / 146 (0.68%) 1 |
| Eye irritation subjects affected / exposed occurrences (all) | 0 / 146 (0.00%) 0 | 0 / 147 (0.00%) 0 | 1 / 146 (0.68%) 1 |

| | | | |
|--|--|-----------------|-----------------|
| Keratitis | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 0 / 147 (0.00%) | 0 / 146 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eyelid erosion | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Anal fissure | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 1 | 0 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 0 / 147 (0.00%) | 0 / 146 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 1 | 1 |
| Gastritis | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 0 / 147 (0.00%) | 0 / 146 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 0 / 146 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Actinic keratosis | Additional description: not in the treatment/ observation area | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 0 | 1 |
| Eczema | | | |
| subjects affected / exposed | 4 / 146 (2.74%) | 4 / 147 (2.72%) | 6 / 146 (4.11%) |
| occurrences (all) | 4 | 4 | 6 |
| Androgenetic alopecia | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 0 / 147 (0.00%) | 3 / 146 (2.05%) |
| occurrences (all) | 1 | 0 | 3 |
| Unguis incarnatus | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 0 | 1 |
| Pruritus | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 146 (0.68%) | 2 / 147 (1.36%) | 3 / 146 (2.05%) |
| occurrences (all) | 1 | 2 | 3 |
| Erythema | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 3 / 147 (2.04%) | 3 / 146 (2.05%) |
| occurrences (all) | 0 | 3 | 3 |
| Skin irritation | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 0 / 146 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Stasis dermatitis | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 0 / 146 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperkeratosis | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 0 | 1 |
| Dermatitis contact | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 3 / 147 (2.04%) | 1 / 146 (0.68%) |
| occurrences (all) | 1 | 3 | 1 |
| Rosacea | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 0 / 146 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 1 / 147 (0.68%) | 0 / 146 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Eczema nummular | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 0 | 1 |
| Hand dermatitis | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 0 | 1 |
| Intertrigo | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 0 / 146 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Seborrhoeic dermatitis | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 0 / 147 (0.00%) | 0 / 146 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal and urinary disorders | | | |

| | | | |
|---|----------------------|----------------------|----------------------|
| Urge incontinence subjects affected / exposed occurrences (all) | 0 / 146 (0.00%) 0 | 1 / 147 (0.68%) 1 | 0 / 146 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms subjects affected / exposed occurrences (all) | 0 / 146 (0.00%) 0 | 1 / 147 (0.68%) 1 | 0 / 146 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 1 / 146 (0.68%) 1 | 1 / 147 (0.68%) 1 | 0 / 146 (0.00%) 0 |
| Synovial cyst subjects affected / exposed occurrences (all) | 0 / 146 (0.00%) 0 | 0 / 147 (0.00%) 0 | 1 / 146 (0.68%) 1 |
| Invertebral disc disorder subjects affected / exposed occurrences (all) | 0 / 146 (0.00%) 0 | 1 / 147 (0.68%) 1 | 0 / 146 (0.00%) 0 |
| Infections and infestations | | | |
| Onychomycosis subjects affected / exposed occurrences (all) | 0 / 146 (0.00%) 0 | 0 / 147 (0.00%) 0 | 1 / 146 (0.68%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 3 / 146 (2.05%) 3 | 6 / 147 (4.08%) 6 | 5 / 146 (3.42%) 5 |
| Eczema infected subjects affected / exposed occurrences (all) | 2 / 146 (1.37%) 2 | 1 / 147 (0.68%) 1 | 2 / 146 (1.37%) 2 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 3 / 146 (2.05%) 3 | 5 / 147 (3.40%) 5 | 6 / 146 (4.11%) 6 |
| Bronchitis subjects affected / exposed occurrences (all) | 1 / 146 (0.68%) 1 | 0 / 147 (0.00%) 0 | 1 / 146 (0.68%) 1 |
| Pyoderma subjects affected / exposed occurrences (all) | 0 / 146 (0.00%) 0 | 1 / 147 (0.68%) 1 | 1 / 146 (0.68%) 1 |
| Folliculitis | | | |

| | | | |
|------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 146 (0.68%) | 1 / 147 (0.68%) | 1 / 146 (0.68%) |
| occurrences (all) | 1 | 1 | 1 |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 0 | 1 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 0 / 146 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urethritis | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 0 / 146 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 1 / 146 (0.68%) | 0 / 147 (0.00%) | 0 / 146 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 2 / 147 (1.36%) | 0 / 146 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 0 / 146 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 0 / 146 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pulpitis dental | | | |
| subjects affected / exposed | 2 / 146 (1.37%) | 0 / 147 (0.00%) | 0 / 146 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Epididymitis ureaplasma | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 0 / 146 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Spinal cord abscess | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 1 / 147 (0.68%) | 0 / 146 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
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| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 146 (0.00%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 2 / 146 (1.37%) | 0 / 147 (0.00%) | 1 / 146 (0.68%) |
| occurrences (all) | 2 | 0 | 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported