



Clinical trial results:

Double-blind, randomised clinical study comparing efficacy and safety of Clindamycin/Benzoyl Peroxide Gel (10 mg/g + 30 mg/g) (Test) vs. DUAC 10 mg/g + 30 mg/g Gel (Reference) vs. Vehicle in patients with papulopustular acne

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-000521-13 |
| Trial protocol | CZ |
| Global end of trial date | 01 March 2021 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 09 April 2022 |
| First version publication date | 09 April 2022 |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | 17-01/ClinBPO-30 |
|-----------------------|------------------|

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 | Clinical Research Department, Dermapharm AG, +49 89641860, Clinicaltrials.Dermapharm@dermapharm.com |
| Scientific contact | Clinical Research Department, Dermapharm AG, +49 89641860, Clinicaltrials.Dermapharm@dermapharm.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 | 21 October 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 March 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 March 2021 |
| 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 gel containing 10 mg/g Clindamycin and 30 mg/g Benzoyl peroxide vs. DUAC 10 mg/g + 30 mg/g Gel (Reference) vs. vehicle in patients with papulopustular acne

Protection of trial subjects:

In the current clinical trial patients below the age of 18 have been included. In such a case, an age-appropriate written subject information sheet was handed over to adolescent patients and an appropriate information session was to be performed by the investigator. The legal guardian(s) received a comparable document and an information session for adults. Before the start of screening and randomisation for the current clinical trial, the legal guardian(s) had to sign the informed consent form(s) and the adolescent patient the informed assent form. In case any of the parties (legal guardian(s) or adolescent patient) refused their consent, a participation of the adolescent patient in the trial was not possible.

Background therapy:

There was no background therapy.

Evidence for comparator:

The comparator contains the same ingredients in the same concentration as the test product and has a marketing license for the study indication.

| | |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment | 03 April 2019 |
| 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 | Czechia: 676 |
| Worldwide total number of subjects | 676 |
| EEA total number of subjects | 676 |

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) | 378 |
| Adults (18-64 years) | 298 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

16 study centers in Czechia; first patient first visit: 25 April 2019; last patient last visit: 01 March 2021

Pre-assignment

Screening details:

Main criteria for inclusion: Women, men and adolescents of ≥ 12 years of age; Diagnosis of "papulopustular acne" according to generally accepted criteria; On the face, ≥ 25 non-inflammatory lesions and ≥ 20 inflammatory lesions, thereof ≤ 2 nodular lesions; Investigator's Global Assessment (IGA) of acne severity grade 2, 3 or 4

Period 1

| | |
|------------------------------|----------------------------------------------|
| Period 1 title | Treatment 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:

The tubes containing the study medications were neutral white. The attached labels were identical for all three preparations. All three study medications were indistinguishable with respect to visual or odorous characteristics. The random code was transferred to the data base not before the following actions were completed: data base closure, finalisation of the statistical analysis plan, a Blind Data Review and a subsequent Blind Data Report.

Arms

| | |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes |
| Arm title | ClinBPO 30 |

Arm description:

Test product

| | |
|----------------------------------------|------------------------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Clindamycin/Benzoyl Peroxide Gel (10 mg/g + 30 mg/g) |
| Investigational medicinal product code | D10AF51 |
| Other name | |
| Pharmaceutical forms | Gel |
| Routes of administration | Cutaneous use |

Dosage and administration details:

A thin layer of gel should be applied to the affected area once a day. The treatment area was defined as the acne affected areas on the face whereas face was considered as the area bounded by ears, hairline and lower margin of the mandibles. Contact with the mouth, eyes, lips, other mucous membranes or areas of irritated or broken skin should be avoided.

| | |
|------------------|--------------------------|
| Arm title | Duac (10 mg/g + 30 mg/g) |
|------------------|--------------------------|

Arm description:

Reference Product

| | |
|----------------------------------------|--------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Duac (10 mg/g + 30 mg/g) |
| Investigational medicinal product code | D10AF51 |
| Other name | |
| Pharmaceutical forms | Gel |
| Routes of administration | Cutaneous use |

Dosage and administration details:

A thin layer of gel should be applied to the affected area once a day. The treatment area was defined as the acne affected areas on the face whereas face was considered as the area bounded by ears, hairline and lower margin of the mandibles. Contact with the mouth, eyes, lips, other mucous membranes or

areas of irritated or broken skin should be avoided.

| | |
|----------------------------------------|---------------|
| Arm title | Vehicle |
| Arm description: - | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | D10AF51 |
| Other name | |
| Pharmaceutical forms | Gel |
| Routes of administration | Cutaneous use |

Dosage and administration details:

A thin layer of gel should be applied to the affected area once a day. The treatment area was defined as the acne affected areas on the face whereas face was considered as the area bounded by ears, hairline and lower margin of the mandibles. Contact with the mouth, eyes, lips, other mucous membranes or areas of irritated or broken skin should be avoided.

| Number of subjects in period 1 | ClinBPO 30 | Duac (10 mg/g + 30 mg/g) | Vehicle |
|---------------------------------------|------------|--------------------------|---------|
| Started | 223 | 225 | 228 |
| Completed | 211 | 213 | 199 |
| Not completed | 12 | 12 | 29 |
| Consent withdrawn by subject | 1 | 3 | 1 |
| Poor tolerability (patient) | 3 | 1 | 1 |
| Adverse event, non-fatal | 2 | 2 | 2 |
| Technical-logistic reasons | 2 | - | - |
| COVID-19 related | 1 | - | 2 |
| Lost to follow-up | 1 | - | 1 |
| Lack of efficacy | 2 | 6 | 22 |

Baseline characteristics

Reporting groups

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

| Reporting group values | Treatment Period | Total | |
|----------------------------------------------------|------------------|-------|--|
| Number of subjects | 676 | 676 | |
| 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) | 378 | 378 | |
| Adults (18-64 years) | 298 | 298 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 437 | 437 | |
| Male | 239 | 239 | |

Subject analysis sets

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

Subject analysis set description:

Comprises all randomised patients who had administered the study medication at least once and who provided at least one safety related outcome.

| | |
|----------------------------|---------------|
| Subject analysis set title | FAS |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Consists of all patients as randomised who received study medication at least once and have a baseline assessment and at least one post-baseline assessment of the number of papulopustular acne lesions.

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

Subject analysis set description:

Comprises all patients of the FAS who do not exhibit any major protocol violations.

| Reporting group values | Safety data set | FAS | PP |
|----------------------------------------------------|-----------------|-----|-----|
| Number of subjects | 676 | 673 | 628 |
| 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) | 378 | 377 | 364 |
| Adults (18-64 years) | 298 | 296 | 264 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 437 | 435 | 394 |
| Male | 239 | 238 | 234 |

End points

End points reporting groups

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Reporting group title | ClinBPO 30 |
| Reporting group description: | |
| Test product | |
| Reporting group title | Duac (10 mg/g + 30 mg/g) |
| Reporting group description: | |
| Reference Product | |
| Reporting group title | Vehicle |
| Reporting group description: - | |
| Subject analysis set title | Safety data set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Comprises all randomised patients who had administered the study medication at least once and who provided at least one safety related outcome. | |
| Subject analysis set title | FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| Consists of all patients as randomised who received study medication at least once and have a baseline assessment and at least one post-baseline assessment of the number of papulopustular acne lesions. | |
| Subject analysis set title | PP |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Comprises all patients of the FAS who do not exhibit any major protocol violations. | |

Primary: Treatment effect (inflammatory lesions)

| | |
|-----------------------------------------------------------------------------------------|-----------------------------------------|
| End point title | Treatment effect (inflammatory lesions) |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| Treatment start (Visit V1) to end-of-treatment (EOT) examination at Visit V8 (week 12). | |

| End point values | ClinBPO 30 | Duac (10 mg/g + 30 mg/g) | Vehicle | |
|--------------------------------------|-----------------|--------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 207 | 213 | 227 | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | 82.7 (± 24.21) | 83.7 (± 20.86) | 51.5 (± 41.57) | |

Statistical analyses

| | |
|-------------------------------------------------------------------------------------------------------|----------------------|
| Statistical analysis title | Analysis of efficacy |
| Statistical analysis description: | |
| The first part of the primary objective of this study was to show therapeutic equivalence of the test | |

preparation ClinBPO 30 as compared to the reference DUAC. Therapeutic equivalence was statistically proven if the two-sided 95% confidence interval (CI) for μ INFL-ClinBPO - μ INFL-DUAC was completely contained within [-10.0, 10.0].

| | |
|-----------------------------------------|---------------------------------------|
| Comparison groups | ClinBPO 30 v Duac (10 mg/g + 30 mg/g) |
| Number of subjects included in analysis | 420 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.38 |
| upper limit | 3.3 |

| | |
|-----------------------------------|----------------------------------|
| Statistical analysis title | Superiority of Test over Vehicle |
|-----------------------------------|----------------------------------|

Statistical analysis description:

In order to verify assay sensitivity of the study design, superiority of the two active preparations over vehicle was tested by means of two-sided significance tests with $\alpha = 0.05$. The primary test of superiority was carried out for the ITT data set.

| | |
|-----------------------------------------|----------------------|
| Comparison groups | ClinBPO 30 v Vehicle |
| Number of subjects included in analysis | 434 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | t-test, 2-sided |

| | |
|-----------------------------------|---------------------------------------|
| Statistical analysis title | Superiority of Reference over Vehicle |
|-----------------------------------|---------------------------------------|

Statistical analysis description:

In order to verify assay sensitivity of the study design, superiority of the two active preparations over vehicle was tested by means of two-sided significance tests with $\alpha = 0.05$. The primary test of superiority was carried out for the ITT data set.

| | |
|-----------------------------------------|------------------------------------|
| Comparison groups | Vehicle v Duac (10 mg/g + 30 mg/g) |
| Number of subjects included in analysis | 440 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | t-test, 2-sided |

Primary: Treatment effect (total number of lesions)

| | |
|-----------------|--------------------------------------------|
| End point title | Treatment effect (total number of lesions) |
|-----------------|--------------------------------------------|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Treatment start (Visit V1) to end-of-treatment (EOT) examination at Visit V8 (week 12).

| End point values | ClinBPO 30 | Duac (10 mg/g + 30 mg/g) | Vehicle | |
|--------------------------------------|-----------------|--------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 207 | 213 | 227 | |
| Units: percentage change | | | | |
| arithmetic mean (standard deviation) | 75.1 (± 23.27) | 75.9 (± 22.55) | 43.7 (± 36.84) | |

Statistical analyses

| Statistical analysis title | Analysis of efficacy |
|----------------------------|----------------------|
|----------------------------|----------------------|

Statistical analysis description:

The first part of the primary objective of this study was to show therapeutic equivalence of the test preparation ClinBPO 30 as compared to the reference DUAC. Therapeutic equivalence was statistically proven if the two-sided 95% confidence interval (CI) for μ TOTAL-ClinBPO - μ TOTAL-DUAC was completely contained within [-10.0, 10.0].

| | |
|-----------------------------------------|---------------------------------------|
| Comparison groups | ClinBPO 30 v Duac (10 mg/g + 30 mg/g) |
| Number of subjects included in analysis | 420 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.23 |
| upper limit | 3.56 |

| Statistical analysis title | Superiority of Test over Vehicle |
|----------------------------|----------------------------------|
|----------------------------|----------------------------------|

Statistical analysis description:

In order to verify assay sensitivity of the study design, superiority of the two active preparations over vehicle was tested by means of two-sided significance tests with $\alpha = 0.05$. The primary test of superiority was carried out for the ITT data set.

| | |
|-----------------------------------------|----------------------|
| Comparison groups | ClinBPO 30 v Vehicle |
| Number of subjects included in analysis | 434 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | t-test, 2-sided |

| Statistical analysis title | Superiority of Reference over Vehicle |
|----------------------------|---------------------------------------|
|----------------------------|---------------------------------------|

Statistical analysis description:

In order to verify assay sensitivity of the study design, superiority of the two active preparations over vehicle was tested by means of two-sided significance tests with $\alpha = 0.05$. The primary test of superiority was carried out for the ITT data set.

| | |
|-----------------------------------------|------------------------------------|
| Comparison groups | Vehicle v Duac (10 mg/g + 30 mg/g) |
| Number of subjects included in analysis | 440 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | t-test, 2-sided |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From inclusion visit (day 0, Visit V1) to end-of-treatment (EOT) examination at Visit V8 (week 12).

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | ClinBPO 30 |
|-----------------------|------------|

Reporting group description:

Test product

| | |
|-----------------------|--------------------------|
| Reporting group title | Duac (10 mg/g + 30 mg/g) |
|-----------------------|--------------------------|

Reporting group description:

Reference Product

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

Reporting group description: -

| Serious adverse events | ClinBPO 30 | Duac (10 mg/g + 30 mg/g) | Vehicle |
|---------------------------------------------------|-----------------|--------------------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 224 (0.45%) | 0 / 228 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Infections and infestations | | | |
| Complicated appendicitis | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 224 (0.45%) | 0 / 228 (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 |

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

| Non-serious adverse events | ClinBPO 30 | Duac (10 mg/g + 30 mg/g) | Vehicle |
|---------------------------------------------------------------------|-------------------|--------------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 55 / 223 (24.66%) | 62 / 224 (27.68%) | 46 / 228 (20.18%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Gastroenteropancreatic neuroendocrine tumour disease | | | |

| | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |
| Melanocytic naevus subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |
| Skin papilloma subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |
| Pregnancy, puerperium and perinatal conditions Pregnancy subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 0 / 224 (0.00%) 0 | 1 / 228 (0.44%) 1 |
| General disorders and administration site conditions Application site dermatitis subjects affected / exposed occurrences (all) | 2 / 223 (0.90%) 2 | 1 / 224 (0.45%) 1 | 1 / 228 (0.44%) 1 |
| Application site dryness subjects affected / exposed occurrences (all) | 12 / 223 (5.38%) 12 | 15 / 224 (6.70%) 15 | 5 / 228 (2.19%) 5 |
| Application site erythema subjects affected / exposed occurrences (all) | 9 / 223 (4.04%) 9 | 9 / 224 (4.02%) 9 | 4 / 228 (1.75%) 4 |
| Application site exfoliation subjects affected / exposed occurrences (all) | 3 / 223 (1.35%) 3 | 2 / 224 (0.89%) 2 | 0 / 228 (0.00%) 0 |
| Application site hypersensitivity subjects affected / exposed occurrences (all) | 2 / 223 (0.90%) 2 | 3 / 224 (1.34%) 3 | 1 / 228 (0.44%) 1 |
| Application site irritation subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |
| Application site pain subjects affected / exposed occurrences (all) | 6 / 223 (2.69%) 6 | 7 / 224 (3.13%) 7 | 6 / 228 (2.63%) 6 |
| Application site plaque | | | |

| | | | |
|---------------------------------------------------------------------------------------------------------------|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 0 / 224 (0.00%) 0 | 1 / 228 (0.44%) 1 |
| Application site pruritus subjects affected / exposed occurrences (all) | 2 / 223 (0.90%) 3 | 3 / 224 (1.34%) 3 | 1 / 228 (0.44%) 1 |
| Application site scab subjects affected / exposed occurrences (all) | 1 / 223 (0.45%) 1 | 0 / 224 (0.00%) 0 | 0 / 228 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 1 / 223 (0.45%) 1 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |
| Immune system disorders Milk allergy subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 0 / 224 (0.00%) 0 | 1 / 228 (0.44%) 1 |
| Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all) | 1 / 223 (0.45%) 1 | 0 / 224 (0.00%) 0 | 2 / 228 (0.88%) 2 |
| Polycystic ovaries subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 0 / 224 (0.00%) 0 | 1 / 228 (0.44%) 1 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 5 / 223 (2.24%) 5 | 2 / 224 (0.89%) 2 | 1 / 228 (0.44%) 1 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |
| Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all) | 1 / 223 (0.45%) 1 | 0 / 224 (0.00%) 0 | 0 / 228 (0.00%) 0 |
| Investigations Arthroscopy | | | |

| | | | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |
| Injury, poisoning and procedural complications Joint injury subjects affected / exposed occurrences (all) | 1 / 223 (0.45%) 1 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all) | 3 / 223 (1.35%) 4 1 / 223 (0.45%) 1 | 3 / 224 (1.34%) 4 0 / 224 (0.00%) 0 | 2 / 228 (0.88%) 2 0 / 228 (0.00%) 0 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 1 / 223 (0.45%) 1 | 0 / 224 (0.00%) 0 | 0 / 228 (0.00%) 0 |
| Ear and labyrinth disorders Motion sickness subjects affected / exposed occurrences (all) | 1 / 223 (0.45%) 1 | 0 / 224 (0.00%) 0 | 0 / 228 (0.00%) 0 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Lip dry | 1 / 223 (0.45%) 1 0 / 223 (0.00%) 0 0 / 223 (0.00%) 0 1 / 223 (0.45%) 1 | 0 / 224 (0.00%) 0 1 / 224 (0.45%) 1 0 / 224 (0.00%) 0 0 / 224 (0.00%) 0 | 1 / 228 (0.44%) 1 0 / 228 (0.00%) 0 1 / 228 (0.44%) 1 0 / 228 (0.00%) 0 |

| | | | |
|-------------------------------------------------------------------------------|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |
| Tooth malformation subjects affected / exposed occurrences (all) | 1 / 223 (0.45%) 1 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |
| Toothache subjects affected / exposed occurrences (all) | 1 / 223 (0.45%) 1 | 0 / 224 (0.00%) 0 | 0 / 228 (0.00%) 0 |
| Skin and subcutaneous tissue disorders | | | |
| Acne subjects affected / exposed occurrences (all) | 1 / 223 (0.45%) 1 | 0 / 224 (0.00%) 0 | 0 / 228 (0.00%) 0 |
| Dermatitis allergic subjects affected / exposed occurrences (all) | 1 / 223 (0.45%) 1 | 0 / 224 (0.00%) 0 | 0 / 228 (0.00%) 0 |
| Dermatitis contact subjects affected / exposed occurrences (all) | 1 / 223 (0.45%) 1 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |
| Dry skin subjects affected / exposed occurrences (all) | 1 / 223 (0.45%) 1 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |
| Erythema subjects affected / exposed occurrences (all) | 3 / 223 (1.35%) 3 | 1 / 224 (0.45%) 1 | 1 / 228 (0.44%) 1 |
| Hand dermatitis subjects affected / exposed occurrences (all) | 2 / 223 (0.90%) 2 | 0 / 224 (0.00%) 0 | 0 / 228 (0.00%) 0 |
| Perioral dermatitis subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 0 / 224 (0.00%) 0 | 1 / 228 (0.44%) 1 |
| Photosensitivity reaction subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 0 / 224 (0.00%) 0 | 1 / 228 (0.44%) 1 |
| Pruritus subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |

| | | | |
|------------------------------------------------------------------------------------------------------------------|----------------------|----------------------|----------------------|
| Skin exfoliation subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |
| Solar dermatitis subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |
| Renal and urinary disorders Urinary tract discomfort subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 0 / 224 (0.00%) 0 | 1 / 228 (0.44%) 1 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |
| Myalgia subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |
| Infections and infestations Body tinea subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |
| Bronchitis subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 3 / 224 (1.34%) 3 | 3 / 228 (1.32%) 3 |
| COVID-19 subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 1 / 224 (0.45%) 1 | 2 / 228 (0.88%) 2 |
| Cystitis subjects affected / exposed occurrences (all) | 1 / 223 (0.45%) 1 | 0 / 224 (0.00%) 0 | 0 / 228 (0.00%) 0 |
| Furuncle subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 1 / 224 (0.45%) 1 | 0 / 228 (0.00%) 0 |
| Gastrointestinal viral infection subjects affected / exposed occurrences (all) | 0 / 223 (0.00%) 0 | 0 / 224 (0.00%) 0 | 1 / 228 (0.44%) 1 |

| | | | |
|-----------------------------------|-----------------|-----------------|-----------------|
| Genital herpes | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 224 (0.45%) | 0 / 228 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hordeolum | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 0 / 224 (0.00%) | 1 / 228 (0.44%) |
| occurrences (all) | 0 | 0 | 1 |
| Impetigo | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 1 / 224 (0.45%) | 0 / 228 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 4 / 223 (1.79%) | 3 / 224 (1.34%) | 1 / 228 (0.44%) |
| occurrences (all) | 4 | 3 | 1 |
| Oral herpes | | | |
| subjects affected / exposed | 2 / 223 (0.90%) | 1 / 224 (0.45%) | 1 / 228 (0.44%) |
| occurrences (all) | 3 | 1 | 1 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 223 (0.45%) | 1 / 224 (0.45%) | 1 / 228 (0.44%) |
| occurrences (all) | 1 | 1 | 1 |
| Pulpitis dental | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 0 / 224 (0.00%) | 1 / 228 (0.44%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhinitis | | | |
| subjects affected / exposed | 2 / 223 (0.90%) | 1 / 224 (0.45%) | 2 / 228 (0.88%) |
| occurrences (all) | 2 | 1 | 2 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 223 (1.35%) | 5 / 224 (2.23%) | 6 / 228 (2.63%) |
| occurrences (all) | 5 | 5 | 7 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 223 (0.00%) | 2 / 224 (0.89%) | 0 / 228 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Viral infection | | | |
| subjects affected / exposed | 2 / 223 (0.90%) | 1 / 224 (0.45%) | 1 / 228 (0.44%) |
| occurrences (all) | 3 | 1 | 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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|---------------|
| None reported |
|---------------|

Notes: