



Clinical trial results:

A 24-Week Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study Evaluating the Efficacy and Safety of Intranasal Administration of 186 and 372 g of OPN-375 Twice a Day (BID) in Subjects with Chronic Sinusitis With or Without the Presence of Nasal Polyps

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2019-000368-12 |
| Trial protocol | GB BG |
| Global end of trial date | 19 January 2022 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 01 April 2023 |
| First version publication date | 01 April 2023 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | OPN-FLU-CS-3205 |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | IND: 110089 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | OptiNose US, Inc. |
| Sponsor organisation address | 1020 Stony Hill Road, Suite 300, Yardley, PA, United States, 19067 |
| Public contact | Global Clinical Operations, OptiNose US, Inc., john.messina@optinose.com |
| Scientific contact | Global Clinical Operations, OptiNose US, Inc., john.messina@optinose.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 | 19 January 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 19 January 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 19 January 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the efficacy of intranasal administration of twice-daily doses of 186 and 372 µg of OPN-375 (fluticasone propionate) with placebo in subjects with chronic sinusitis using the following co-primary endpoints:

- change from baseline in symptoms as measured by a composite score of nasal symptoms (CSNS): congestion, facial pain or pressure sensation, and nasal discharge (anterior and/or posterior) at the end of Week 4

and

- change from baseline to Week 24/Early Termination (ET) in the average percent of the volume opacified (APOV) in the ethmoid and maxillary sinuses

Protection of trial subjects:

Subjects will be informed that they are free to withdraw from study treatment and/or the study at any time at their own request without prejudice to their future medical care, or that they may be withdrawn at any time at the discretion of the investigator or Sponsor for safety, nonadherence to protocol requirements, or administrative reasons (eg, termination of study by Sponsor). Subjects wishing to withdraw from study treatment will be strongly encouraged to continue in the study and have all scheduled study procedures performed.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 01 November 2018 |
| 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 | Russian Federation: 24 |
| Country: Number of subjects enrolled | Canada: 16 |
| Country: Number of subjects enrolled | United States: 183 |
| Country: Number of subjects enrolled | Poland: 90 |
| Country: Number of subjects enrolled | Sweden: 8 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Country: Number of subjects enrolled | Bulgaria: 7 |
| Country: Number of subjects enrolled | Georgia: 2 |
| Worldwide total number of subjects | 332 |
| EEA total number of subjects | 105 |

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) | 277 |
| From 65 to 84 years | 54 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

This study was carried out in subjects with chronic sinusitis with or without nasal polyps.

Pre-assignment

Screening details:

Subjects who met eligibility criteria at screening were dispensed a single-blind kit containing 2 placebo units marked "1" and "2" for use during the 7- to 21-day. Subjects self-administered 1 spray per nostril each morning and evening. Symptoms were assessed to ensure symptom eligibility criteria and a CT scan was obtained if necessary.

Pre-assignment period milestones

| | |
|------------------------------|--------------------|
| Number of subjects started | 556 ^[1] |
| Number of subjects completed | 332 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---------------------------------------|
| Reason: Number of subjects | Not eligible for study treatment: 224 |
|----------------------------|---------------------------------------|

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 224 subjects failed screening and were never enrolled into the study

Period 1

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

Arms

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

Arm description:

Placebo nasal spray, 1 or 2 sprays per nostril twice daily

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

Dosage and administration details:

1 or 2 sprays per nostril twice daily

| | |
|------------------|----------------------|
| Arm title | OPN-375 (186 µg BID) |
|------------------|----------------------|

Arm description:

OPN-375 1 spray per nostril (186 µg) twice daily (BID)

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | OPN-375 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Nasal spray |
| Routes of administration | Nasal use |

Dosage and administration details:
1 spray per nostril (186 µg per dose)

| | |
|---|----------------------|
| Arm title | OPN-375 (372 µg BID) |
| Arm description: OPN-375 2 sprays per nostril (372 µg) twice daily (BID) | |
| Arm type | Experimental |
| Investigational medicinal product name | OPN-375 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Nasal spray |
| Routes of administration | Nasal use |

Dosage and administration details:
2 sprays per nostril (372 µg per dose)

| Number of subjects in period 1 | Placebo | OPN-375 (186 µg BID) | OPN-375 (372 µg BID) |
|---------------------------------------|---------|----------------------|----------------------|
| Started | 112 | 111 | 109 |
| Completed | 96 | 102 | 101 |
| Not completed | 16 | 9 | 8 |
| Consent withdrawn by subject | 1 | - | 1 |
| Adverse event, non-fatal | 3 | 2 | 2 |
| Not specified | - | 2 | 2 |
| Lost to follow-up | 2 | 1 | 1 |
| Lack of efficacy | 9 | 4 | 2 |
| Protocol deviation | 1 | - | - |

Baseline characteristics

Reporting groups

| | |
|--|----------------------|
| Reporting group title | Placebo |
| Reporting group description: Placebo nasal spray, 1 or 2 sprays per nostril twice daily | |
| Reporting group title | OPN-375 (186 µg BID) |
| Reporting group description: OPN-375 1 spray per nostril (186 µg) twice daily (BID) | |
| Reporting group title | OPN-375 (372 µg BID) |
| Reporting group description: OPN-375 2 sprays per nostril (372 µg) twice daily (BID) | |

| Reporting group values | Placebo | OPN-375 (186 µg BID) | OPN-375 (372 µg BID) |
|---|---------|----------------------|----------------------|
| Number of subjects | 112 | 111 | 109 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 89 | 95 | 93 |
| From 65-84 years | 23 | 16 | 15 |
| 85 years and over | 0 | 0 | 1 |
| Age continuous Units: years | | | |
| arithmetic mean | 49.2 | 48.4 | 49.6 |
| standard deviation | ± 15.26 | ± 13.85 | ± 13.49 |
| Gender categorical Units: Subjects | | | |
| Female | 51 | 47 | 43 |
| Male | 61 | 64 | 66 |
| Race Units: Subjects | | | |
| White | 101 | 99 | 99 |
| American Indian or Alaska Native | 0 | 1 | 0 |
| Black or African American | 6 | 10 | 4 |
| Asian | 4 | 1 | 5 |
| Other | 1 | 0 | 1 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 8 | 1 | 9 |
| Not Hispanic or Latino | 104 | 110 | 100 |
| Previous or current diagnosis of nasal polyps Units: Subjects | | | |
| Yes | 78 | 78 | 77 |
| No | 34 | 33 | 32 |
| Number of acute sinusitis exacerbations treated with an antibiotic or oral steroids in last year Units: Subjects | | | |
| 0 acute sinusitis exacerbations | 50 | 48 | 49 |

| | | | |
|--|----------|----------|----------|
| 1 acute sinusitis exacerbation | 22 | 23 | 29 |
| 2 acute sinusitis exacerbations | 17 | 15 | 11 |
| 3 acute sinusitis exacerbations | 14 | 13 | 9 |
| 4 acute sinusitis exacerbations | 5 | 9 | 9 |
| 5 acute sinusitis exacerbations | 2 | 2 | 1 |
| 6 acute sinusitis exacerbations | 2 | 0 | 1 |
| 7 acute sinusitis exacerbations | 0 | 1 | 0 |
| Nasal Polyp (Subgroups for Analyses in the Full Analysis Set) Units: Subjects | | | |
| Present | 69 | 69 | 67 |
| Absent | 41 | 41 | 40 |
| Not part of the Full Analysis Set | 2 | 1 | 2 |
| Prior Sinus Surgery (Subgroups for Analyses in the Full Analysis Set) | | | |
| Prior Sinus Surgery only counts any ethmoidectomy or maxillary antrostomy. | | | |
| Units: Subjects | | | |
| Yes | 44 | 51 | 42 |
| No | 66 | 59 | 65 |
| Not part of the Full Analysis Set | 2 | 1 | 2 |
| Weight Units: kilogram | | | |
| arithmetic mean | 84.04 | 82.74 | 83.78 |
| standard deviation | ± 21.610 | ± 20.882 | ± 18.803 |

| | | | |
|--|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 332 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 277 | | |
| From 65-84 years | 54 | | |
| 85 years and over | 1 | | |
| Age continuous Units: years | | | |
| arithmetic mean | - | | |
| standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 141 | | |
| Male | 191 | | |
| Race Units: Subjects | | | |
| White | 299 | | |
| American Indian or Alaska Native | 1 | | |
| Black or African American | 20 | | |
| Asian | 10 | | |
| Other | 2 | | |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 18 | | |
| Not Hispanic or Latino | 314 | | |
| Previous or current diagnosis of nasal | | | |

| | | | |
|--|-----|--|--|
| polyps | | | |
| Units: Subjects | | | |
| Yes | 233 | | |
| No | 99 | | |
| Number of acute sinusitis exacerbations treated with an antibiotic or oral steroids in last year | | | |
| Units: Subjects | | | |
| 0 acute sinusitis exacerbations | 147 | | |
| 1 acute sinusitis exacerbation | 74 | | |
| 2 acute sinusitis exacerbations | 43 | | |
| 3 acute sinusitis exacerbations | 36 | | |
| 4 acute sinusitis exacerbations | 23 | | |
| 5 acute sinusitis exacerbations | 5 | | |
| 6 acute sinusitis exacerbations | 3 | | |
| 7 acute sinusitis exacerbations | 1 | | |
| Nasal Polyp (Subgroups for Analyses in the Full Analysis Set) | | | |
| Units: Subjects | | | |
| Present | 205 | | |
| Absent | 122 | | |
| Not part of the Full Analysis Set | 5 | | |
| Prior Sinus Surgery (Subgroups for Analyses in the Full Analysis Set) | | | |
| Prior Sinus Surgery only counts any ethmoidectomy or maxillary antrostomy. | | | |
| Units: Subjects | | | |
| Yes | 137 | | |
| No | 190 | | |
| Not part of the Full Analysis Set | 5 | | |
| Weight | | | |
| Units: kilogram | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

End points

End points reporting groups

| | |
|--|----------------------|
| Reporting group title | Placebo |
| Reporting group description: Placebo nasal spray, 1 or 2 sprays per nostril twice daily | |
| Reporting group title | OPN-375 (186 µg BID) |
| Reporting group description: OPN-375 1 spray per nostril (186 µg) twice daily (BID) | |
| Reporting group title | OPN-375 (372 µg BID) |
| Reporting group description: OPN-375 2 sprays per nostril (372 µg) twice daily (BID) | |

Primary: Change from Baseline to Week 4 in the 7-Day Average of Instantaneous Morning Composite Symptom Score

| | |
|--|--|
| End point title | Change from Baseline to Week 4 in the 7-Day Average of Instantaneous Morning Composite Symptom Score |
| End point description: LS = least squares. CSS = composite symptom score. -9999 = not applicable 0000 = not applicable | |
| End point type | Primary |
| End point timeframe: Baseline to Week 4. | |

| End point values | Placebo | OPN-375 (186 µg BID) | OPN-375 (372 µg BID) | |
|--|-----------------------|------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 110 | 110 | 107 | |
| Units: LS Mean Change from Baseline in CSS | | | | |
| least squares mean (confidence interval 95%) | | | | |
| LS Mean Change (from baseline) | -0.62 (-9999 to 0000) | -1.58 (-9999 to 0000) | -1.60 (-9999 to 0000) | |
| LS Mean Difference (active minus placebo) | 0000 (0000 to 0000) | -0.97 (-1.41 to -0.52) | -0.98 (-1.43 to -0.54) | |

Statistical analyses

| | |
|--|------------------------|
| Statistical analysis title | P-value versus Placebo |
| Statistical analysis description: P-value versus Placebo of OPN-375 (186 µg BID) and P-value versus Placebo of OPN-375 (372 µg BID). Inferential statistics are based on a linear mixed model for repeated measures (MMRM) including | |

categorical effects for previous sinus surgery, nasal polyp status, treatment, week (2, 4), treatment-by-week interaction, and continuous covariate: baseline 7-day average score, with baseline score-by-week interaction.

| | |
|---|---|
| Comparison groups | OPN-375 (186 µg BID) v OPN-375 (372 µg BID) v Placebo |
| Number of subjects included in analysis | 327 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | MMRM |

Primary: Change from Baseline to Week 24/ET in APOV in Ethmoid and Maxillary Sinuses Combined

| | |
|---|--|
| End point title | Change from Baseline to Week 24/ET in APOV in Ethmoid and Maxillary Sinuses Combined |
| End point description: ET = early termination. APOV = average of the percentages of opacified volume. LS = least squares. -9999 = not applicable. 9999 = not applicable. | |
| End point type | Primary |
| End point timeframe: Baseline to Week 24. | |

| End point values | Placebo | OPN-375 (186 µg BID) | OPN-375 (372 µg BID) | |
|--|-----------------------|------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 110 | 110 | 107 | |
| Units: LS Mean Change from Baseline | | | | |
| least squares mean (confidence interval 95%) | | | | |
| LS Mean Change (from baseline) | -1.60 (-9999 to 9999) | -5.58 (-9999 to 9999) | -6.20 (-9999 to 9999) | |
| LS Mean Difference (active minus placebo) | 9999 (-9999 to 9999) | -3.98 (-7.86 to -0.09) | -4.59 (-8.41 to -0.78) | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | P-value versus Placebo for OPN-375 (186 µg BID) |
| Statistical analysis description: Inferential statistics are based on multiple imputation of a linear analysis of covariance (ANCOVA) model including categorical effects for nasal polyp status, previous sinus surgery, treatment, and continuous baseline value as covariate. | |
| Comparison groups | OPN-375 (186 µg BID) v Placebo |

| | |
|---|---------------|
| Number of subjects included in analysis | 220 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.045 |
| Method | ANCOVA |

| | |
|---|---|
| Statistical analysis title | P-value versus Placebo for OPN-375 (372 µg BID) |
| Comparison groups | Placebo v OPN-375 (372 µg BID) |
| Number of subjects included in analysis | 217 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.018 |
| Method | ANCOVA |

Notes:

[1] - Inferential statistics are based on multiple imputation of a linear analysis of covariance (ANCOVA) model including categorical effects for nasal polyp status, previous sinus surgery, treatment, and continuous baseline value as covariate.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Pretreatment (Screening/Run-in) period to end of treatment (Week 24)

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 24 |
|--------------------|----|

Reporting groups

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

Reporting group description:

All enrolled/randomized subjects who received at least 1 dose of placebo

| | |
|-----------------------|----------------|
| Reporting group title | OPN-375 186 µg |
|-----------------------|----------------|

Reporting group description:

All enrolled/randomized subjects who received at least 1 dose of randomized study treatment (186 µg twice daily).

| | |
|-----------------------|----------------|
| Reporting group title | OPN-375 372 µg |
|-----------------------|----------------|

Reporting group description:

All enrolled/randomized subjects who received at least 1 dose of randomized study treatment (372 µg twice daily).

| Serious adverse events | Placebo | OPN-375 186 µg | OPN-375 372 µg |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 112 (2.68%) | 1 / 111 (0.90%) | 2 / 109 (1.83%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 1 / 112 (0.89%) | 0 / 111 (0.00%) | 0 / 109 (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 | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 0 / 111 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 111 (0.90%) | 0 / 109 (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 |
| Reproductive system and breast disorders | | | |
| Adenomyosis | | | |
| subjects affected / exposed | 1 / 112 (0.89%) | 0 / 111 (0.00%) | 0 / 109 (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 |
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 112 (0.89%) | 0 / 111 (0.00%) | 0 / 109 (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 |
| Gastrointestinal disorders | | | |
| Alcoholic pancreatitis | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 0 / 111 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 2 / 112 (1.79%) | 0 / 111 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia staphylococcal | | | |
| subjects affected / exposed | 1 / 112 (0.89%) | 0 / 111 (0.00%) | 0 / 109 (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 |

Frequency threshold for reporting non-serious adverse events: 1.5 %

| Non-serious adverse events | Placebo | OPN-375 186 µg | OPN-375 372 µg |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 58 / 112 (51.79%) | 57 / 111 (51.35%) | 52 / 109 (47.71%) |
| Investigations | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| Intraocular pressure increased subjects affected / exposed occurrences (all) | 0 / 112 (0.00%) 0 | 2 / 111 (1.80%) 2 | 0 / 109 (0.00%) 0 |
| Injury, poisoning and procedural complications Vaccination complication subjects affected / exposed occurrences (all) | 3 / 112 (2.68%) 3 | 0 / 111 (0.00%) 0 | 0 / 109 (0.00%) 0 |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 0 / 112 (0.00%) 0 | 2 / 111 (1.80%) 2 | 1 / 109 (0.92%) 1 |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 1 / 112 (0.89%) 2 | 2 / 111 (1.80%) 2 | 3 / 109 (2.75%) 4 |
| Dizziness subjects affected / exposed occurrences (all) | 0 / 112 (0.00%) 0 | 0 / 111 (0.00%) 0 | 3 / 109 (2.75%) 3 |
| Parosmia subjects affected / exposed occurrences (all) | 1 / 112 (0.89%) 1 | 0 / 111 (0.00%) 0 | 2 / 109 (1.83%) 4 |
| Sinus headache subjects affected / exposed occurrences (all) | 2 / 112 (1.79%) 2 | 0 / 111 (0.00%) 0 | 0 / 109 (0.00%) 0 |
| Ear and labyrinth disorders Ear discomfort subjects affected / exposed occurrences (all) | 0 / 112 (0.00%) 0 | 2 / 111 (1.80%) 2 | 0 / 109 (0.00%) 0 |
| Eye disorders Cataract nuclear subjects affected / exposed occurrences (all) | 0 / 112 (0.00%) 0 | 5 / 111 (4.50%) 5 | 4 / 109 (3.67%) 4 |
| Cataract cortical subjects affected / exposed occurrences (all) | 1 / 112 (0.89%) 1 | 6 / 111 (5.41%) 6 | 2 / 109 (1.83%) 3 |
| Cataract subcapsular | | | |

| | | | |
|--|---|----------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 2 / 112 (1.79%) 2 | 1 / 111 (0.90%) 1 | 1 / 109 (0.92%) 2 |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 2 / 112 (1.79%) 2 | 1 / 111 (0.90%) 1 | 2 / 109 (1.83%) 2 |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) | 1 / 112 (0.89%) 1 | 5 / 111 (4.50%) 8 | 13 / 109 (11.93%) 15 |
| Asthma subjects affected / exposed occurrences (all) | 1 / 112 (0.89%) 2 | 5 / 111 (4.50%) 6 | 4 / 109 (3.67%) 4 |
| Nasal polyps subjects affected / exposed occurrences (all) | Additional description: One subject reported an AE of "nasal polyps exacerbation" which was coded to the MedDRA preferred term of "nasal polyps". | | |
| | 8 / 112 (7.14%) 10 | 4 / 111 (3.60%) 4 | 2 / 109 (1.83%) 2 |
| Nasal congestion subjects affected / exposed occurrences (all) | 5 / 112 (4.46%) 6 | 1 / 111 (0.90%) 1 | 2 / 109 (1.83%) 4 |
| Nasal mucosal erosion subjects affected / exposed occurrences (all) | 0 / 112 (0.00%) 0 | 2 / 111 (1.80%) 2 | 1 / 109 (0.92%) 1 |
| Haemoptysis subjects affected / exposed occurrences (all) | 0 / 112 (0.00%) 0 | 2 / 111 (1.80%) 3 | 0 / 109 (0.00%) 0 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 2 / 112 (1.79%) 2 | 0 / 111 (0.00%) 0 | 1 / 109 (0.92%) 1 |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 0 / 112 (0.00%) 0 | 2 / 111 (1.80%) 2 | 0 / 109 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders Arthralgia | | | |

| | | | |
|---|--|-----------------|-----------------|
| subjects affected / exposed | 0 / 112 (0.00%) | 0 / 111 (0.00%) | 3 / 109 (2.75%) |
| occurrences (all) | 0 | 0 | 4 |
| Back pain | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 0 / 111 (0.00%) | 2 / 109 (1.83%) |
| occurrences (all) | 0 | 0 | 2 |
| Infections and infestations | | | |
| Sinusitis | | | |
| subjects affected / exposed | 9 / 112 (8.04%) | 7 / 111 (6.31%) | 6 / 109 (5.50%) |
| occurrences (all) | 14 | 7 | 6 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 112 (2.68%) | 6 / 111 (5.41%) | 3 / 109 (2.75%) |
| occurrences (all) | 3 | 6 | 3 |
| Acute sinusitis | | | |
| subjects affected / exposed | 4 / 112 (3.57%) | 5 / 111 (4.50%) | 2 / 109 (1.83%) |
| occurrences (all) | 4 | 6 | 2 |
| COVID-19 | | | |
| subjects affected / exposed | 6 / 112 (5.36%) | 2 / 111 (1.80%) | 5 / 109 (4.59%) |
| occurrences (all) | 6 | 2 | 5 |
| Chronic sinusitis | Additional description: All AEs that coded to the MedDRA preferred term of "chronic sinusitis" experienced a CRS exacerbation. | | |
| subjects affected / exposed | 7 / 112 (6.25%) | 5 / 111 (4.50%) | 1 / 109 (0.92%) |
| occurrences (all) | 8 | 5 | 2 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 112 (2.68%) | 3 / 111 (2.70%) | 1 / 109 (0.92%) |
| occurrences (all) | 4 | 3 | 1 |
| Influenza | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 3 / 111 (2.70%) | 0 / 109 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 112 (2.68%) | 1 / 111 (0.90%) | 1 / 109 (0.92%) |
| occurrences (all) | 3 | 1 | 1 |
| Otitis media | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 2 / 111 (1.80%) | 0 / 109 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| COVID-19 pneumonia | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 112 (1.79%) | 0 / 111 (0.00%) | 0 / 109 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 13 February 2019 | Required subjects to administer 2 sprays per nostril for each dose of randomized study treatment; identified the co-primary endpoint related to nasal symptoms as the CSNS ("CSS" in all reports including this CSR); extended the single-blind run-in period from 14 to 21 days; modified inclusion/exclusion criteria; added assessments of NP grading to Weeks 4, 12, and 24; added IOP >21 mmHg, nasal septal perforation, and new onset or worsening of cataracts to withdrawal criteria; and provided additional details/clarifications for primary and IAs. |
| 05 December 2019 | Modified inclusion/exclusion criteria; added a biomarker substudy (no analysis done due to low number of participating subjects); revised the endpoint related to sinus volume occupied by disease from evaluating "each" maxillary and ethmoid sinus occupied by disease to evaluating the "worst" maxillary and "worst" ethmoid sinus; and added an assessment of the impact of treatment on subjects approved for surgery who no longer elect to undergo surgery. |
| 15 June 2020 | Amendments 3 (15 June 2022) and 4 (21 August 2020): Modified the protocol in reaction to the COVID-19 pandemic. Most notably, nasal endoscopy and associated polyp grading were removed from Visits 3 and 5; ocular examinations were removed; and subjects were allowed to delay the Week 24 Visit in case of COVID-19 or any upper respiratory infection and continue taking study drug until they could have the Week 24 Visit. Also, remote visits were allowed as needed and provisions were made for completing PROs remotely. |
| 21 August 2020 | Amendments 3 (15 June 2022) and 4 (21 August 2020): Modified the protocol in reaction to the COVID-19 pandemic. Most notably, nasal endoscopy and associated polyp grading were removed from Visits 3 and 5; ocular examinations were removed; and subjects were allowed to delay the Week 24 Visit in case of COVID-19 or any upper respiratory infection and continue taking study drug until they could have the Week 24 Visit. Also, remote visits were allowed as needed and provisions were made for completing PROs remotely. |
| 23 July 2021 | Modified key secondary and other secondary objectives/endpoints by moving SF-36 MCS and PCS endpoints from key secondary to other secondary; added key secondary objectives/endpoints to be analyzed using pooled data from Studies 3205 and 3206; and updated sample size text. |
| 07 January 2022 | Modified key secondary and other secondary objectives/endpoints by moving SNOT-22 total score from key secondary to other secondary; moving SNOT22 and PSQI endpoints to be analyzed using pooled data from Studies 3205 and 3206 from key secondary to other secondary; and adding CSS total score and frequency of acute exacerbations of chronic sinusitis (both analyzed using pooled data from Studies 3205 and 3206) in subjects who were using a standard nasal steroid at study entry to key secondary objectives. Other changes were removal of the biomarker substudy, updates of statistical methods to reflect the changes in key and other secondary objectives/endpoints, and modifications/clarifications to poor score assignments for various endpoints in case of intercurrent events and sensitivity analyses for the APOV co-primary endpoint. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported