

**Clinical trial results:**

**A 16-Week Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study Evaluating the Efficacy and Safety of Intranasal Administration of 100, 200, and 400 µg of Fluticasone Propionate Twice a Day (bid) Using a Novel Bi-directional Device in Subjects with Bilateral Nasal Polyposis Followed by an 8-week, Open-label Extension Phase to Assess Safety.**

**Summary**

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-004887-31 |
| Trial protocol           | GB             |
| Global end of trial date | 03 July 2015   |

**Results information**

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 02 January 2021 |
| First version publication date | 02 January 2021 |

**Trial information****Trial identification**

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | OPN-FLU-NP-3102 |
|-----------------------|-----------------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01624662 |
| WHO universal trial number (UTN)   | -           |

Notes:

**Sponsors**

|                              |                                                                                                                                                          |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | OptiNose US, Inc                                                                                                                                         |
| Sponsor organisation address | 1020 Stony Hill Road, Suite 300, Yardley, United States, PA 19067                                                                                        |
| Public contact               | Jennifer Carothers,<br>Vice President Global Clinical Operations & Outsourcing,<br>OptiNose US, Inc, +1 267 364-3500,<br>jennifer.carothers@optinose.com |
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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                       | 04 March 2016 |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 11 May 2015   |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 03 July 2015  |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the efficacy of intranasal administration of 100, 200, and 400 µg twice daily (bid) of OPN-375 with matching placebo in subjects with bilateral nasal polyposis and nasal congestion. Two co-primary endpoints were used in the study:

- 1) reduction of nasal congestion/obstruction symptoms at the end of Week 4 of the double-blind treatment phase measured by the 7-day average instantaneous morning diary symptom scores (ADS7-IA); and
- 2) reduction in total polyp grade (sum of scores from both nasal cavities) at Week 16 of the double-blind treatment phase as determined by a nasal polyp grading scale score measured by nasoendoscopy.

Protection of trial subjects:

This clinical study was conducted in compliance with the protocol, ethical principles that have their origin in the Declaration of Helsinki in its revised edition, the guidelines of International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) (CPMP/ICH/135/95), European Union (EU) Clinical Trials Directive 2001/20/EC, EU Commission Directive 2005/28/EC, applicable US FDA Regulations, and with local laws and regulations in any country of conduct.

Background therapy:

Allowed concomitant medications:

- Acetaminophen and NSAIDs were permitted for analgesia; ASA was permitted for cardiovascular prophylaxis. ASA and NSAIDs were not allowed for subjects with a documented sensitivity to these medications.
- Antibiotic medications were permitted (except for those prohibited) for bacterial infections that developed during the study. Subjects, who were taking prophylactic antibiotics, were allowed to enter the study as long as they intended to continue the antibiotics for the duration of the study.
- Intranasal saline spray was permitted with the exception that it could not be used within 2 hours before or after study drug administration.
- Saline lavage was permitted only for those subjects regularly using it before study entry; subjects could not initiate use during the study, and could not change usage during the study. Saline lavage was not performed within 2 hours before or after study drug administration.
- Stable doses of leukotriene receptor antagonists, beta-blockers, and neuroleptics.
- Low to medium strength topical corticosteroids for dermatologic purposes.
- Other concomitant medications were allowed, if not specifically listed as prohibited.

Subjects with comorbid asthma or COPD at study entry, inhaled corticosteroid use was limited to stable doses of no more than 1000 µg/day of beclomethasone (or equivalent). Subjects had to be on a stable dose for least 3 months prior to Visit 1 with plans to continue use throughout the study.

Use of rescue medication was not allowed during the single-blind run-in or before the Week 4 visit of the double-blind treatment phase. Subjects were allowed to use OTC loratadine 10 mg per day or another country-available, non-sedating antihistamine (eg, cetirizine, levocetirizine, desloratadine) at the label-recommended usual dose per day as rescue medication following the Week 4 visit in the double-blind treatment phase and throughout the open-label extension phase of the study.

Evidence for comparator: -

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 30 October 2013 |
| 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 | Romania: 55       |
| Country: Number of subjects enrolled | South Africa: 44  |
| Country: Number of subjects enrolled | Ukraine: 54       |
| Country: Number of subjects enrolled | Poland: 131       |
| Country: Number of subjects enrolled | United States: 39 |
| Worldwide total number of subjects   | 323               |
| EEA total number of subjects         | 186               |

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)                      | 300 |
| From 65 to 84 years                       | 23  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

A total of 456 subjects were screened, 434 subjects entered the single-blind run-in phase, and a total of 323 subjects were subsequently enrolled and randomized (ITT Population) at 38 centers into the double-blind phase.

### Pre-assignment

Screening details:

Assessments included nasoendoscopy-related (nasal examination, nasoendoscopy, and surgical intervention assessment) procedures, ocular examinations, clinical laboratory tests, physical examination, and confirmation of ability to use the OptiNose drug delivery system. Subjects also completed a medical evaluation questionnaire.

### Pre-assignment period milestones

|                              |                    |
|------------------------------|--------------------|
| Number of subjects started   | 434 <sup>[1]</sup> |
| Number of subjects completed | 323                |

### Pre-assignment subject non-completion reasons

|                            |                         |
|----------------------------|-------------------------|
| Reason: Number of subjects | Physician decision: 111 |
|----------------------------|-------------------------|

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: During the pretreatment phase subjects administered morning and evening doses of placebo and completed a daily diary immediately prior to morning and evening doses. This consisted of recording both instantaneous (evaluation of symptom severity immediately preceding the time of scoring) and reflective (evaluation of symptom severity over the previous 12 hours) scores for nasal symptoms. At the end of the pretreatment phase, eligible subjects entered into the double-blind treatment phase.

### Period 1

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

Blinding implementation details:

During the double-blind treatment phase of the study, subjects, the investigator and study center personnel at each center, and the sponsor or its designated personnel directly involved in the clinical study, remained blinded to study treatment. The investigator was not provided with the randomization code.

### Arms

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

Arm description:

Matched placebo BID x 16 weeks

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

Dosage and administration details:

EDS-Placebo: Matched placebo BID x 16 weeks

100: OPN-375 100 mcg BID x 16 weeks  
 200: OPN-375 200 mcg BID x 16 weeks  
 400: OPN-375 400 mcg BID x 16 weeks

|                                                                                                                                                                                                        |                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| <b>Arm title</b>                                                                                                                                                                                       | OPN-375 100 mcg                 |
| Arm description:<br>OPN-375 100 mcg BID x 16 weeks                                                                                                                                                     |                                 |
| Arm type                                                                                                                                                                                               | Experimental                    |
| Investigational medicinal product name                                                                                                                                                                 | OPTINOSE FLUTICASONE PROPIONATE |
| Investigational medicinal product code                                                                                                                                                                 | OPN-375                         |
| Other name                                                                                                                                                                                             |                                 |
| Pharmaceutical forms                                                                                                                                                                                   | Nasal spray, suspension         |
| Routes of administration                                                                                                                                                                               | Intranasal use                  |
| Dosage and administration details:<br>EDS-Placebo: Matched placebo BID x 16 weeks<br>100: OPN-375 100 mcg BID x 16 weeks<br>200: OPN-375 200 mcg BID x 16 weeks<br>400: OPN-375 400 mcg BID x 16 weeks |                                 |
| <b>Arm title</b>                                                                                                                                                                                       | OPN-375 200 mcg                 |
| Arm description:<br>OPN-375 200 mcg BID x 16 weeks.                                                                                                                                                    |                                 |
| Arm type                                                                                                                                                                                               | Experimental                    |
| Investigational medicinal product name                                                                                                                                                                 | OPTINOSE FLUTICASONE PROPIONATE |
| Investigational medicinal product code                                                                                                                                                                 | OPN-375                         |
| Other name                                                                                                                                                                                             |                                 |
| Pharmaceutical forms                                                                                                                                                                                   | Nasal spray, suspension         |
| Routes of administration                                                                                                                                                                               | Intranasal use                  |
| Dosage and administration details:<br>EDS-Placebo: Matched placebo BID x 16 weeks<br>100: OPN-375 100 mcg BID x 16 weeks<br>200: OPN-375 200 mcg BID x 16 weeks<br>400: OPN-375 400 mcg BID x 16 weeks |                                 |
| <b>Arm title</b>                                                                                                                                                                                       | OPN-375 400 mcg                 |
| Arm description:<br>OPN-375 400 mcg BID x 16 weeks                                                                                                                                                     |                                 |
| Arm type                                                                                                                                                                                               | Experimental                    |
| Investigational medicinal product name                                                                                                                                                                 | OPTINOSE FLUTICASONE PROPIONATE |
| Investigational medicinal product code                                                                                                                                                                 | OPN-375                         |
| Other name                                                                                                                                                                                             |                                 |
| Pharmaceutical forms                                                                                                                                                                                   | Nasal spray, suspension         |
| Routes of administration                                                                                                                                                                               | Intranasal use                  |
| Dosage and administration details:<br>EDS-Placebo: Matched placebo BID x 16 weeks<br>100: OPN-375 100 mcg BID x 16 weeks<br>200: OPN-375 200 mcg BID x 16 weeks<br>400: OPN-375 400 mcg BID x 16 weeks |                                 |

| Number of subjects in period 1 | EDS-Placebo | OPN-375 100 mcg | OPN-375 200 mcg |
|--------------------------------|-------------|-----------------|-----------------|
| Started                        | 80          | 81              | 80              |
| Completed                      | 70          | 78              | 76              |
| Not completed                  | 10          | 3               | 4               |
| Consent withdrawn by subject   | 3           | -               | 3               |
| Adverse event, non-fatal       | 2           | 1               | 1               |
| Protocol violation             | -           | 1               | -               |
| Lack of efficacy               | 5           | 1               | -               |

| Number of subjects in period 1 | OPN-375 400 mcg |
|--------------------------------|-----------------|
| Started                        | 82              |
| Completed                      | 82              |
| Not completed                  | 0               |
| Consent withdrawn by subject   | -               |
| Adverse event, non-fatal       | -               |
| Protocol violation             | -               |
| Lack of efficacy               | -               |

## Period 2

|                              |                  |
|------------------------------|------------------|
| Period 2 title               | Open-label Phase |
| Is this the baseline period? | No               |
| Allocation method            | Not applicable   |
| Blinding used                | Not blinded      |

Blinding implementation details:

During the open-label treatment extension phase, all individuals involved in the study were aware that the treatment was open-label OPN-375 400 µg bid, but remained unaware of which treatment had been received during the prior 16 weeks.

## Arms

|           |                 |
|-----------|-----------------|
| Arm title | OPN-375 400 mcg |
|-----------|-----------------|

Arm description:

At the Week 16 visit, subjects received 2 study drug kits. One kit was used during Weeks 17 to 20 and the other kit was used during Weeks 21 to 24. During the open-label extension phase, all subjects received OPN-375 400 µg bid.

|                                        |                                 |
|----------------------------------------|---------------------------------|
| Arm type                               | Experimental                    |
| Investigational medicinal product name | OPTINOSE FLUTICASONE PROPIONATE |
| Investigational medicinal product code | OPN-375                         |
| Other name                             |                                 |
| Pharmaceutical forms                   | Nasal spray, suspension         |
| Routes of administration               | Intranasal use                  |

Dosage and administration details:

OPN-375 400 mcg BID x 8 weeks

| <b>Number of subjects in period 2<sup>[2]</sup></b> | OPN-375 400 mcg |
|-----------------------------------------------------|-----------------|
| Started                                             | 299             |
| Completed                                           | 294             |
| Not completed                                       | 5               |
| Consent withdrawn by subject                        | 1               |
| Adverse event, non-fatal                            | 3               |
| Lack of efficacy                                    | 1               |

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Notes:

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

Justification: 17 patients did not start the open label phase for the following reasons:  
lack of efficacy (6), subject withdrawal (6) adverse events (4) protocol deviations (1)

## Baseline characteristics

### Reporting groups

|                                                                 |                 |
|-----------------------------------------------------------------|-----------------|
| Reporting group title                                           | EDS-Placebo     |
| Reporting group description:<br>Matched placebo BID x 16 weeks  |                 |
| Reporting group title                                           | OPN-375 100 mcg |
| Reporting group description:<br>OPN-375 100 mcg BID x 16 weeks  |                 |
| Reporting group title                                           | OPN-375 200 mcg |
| Reporting group description:<br>OPN-375 200 mcg BID x 16 weeks. |                 |
| Reporting group title                                           | OPN-375 400 mcg |
| Reporting group description:<br>OPN-375 400 mcg BID x 16 weeks  |                 |

| Reporting group values                                              | EDS-Placebo | OPN-375 100 mcg | OPN-375 200 mcg |
|---------------------------------------------------------------------|-------------|-----------------|-----------------|
| Number of subjects                                                  | 80          | 81              | 80              |
| Age categorical<br>Units: Subjects                                  |             |                 |                 |
| In utero                                                            | 0           | 0               | 0               |
| Preterm newborn infants<br>(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)                                                | 73          | 74              | 74              |
| From 65-84 years                                                    | 7           | 7               | 6               |
| 85 years and over                                                   | 0           | 0               | 0               |
| Age continuous<br>Units: years                                      |             |                 |                 |
| arithmetic mean                                                     | 46.7        | 46.7            | 44.8            |
| standard deviation                                                  | ± 11.95     | ± 13.72         | ± 12.87         |
| Gender categorical<br>Units: Subjects                               |             |                 |                 |
| Female                                                              | 38          | 39              | 34              |
| Male                                                                | 42          | 42              | 46              |
| Race/Ethnicity<br>Units: Subjects                                   |             |                 |                 |
| White                                                               | 76          | 76              | 76              |
| Black / African American                                            | 3           | 3               | 3               |
| Asian                                                               | 0           | 0               | 0               |
| Other                                                               | 1           | 2               | 1               |
| Use of ICS treatment for polyps in past 10 years<br>Units: Subjects |             |                 |                 |



|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |    |    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|----|----|
| Participants with ICS treatment for polyps                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 73 | 67 | 70 |
| Participants with no ICS treatment for polyps                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 7  | 14 | 10 |
| Nasal congestion/obstruction score (-7 day instantaneous morning)                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |    |    |    |
| <p>Nasal symptoms were recorded in e-diary each morning for the 7 day period preceding the screening visit, evaluating symptom severity immediately preceding the time of scoring (instantaneous).</p> <p>Nasal Symptom Score</p> <p>0: None</p> <p>1. Mild: symptoms clearly present, but minimal awareness, and easily tolerated</p> <p>2. Moderate: definite awareness of symptoms that is bothersome but tolerable</p> <p>3. Severe: symptoms that are hard to tolerate, cause interference with activities or daily living</p> |    |    |    |
| Units: Units on scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |    |    |    |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |    |    |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |    |    |    |
| Rhinorrhea Score (7-day instantaneous morning)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |    |    |    |
| <p>Nasal symptoms were recorded in e-diary each morning for the 7 day period preceding the screening visit, evaluating symptom severity immediately preceding the time of scoring (instantaneous).</p> <p>Nasal Symptom Score</p> <p>0: None</p> <p>1. Mild: symptoms clearly present, but minimal awareness, and easily tolerated</p> <p>2. Moderate: definite awareness of symptoms that is bothersome but tolerable</p> <p>3. Severe: symptoms that are hard to tolerate, cause interference with activities or daily living</p> |    |    |    |
| Units: Units on a scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |    |    |    |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |    |    |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |    |    |    |
| Facial Pain or Pressure Score (-7 day instantaneous morning)                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |    |    |    |
| <p>Nasal symptoms were recorded in e-diary each morning for the 7 day period preceding the screening visit, evaluating symptom severity immediately preceding the time of scoring (instantaneous).</p> <p>Nasal Symptom Score</p> <p>0: None</p> <p>1. Mild: symptoms clearly present, but minimal awareness, and easily tolerated</p> <p>2. Moderate: definite awareness of symptoms that is bothersome but tolerable</p> <p>3. Severe: symptoms that are hard to tolerate, cause interference with activities or daily living</p> |    |    |    |
| Units: Units on a scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |    |    |    |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |    |    |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |    |    |    |
| Hyposmia Score (-7 day instantaneous morning)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |    |    |    |
| <p>Nasal symptoms were recorded in e-diary each morning for the 7 day period preceding the screening visit, evaluating symptom severity immediately preceding the time of scoring (instantaneous).</p> <p>Nasal Symptom Score</p> <p>0: Normal</p> <p>1: Slightly impaired</p> <p>2: Moderately impaired</p> <p>3: Absent</p>                                                                                                                                                                                                       |    |    |    |
| Units: Units on a scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |    |    |    |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |    |    |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |    |    |    |
| Sinonasal Outcome Test 22 (SNOT-22) Total Score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |    |    |    |
| <p>SNOT-22 is a subject-completed questionnaire that consists of 22 questions. The questions on the SNOT-22 efficacy evaluation were used to calculate a total score. 22 questions are divided among 4 subscales: Rhinologic (7 questions), Ear/Facial Symptoms (4 questions), Sleep Function (3 questions), and Psychological Issues (6 questions). Each item was rated on the 5-point scale. The total score can range from 0-110, 0 being the best and 110 being the worst.</p> <p>0: No problem</p> <p>1. Very mild problem</p> |    |    |    |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                 |       |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-------|--|
| 2. Mild or slight problem<br>3. Moderate problem<br>4. Severe problem<br>5. Problem as bad as it can be                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                 |       |  |
| Units: Units on a scale<br>arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                 |       |  |
| Medical Outcomes Study Sleep Scale Revised (MOS Sleep-R)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                 |       |  |
| The MOS Sleep-R is a brief, self-administered, validated questionnaire designed to measure key aspects of sleep, such as disturbance, adequacy, somnolence, and quantity. The 12-item version with a 4-week recall was used in this study. The score range for the 12-item version is 0 to 100, lower scores indicating better sleep and higher scores indicating worse sleep. The scale yields a Sleep Problem Index and scores on the following 6 subscales: Sleep Disturbance, Snoring, Shortness of Breath or Headache, Sleep Adequacy, Sleep Somnolence, and Sleep Quantity.         |                 |       |  |
| Units: Units on a scale<br>arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                 |       |  |
| Rhinosinusitis Disability Index (RSDI) Total Score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                 |       |  |
| The RSDI is a subject-completed instrument that evaluates the self-perceived impact of disease specific head and neck disorders. The RSDI has 30 items in 3 domains: Physical (11 items), Functional (9 items), and Emotional (10 items). The RSDI scale ranges from 0-120, 0 being better quality of life and less impact of CRS on daily function and 120 being worse quality of life and more impact of CRS on daily function.                                                                                                                                                         |                 |       |  |
| Units: Units on a scale<br>arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                 |       |  |
| Short Form (36) Health Survey Version 2 (SF-36v2) - Mental Component                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                 |       |  |
| The SF-36v2 is a multipurpose, scaled, 36-item, subject-completed validated questionnaire that measures 8 domains of health: limitations in physical activities, limitations in social activities, limitations in usual role activities, bodily pain, general mental health, limitations in usual role activities, vitality, and general health. It yields scale scores for each of the 8 health domains, and 2 summary measures of physical and mental health. Each scale range is from 0-100. A lower score means more disability and a higher score means less disability.             |                 |       |  |
| Units: Units on a scale<br>arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                 |       |  |
| Short Form (36) Health Survey Version 2 (SF-36v2) - Physical Component                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                 |       |  |
| The SF-36v2 is a multipurpose, scaled, 36-item, subject-completed validated questionnaire that measures 8 domains of health: limitations in physical activities, limitations in social activities, limitations in usual role activities, bodily pain, general mental health, limitations in usual role activities, vitality, and general health perceptions. It yields scale scores for each of the 8 health domains, and 2 summary measures of physical and mental health. Each scale range is from 0-100. A lower score means more disability and a higher score means less disability. |                 |       |  |
| Units: Units on a scale<br>arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                 |       |  |
| Peak Nasal Inspiratory Flow (PNIF)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                 |       |  |
| The PNIF is an assessment of nasal passage obstruction and was measured using an In-Check portable nasal inspiratory flow meter. To measure PNIF, a mask was placed over the nose during inspiration and inspiratory flow was recorded. Each subject inhaled 3 times and each measurement was recorded. The PNIF value used was the greatest of the 3 results at each time point.                                                                                                                                                                                                         |                 |       |  |
| Units: Units on a scale<br>arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                 |       |  |
| <b>Reporting group values</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | OPN-375 400 mcg | Total |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |         |     |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-----|--|
| Number of subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 82      | 323 |  |
| Age categorical                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |         |     |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |         |     |  |
| In utero                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 0       | 0   |  |
| Preterm newborn infants<br>(gestational age < 37 wks)                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 0       | 0   |  |
| Newborns (0-27 days)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0       | 0   |  |
| Infants and toddlers (28 days-23<br>months)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 0       | 0   |  |
| Children (2-11 years)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 0       | 0   |  |
| Adolescents (12-17 years)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 0       | 0   |  |
| Adults (18-64 years)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 79      | 300 |  |
| From 65-84 years                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 3       | 23  |  |
| 85 years and over                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 0       | 0   |  |
| Age continuous                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |     |  |
| Units: years                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |         |     |  |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 45      |     |  |
| standard deviation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | ± 12.14 | -   |  |
| Gender categorical                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |     |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |         |     |  |
| Female                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 26      | 137 |  |
| Male                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 56      | 186 |  |
| Race/Ethnicity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |     |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |         |     |  |
| White                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 76      | 304 |  |
| Black / African American                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 4       | 13  |  |
| Asian                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 0       | 0   |  |
| Other                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 2       | 6   |  |
| Use of ICS treatment for polyps in past<br>10 years                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |         |     |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |         |     |  |
| Participants with ICS treatment for<br>polyps                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 70      | 280 |  |
| Participants with no ICS treatment<br>for polyps                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 12      | 43  |  |
| Nasal congestion/obstruction score (-7<br>day instantaneous morning)                                                                                                                                                                                                                                                                                                                                                                                                                                                                |         |     |  |
| <p>Nasal symptoms were recorded in e-diary each morning for the 7 day period preceding the screening visit, evaluating symptom severity immediately preceding the time of scoring (instantaneous).</p> <p>Nasal Symptom Score</p> <p>0: None</p> <p>1. Mild: symptoms clearly present, but minimal awareness, and easily tolerated</p> <p>2. Moderate: definite awareness of symptoms that is bothersome but tolerable</p> <p>3. Severe: symptoms that are hard to tolerate, cause interference with activities or daily living</p> |         |     |  |
| Units: Units on scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |         |     |  |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |         |     |  |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |         | -   |  |
| Rhinorrhea Score (7-day instantaneous<br>morning)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |         |     |  |
| <p>Nasal symptoms were recorded in e-diary each morning for the 7 day period preceding the screening visit, evaluating symptom severity immediately preceding the time of scoring (instantaneous).</p> <p>Nasal Symptom Score</p> <p>0: None</p> <p>1. Mild: symptoms clearly present, but minimal awareness, and easily tolerated</p> <p>2. Moderate: definite awareness of symptoms that is bothersome but tolerable</p> <p>3. Severe: symptoms that are hard to tolerate, cause interference with activities or daily living</p> |         |     |  |
| Units: Units on a scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |         |     |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |  |   |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|---|--|
| arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  | - |  |
| Facial Pain or Pressure Score (-7 day instantaneous morning)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |  |   |  |
| <p>Nasal symptoms were recorded in e-diary each morning for the 7 day period preceding the screening visit, evaluating symptom severity immediately preceding the time of scoring (instantaneous).</p> <p>Nasal Symptom Score</p> <p>0: None</p> <p>1. Mild: symptoms clearly present, but minimal awareness, and easily tolerated</p> <p>2. Moderate: definite awareness of symptoms that is bothersome but tolerable</p> <p>3. Severe: symptoms that are hard to tolerate, cause interference with activities or daily living</p>                                                                                                                            |  |   |  |
| Units: Units on a scale<br>arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  | - |  |
| Hyposmia Score (-7 day instantaneous morning)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |  |   |  |
| <p>Nasal symptoms were recorded in e-diary each morning for the 7 day period preceding the screening visit, evaluating symptom severity immediately preceding the time of scoring (instantaneous).</p> <p>Nasal Symptom Score</p> <p>0: Normal</p> <p>1: Slightly impaired</p> <p>2: Moderately impaired</p> <p>3: Absent</p>                                                                                                                                                                                                                                                                                                                                  |  |   |  |
| Units: Units on a scale<br>arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  | - |  |
| Sinonasal Outcome Test 22 (SNOT-22)<br>Total Score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  |   |  |
| <p>SNOT-22 is a subject-completed questionnaire that consists of 22 questions. The questions on the SNOT-22 efficacy evaluation were used to calculate a total score. 22 questions are divided among 4 subscales: Rhinologic (7 questions), Ear/Facial Symptoms (4 questions), Sleep Function (3 questions), and Psychological Issues (6 questions). Each item was rated on the 5-point scale. The total score can range from 0-110, 0 being the best and 110 being the worst.</p> <p>0: No problem</p> <p>1. Very mild problem</p> <p>2. Mild or slight problem</p> <p>3. Moderate problem</p> <p>4. Severe problem</p> <p>5. Problem as bad as it can be</p> |  |   |  |
| Units: Units on a scale<br>arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  | - |  |
| Medical Outcomes Study Sleep Scale Revised (MOS Sleep-R)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |  |   |  |
| <p>The MOS Sleep-R is a brief, self-administered, validated questionnaire designed to measure key aspects of sleep, such as disturbance, adequacy, somnolence, and quantity. The 12-item version with a 4-week recall was used in this study. The score range for the 12-item version is 0 to 100, lower scores indicating better sleep and higher scores indicating worse sleep. The scale yields a Sleep Problem Index and scores on the following 6 subscales: Sleep Disturbance, Snoring, Shortness of Breath or Headache, Sleep Adequacy, Sleep Somnolence, and Sleep Quantity.</p>                                                                       |  |   |  |
| Units: Units on a scale<br>arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |  | - |  |
| Rhinosinusitis Disability Index (RSDI)<br>Total Score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |   |  |
| <p>The RSDI is a subject-completed instrument that evaluates the self-perceived impact of disease specific head and neck disorders. The RSDI has 30 items in 3 domains: Physical (11 items), Functional (9 items), and Emotional (10 items). The RSDI scale ranges from 0-120, 0 being better quality of life and less impact of CRS on daily function and 120 being worse quality of life and more impact of CRS on daily function.</p>                                                                                                                                                                                                                       |  |   |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |  |   |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|---|--|
| Units: Units on a scale<br>arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  | - |  |
| Short Form (36) Health Survey Version 2 (SF-36v2) - Mental Component                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |  |   |  |
| The SF-36v2 is a multipurpose, scaled, 36-item, subject-completed validated questionnaire that measures 8 domains of health: limitations in physical activities, limitations in social activities, limitations in usual role activities, bodily pain, general mental health, limitations in usual role activities, vitality, and general health. It yields scale scores for each of the 8 health domains, and 2 summary measures of physical and mental health. Each scale range is from 0-100. A lower score means more disability and a higher score means less disability.             |  |   |  |
| Units: Units on a scale<br>arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  | - |  |
| Short Form (36) Health Survey Version 2 (SF-36v2) - Physical Component                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |  |   |  |
| The SF-36v2 is a multipurpose, scaled, 36-item, subject-completed validated questionnaire that measures 8 domains of health: limitations in physical activities, limitations in social activities, limitations in usual role activities, bodily pain, general mental health, limitations in usual role activities, vitality, and general health perceptions. It yields scale scores for each of the 8 health domains, and 2 summary measures of physical and mental health. Each scale range is from 0-100. A lower score means more disability and a higher score means less disability. |  |   |  |
| Units: Units on a scale<br>arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  | - |  |
| Peak Nasal Inspiratory Flow (PNIF)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  |   |  |
| The PNIF is an assessment of nasal passage obstruction and was measured using an In-Check portable nasal inspiratory flow meter. To measure PNIF, a mask was placed over the nose during inspiration and inspiratory flow was recorded. Each subject inhaled 3 times and each measurement was recorded. The PNIF value used was the greatest of the 3 results at each time point.                                                                                                                                                                                                         |  |   |  |
| Units: Units on a scale<br>arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |  | - |  |

## Subject analysis sets

|                                                                                                                                                                                                                                                   |                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Subject analysis set title                                                                                                                                                                                                                        | EDS-Placebo FAS     |
| Subject analysis set type                                                                                                                                                                                                                         | Full analysis       |
| Subject analysis set description:<br>Full Analysis Set included all subjects who received at least one dose of study drug, and who had baseline assessments of polyp size (nasoscopy) and recorded morning nasal congestion/obstruction symptoms. |                     |
| Subject analysis set title                                                                                                                                                                                                                        | OPN-375 100 mcg FAS |
| Subject analysis set type                                                                                                                                                                                                                         | Full analysis       |
| Subject analysis set description:<br>Full Analysis Set included all subjects who received at least one dose of study drug, and who had baseline assessments of polyp size (nasoscopy) and recorded morning nasal congestion/obstruction symptoms. |                     |
| Subject analysis set title                                                                                                                                                                                                                        | OPN-375 200 mcg FAS |
| Subject analysis set type                                                                                                                                                                                                                         | Full analysis       |
| Subject analysis set description:<br>Full Analysis Set included all subjects who received at least one dose of study drug, and who had baseline assessments of polyp size (nasoscopy) and recorded morning nasal congestion/obstruction symptoms. |                     |
| Subject analysis set title                                                                                                                                                                                                                        | OPN-375 400 mcg FAS |
| Subject analysis set type                                                                                                                                                                                                                         | Full analysis       |

Subject analysis set description:

Full Analysis Set included all subjects who received at least one dose of study drug, and who had baseline assessments of polyp size (nasoscopy) and recorded morning nasal congestion/obstruction symptoms.

| Reporting group values                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | EDS-Placebo FAS    | OPN-375 100 mcg FAS | OPN-375 200 mcg FAS |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|---------------------|---------------------|
| Number of subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 79                 | 80                  | 80                  |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                    |                     |                     |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over                                                                                                                                                                                                                                                |                    |                     |                     |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation                                                                                                                                                                                                                                                                                                                                                                                                                                  | ±                  | ±                   | ±                   |
| Gender categorical<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                    |                     |                     |
| Female<br>Male                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                    |                     |                     |
| Race/Ethnicity<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                    |                     |                     |
| White<br>Black / African American<br>Asian<br>Other                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                    |                     |                     |
| Use of ICS treatment for polyps in past 10 years<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                      |                    |                     |                     |
| Participants with ICS treatment for polyps<br>Participants with no ICS treatment for polyps                                                                                                                                                                                                                                                                                                                                                                                                              |                    |                     |                     |
| Nasal congestion/obstruction score (-7 day instantaneous morning)                                                                                                                                                                                                                                                                                                                                                                                                                                        |                    |                     |                     |
| Nasal symptoms were recorded in e-diary each morning for the 7 day period preceding the screening visit, evaluating symptom severity immediately preceding the time of scoring (instantaneous).<br>Nasal Symptom Score<br>0: None<br>1. Mild: symptoms clearly present, but minimal awareness, and easily tolerated<br>2. Moderate: definite awareness of symptoms that is bothersome but tolerable<br>3. Severe: symptoms that are hard to tolerate, cause interference with activities or daily living |                    |                     |                     |
| Units: Units on scale<br>arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                         | 2.29<br>1.6 to 3.0 | 2.23<br>1.6 to 3.0  | 2.20<br>1.7 to 3.0  |
| Rhinorrhea Score (7-day instantaneous morning)                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                    |                     |                     |
| Nasal symptoms were recorded in e-diary each morning for the 7 day period preceding the screening                                                                                                                                                                                                                                                                                                                                                                                                        |                    |                     |                     |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |             |             |             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-------------|-------------|
| visit, evaluating symptom severity immediately preceding the time of scoring (instantaneous).<br>Nasal Symptom Score<br>0: None<br>1. Mild: symptoms clearly present, but minimal awareness, and easily tolerated<br>2. Moderate: definite awareness of symptoms that is bothersome but tolerable<br>3. Severe: symptoms that are hard to tolerate, cause interference with activities or daily living                                                                                                                                                                                                                          |             |             |             |
| Units: Units on a scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |             |             |             |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 1.8         | 1.89        | 1.86        |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 0.0 to 3.0  | 0.0 to 3.0  | 0.0 to 3.0  |
| Facial Pain or Pressure Score (-7 day instantaneous morning)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |             |             |             |
| Nasal symptoms were recorded in e-diary each morning for the 7 day period preceding the screening visit, evaluating symptom severity immediately preceding the time of scoring (instantaneous).<br>Nasal Symptom Score<br>0: None<br>1. Mild: symptoms clearly present, but minimal awareness, and easily tolerated<br>2. Moderate: definite awareness of symptoms that is bothersome but tolerable<br>3. Severe: symptoms that are hard to tolerate, cause interference with activities or daily living                                                                                                                        |             |             |             |
| Units: Units on a scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |             |             |             |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 1.46        | 1.46        | 1.48        |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 0.0 to 3.0  | 0.0 to 3.0  | 0.0 to 3.0  |
| Hyposmia Score (-7 day instantaneous morning)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |             |             |             |
| Nasal symptoms were recorded in e-diary each morning for the 7 day period preceding the screening visit, evaluating symptom severity immediately preceding the time of scoring (instantaneous).<br>Nasal Symptom Score<br>0: Normal<br>1: Slightly impaired<br>2: Moderately impaired<br>3: Absent                                                                                                                                                                                                                                                                                                                              |             |             |             |
| Units: Units on a scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |             |             |             |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 2.47        | 2.36        | 2.54        |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 0.0 to 3.0  | 0.0 to 3.0  | 0.9 to 3.0  |
| Sinonasal Outcome Test 22 (SNOT-22) Total Score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |             |             |             |
| SNOT-22 is a subject-completed questionnaire that consists of 22 questions. The questions on the SNOT-22 efficacy evaluation were used to calculate a total score. 22 questions are divided among 4 subscales: Rhinologic (7 questions), Ear/Facial Symptoms (4 questions), Sleep Function (3 questions), and Psychological Issues (6 questions). Each item was rated on the 5-point scale. The total score can range from 0-110, 0 being the best and 110 being the worst.<br>0: No problem<br>1. Very mild problem<br>2. Mild or slight problem<br>3. Moderate problem<br>4. Severe problem<br>5. Problem as bad as it can be |             |             |             |
| Units: Units on a scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |             |             |             |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 52.0        | 48.5        | 48.1        |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 14 to 94    | 9 to 97     | 11 to 92    |
| Medical Outcomes Study Sleep Scale Revised (MOS Sleep-R)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |             |             |             |
| The MOS Sleep-R is a brief, self-administered, validated questionnaire designed to measure key aspects of sleep, such as disturbance, adequacy, somnolence, and quantity. The 12-item version with a 4-week recall was used in this study. The score range for the 12-item version is 0 to 100, lower scores indicating better sleep and higher scores indicating worse sleep. The scale yields a Sleep Problem Index and scores on the following 6 subscales: Sleep Disturbance, Snoring, Shortness of Breath or Headache, Sleep Adequacy, Sleep Somnolence, and Sleep Quantity.                                               |             |             |             |
| Units: Units on a scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |             |             |             |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 41.7        | 40.9        | 43.0        |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 5.6 to 86.1 | 8.3 to 94.4 | 2.8 to 86.1 |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                |                |                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|----------------|----------------|
| Rhinosinusitis Disability Index (RSDI)<br>Total Score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                |                |                |
| The RSDI is a subject-completed instrument that evaluates the self-perceived impact of disease specific head and neck disorders. The RSDI has 30 items in 3 domains: Physical (11 items), Functional (9 items), and Emotional (10 items). The RSDI scale ranges from 0-120, 0 being better quality of life and less impact of CRS on daily function and 120 being worse quality of life and more impact of CRS on daily function.                                                                                                                                                         |                |                |                |
| Units: Units on a scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                |                |                |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 44.9           | 43.9           | 39.7           |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 4 to 98        | 7 to 111       | 2 to 89        |
| Short Form (36) Health Survey Version 2 (SF-36v2) - Mental Component                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                |                |                |
| The SF-36v2 is a multipurpose, scaled, 36-item, subject-completed validated questionnaire that measures 8 domains of health: limitations in physical activities, limitations in social activities, limitations in usual role activities, bodily pain, general mental health, limitations in usual role activities, vitality, and general health. It yields scale scores for each of the 8 health domains, and 2 summary measures of physical and mental health. Each scale range is from 0-100. A lower score means more disability and a higher score means less disability.             |                |                |                |
| Units: Units on a scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                |                |                |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 43.1           | 44.4           | 45.9           |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 21.5 to 63.8   | 12.27 to 61.03 | 19.63 to 64.81 |
| Short Form (36) Health Survey Version 2 (SF-36v2) - Physical Component                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                |                |                |
| The SF-36v2 is a multipurpose, scaled, 36-item, subject-completed validated questionnaire that measures 8 domains of health: limitations in physical activities, limitations in social activities, limitations in usual role activities, bodily pain, general mental health, limitations in usual role activities, vitality, and general health perceptions. It yields scale scores for each of the 8 health domains, and 2 summary measures of physical and mental health. Each scale range is from 0-100. A lower score means more disability and a higher score means less disability. |                |                |                |
| Units: Units on a scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                |                |                |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 45.8           | 46.1           | 46.5           |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 26.97 to 60.07 | 28.61 to 58.86 | 29.56 to 59.43 |
| Peak Nasal Inspiratory Flow (PNIF)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                |                |                |
| The PNIF is an assessment of nasal passage obstruction and was measured using an In-Check portable nasal inspiratory flow meter. To measure PNIF, a mask was placed over the nose during inspiration and inspiratory flow was recorded. Each subject inhaled 3 times and each measurement was recorded. The PNIF value used was the greatest of the 3 results at each time point.                                                                                                                                                                                                         |                |                |                |
| Units: Units on a scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                |                |                |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 119.7          | 123.4          | 107.6          |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 30 to 370      | 30 to 370      | 40 to 350      |

|                                                    |                        |  |  |
|----------------------------------------------------|------------------------|--|--|
| <b>Reporting group values</b>                      | OPN-375 400 mcg<br>FAS |  |  |
| Number of subjects                                 | 82                     |  |  |
| Age categorical                                    |                        |  |  |
| Units: Subjects                                    |                        |  |  |
| In utero                                           |                        |  |  |
| Preterm newborn infants (gestational age < 37 wks) |                        |  |  |
| Newborns (0-27 days)                               |                        |  |  |
| Infants and toddlers (28 days-23 months)           |                        |  |  |
| Children (2-11 years)                              |                        |  |  |
| Adolescents (12-17 years)                          |                        |  |  |
| Adults (18-64 years)                               |                        |  |  |
| From 65-84 years                                   |                        |  |  |
| 85 years and over                                  |                        |  |  |



|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                    |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|--|--|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                    |  |  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | ±                  |  |  |
| Gender categorical<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                    |  |  |
| Female<br>Male                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                    |  |  |
| Race/Ethnicity<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                    |  |  |
| White<br>Black / African American<br>Asian<br>Other                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                    |  |  |
| Use of ICS treatment for polyps in past 10 years<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                    |  |  |
| Participants with ICS treatment for polyps<br>Participants with no ICS treatment for polyps                                                                                                                                                                                                                                                                                                                                                                                                                                      |                    |  |  |
| Nasal congestion/obstruction score (-7 day instantaneous morning)                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                    |  |  |
| <p>Nasal symptoms were recorded in e-diary each morning for the 7 day period preceding the screening visit, evaluating symptom severity immediately preceding the time of scoring (instantaneous).<br/>Nasal Symptom Score</p> <p>0: None</p> <p>1. Mild: symptoms clearly present, but minimal awareness, and easily tolerated</p> <p>2. Moderate: definite awareness of symptoms that is bothersome but tolerable</p> <p>3. Severe: symptoms that are hard to tolerate, cause interference with activities or daily living</p> |                    |  |  |
| Units: Units on scale<br>arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 2.25<br>1.6 to 3.0 |  |  |
| Rhinorrhea Score (7-day instantaneous morning)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                    |  |  |
| <p>Nasal symptoms were recorded in e-diary each morning for the 7 day period preceding the screening visit, evaluating symptom severity immediately preceding the time of scoring (instantaneous).<br/>Nasal Symptom Score</p> <p>0: None</p> <p>1. Mild: symptoms clearly present, but minimal awareness, and easily tolerated</p> <p>2. Moderate: definite awareness of symptoms that is bothersome but tolerable</p> <p>3. Severe: symptoms that are hard to tolerate, cause interference with activities or daily living</p> |                    |  |  |
| Units: Units on a scale<br>arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 1.77<br>0.0 to 3.0 |  |  |
| Facial Pain or Pressure Score (-7 day instantaneous morning)                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                    |  |  |
| <p>Nasal symptoms were recorded in e-diary each morning for the 7 day period preceding the screening visit, evaluating symptom severity immediately preceding the time of scoring (instantaneous).<br/>Nasal Symptom Score</p> <p>0: None</p> <p>1. Mild: symptoms clearly present, but minimal awareness, and easily tolerated</p> <p>2. Moderate: definite awareness of symptoms that is bothersome but tolerable</p> <p>3. Severe: symptoms that are hard to tolerate, cause interference with activities or daily living</p> |                    |  |  |
| Units: Units on a scale<br>arithmetic mean<br>full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 1.35<br>0.0 to 3.0 |  |  |
| Hyposmia Score (-7 day instantaneous)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                    |  |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |               |  |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|--|--|
| morning)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |               |  |  |
| <p>Nasal symptoms were recorded in e-diary each morning for the 7 day period preceding the screening visit, evaluating symptom severity immediately preceding the time of scoring (instantaneous).</p> <p>Nasal Symptom Score</p> <p>0: Normal</p> <p>1: Slightly impaired</p> <p>2: Moderately impaired</p> <p>3: Absent</p>                                                                                                                                                                                                                                                                                                                                  |               |  |  |
| Units: Units on a scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |               |  |  |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 2.33          |  |  |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 0.0 to 3.0    |  |  |
| Sinonasal Outcome Test 22 (SNOT-22)<br>Total Score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |               |  |  |
| <p>SNOT-22 is a subject-completed questionnaire that consists of 22 questions. The questions on the SNOT-22 efficacy evaluation were used to calculate a total score. 22 questions are divided among 4 subscales: Rhinologic (7 questions), Ear/Facial Symptoms (4 questions), Sleep Function (3 questions), and Psychological Issues (6 questions). Each item was rated on the 5-point scale. The total score can range from 0-110, 0 being the best and 110 being the worst.</p> <p>0: No problem</p> <p>1. Very mild problem</p> <p>2. Mild or slight problem</p> <p>3. Moderate problem</p> <p>4. Severe problem</p> <p>5. Problem as bad as it can be</p> |               |  |  |
| Units: Units on a scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |               |  |  |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 47.1          |  |  |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 7 to 103      |  |  |
| Medical Outcomes Study Sleep Scale<br>Revised (MOS Sleep-R)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |               |  |  |
| <p>The MOS Sleep-R is a brief, self-administered, validated questionnaire designed to measure key aspects of sleep, such as disturbance, adequacy, somnolence, and quantity. The 12-item version with a 4-week recall was used in this study. The score range for the 12-item version is 0 to 100, lower scores indicating better sleep and higher scores indicating worse sleep. The scale yields a Sleep Problem Index and scores on the following 6 subscales: Sleep Disturbance, Snoring, Shortness of Breath or Headache, Sleep Adequacy, Sleep Somnolence, and Sleep Quantity.</p>                                                                       |               |  |  |
| Units: Units on a scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |               |  |  |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 39.1          |  |  |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 0.0 to 77.8   |  |  |
| Rhinosinusitis Disability Index (RSDI)<br>Total Score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |               |  |  |
| <p>The RSDI is a subject-completed instrument that evaluates the self-perceived impact of disease specific head and neck disorders. The RSDI has 30 items in 3 domains: Physical (11 items), Functional (9 items), and Emotional (10 items). The RSDI scale ranges from 0-120, 0 being better quality of life and less impact of CRS on daily function and 120 being worse quality of life and more impact of CRS on daily function.</p>                                                                                                                                                                                                                       |               |  |  |
| Units: Units on a scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |               |  |  |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 41.5          |  |  |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 0 to 85       |  |  |
| Short Form (36) Health Survey Version<br>2 (SF-36v2) - Mental Component                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |               |  |  |
| <p>The SF-36v2 is a multipurpose, scaled, 36-item, subject-completed validated questionnaire that measures 8 domains of health: limitations in physical activities, limitations in social activities, limitations in usual role activities, bodily pain, general mental health, limitations in usual role activities, vitality, and general health. It yields scale scores for each of the 8 health domains, and 2 summary measures of physical and mental health. Each scale range is from 0-100. A lower score means more disability and a higher score means less disability.</p>                                                                           |               |  |  |
| Units: Units on a scale                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |               |  |  |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 47.0          |  |  |
| full range (min-max)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 20.6 to 61.63 |  |  |
| Short Form (36) Health Survey Version<br>2 (SF-36v2) - Physical Component                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |               |  |  |

The SF-36v2 is a multipurpose, scaled, 36-item, subject-completed validated questionnaire that measures 8 domains of health: limitations in physical activities, limitations in social activities, limitations in usual role activities, bodily pain, general mental health, limitations in usual role activities, vitality, and general health perceptions. It yields scale scores for each of the 8 health domains, and 2 summary measures of physical and mental health. Each scale range is from 0-100. A lower score means more disability and a higher score means less disability.

|                         |                |  |  |
|-------------------------|----------------|--|--|
| Units: Units on a scale |                |  |  |
| arithmetic mean         | 46.4           |  |  |
| full range (min-max)    | 22.64 to 60.32 |  |  |

|                                    |  |  |  |
|------------------------------------|--|--|--|
| Peak Nasal Inspiratory Flow (PNIF) |  |  |  |
|------------------------------------|--|--|--|

The PNIF is an assessment of nasal passage obstruction and was measured using an In-Check portable nasal inspiratory flow meter. To measure PNIF, a mask was placed over the nose during inspiration and inspiratory flow was recorded. Each subject inhaled 3 times and each measurement was recorded. The PNIF value used was the greatest of the 3 results at each time point.

|                         |           |  |  |
|-------------------------|-----------|--|--|
| Units: Units on a scale |           |  |  |
| arithmetic mean         | 122.7     |  |  |
| full range (min-max)    | 30 to 370 |  |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                      |                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| Reporting group title                                                                                                                                                                                                                                                | EDS-Placebo     |
| Reporting group description:<br>Matched placebo BID x 16 weeks                                                                                                                                                                                                       |                 |
| Reporting group title                                                                                                                                                                                                                                                | OPN-375 100 mcg |
| Reporting group description:<br>OPN-375 100 mcg BID x 16 weeks                                                                                                                                                                                                       |                 |
| Reporting group title                                                                                                                                                                                                                                                | OPN-375 200 mcg |
| Reporting group description:<br>OPN-375 200 mcg BID x 16 weeks.                                                                                                                                                                                                      |                 |
| Reporting group title                                                                                                                                                                                                                                                | OPN-375 400 mcg |
| Reporting group description:<br>OPN-375 400 mcg BID x 16 weeks                                                                                                                                                                                                       |                 |
| Reporting group title                                                                                                                                                                                                                                                | OPN-375 400 mcg |
| Reporting group description:<br>At the Week 16 visit, subjects received 2 study drug kits. One kit was used during Weeks 17 to 20 and the other kit was used during Weeks 21 to 24. During the open-label extension phase, all subjects received OPN-375 400 µg bid. |                 |

|                                                                                                                                                                                                                                                       |                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| Subject analysis set title                                                                                                                                                                                                                            | EDS-Placebo FAS |
| Subject analysis set type                                                                                                                                                                                                                             | Full analysis   |
| Subject analysis set description:<br>Full Analysis Set included all subjects who received at least one dose of study drug, and who had baseline assessments of polyp size (nasoendoscopy) and recorded morning nasal congestion/obstruction symptoms. |                 |

|                                                                                                                                                                                                                                                       |                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Subject analysis set title                                                                                                                                                                                                                            | OPN-375 100 mcg FAS |
| Subject analysis set type                                                                                                                                                                                                                             | Full analysis       |
| Subject analysis set description:<br>Full Analysis Set included all subjects who received at least one dose of study drug, and who had baseline assessments of polyp size (nasoendoscopy) and recorded morning nasal congestion/obstruction symptoms. |                     |

|                                                                                                                                                                                                                                                       |                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Subject analysis set title                                                                                                                                                                                                                            | OPN-375 200 mcg FAS |
| Subject analysis set type                                                                                                                                                                                                                             | Full analysis       |
| Subject analysis set description:<br>Full Analysis Set included all subjects who received at least one dose of study drug, and who had baseline assessments of polyp size (nasoendoscopy) and recorded morning nasal congestion/obstruction symptoms. |                     |

|                                                                                                                                                                                                                                                       |                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Subject analysis set title                                                                                                                                                                                                                            | OPN-375 400 mcg FAS |
| Subject analysis set type                                                                                                                                                                                                                             | Full analysis       |
| Subject analysis set description:<br>Full Analysis Set included all subjects who received at least one dose of study drug, and who had baseline assessments of polyp size (nasoendoscopy) and recorded morning nasal congestion/obstruction symptoms. |                     |

### Primary: Change in 7-day Average Instantaneous Morning Diary Congestion/Obstruction Symptoms

|                                                                                                                                  |                                                                                     |
|----------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| End point title                                                                                                                  | Change in 7-day Average Instantaneous Morning Diary Congestion/Obstruction Symptoms |
| End point description:<br>Assessment was done on Full Analysis Set, that included all subjects who received at least one dose of |                                                                                     |

study drug, and who had baseline assessments of polyp size (nasoendoscopy) and recorded morning nasal congestion/obstruction symptoms.

Subjects reported nasal symptoms using the electronic diary twice daily immediately before dosing.

0: None

1. Mild, symptoms clearly present, but minimal awareness, and easily tolerated

2. Moderate, definite awareness of symptoms that is bothersome but tolerable

3. Severe, symptoms that are hard to tolerate, cause interference with activities or daily living

During the single-blind run-in phase and during the 16-week, double-blind treatment phase, an electronic diary was provided to each subject. Subjects reported both instantaneous (evaluation of symptom severity immediately preceding the time of scoring) and reflective (evaluation of symptoms severity over the previous 12 hours) scores for nasal congestion/obstruction symptoms.

|                                                      |         |
|------------------------------------------------------|---------|
| End point type                                       | Primary |
| End point timeframe:                                 |         |
| Baseline, week 4 of the double-blind treatment phase |         |

| End point values                    | EDS-Placebo     | OPN-375 100 mcg | OPN-375 200 mcg | OPN-375 400 mcg |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 79              | 80              | 80              | 82              |
| Units: Units on a scale             |                 |                 |                 |                 |
| least squares mean (standard error) | -0.24 (± 0.07)  | -0.59 (± 0.07)  | -0.68 (± 0.07)  | -0.62 (± 0.07)  |

## Statistical analyses

|                            |                                    |
|----------------------------|------------------------------------|
| Statistical analysis title | Change in instantaneous AM ADS7-IA |
|----------------------------|------------------------------------|

Statistical analysis description:

Inferential statistics were derived from a generalized linear model (GLM) model with treatment and country factors and baseline ADS7-IA score for nasal congestion/obstruction as a covariate.

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| Comparison groups                       | OPN-375 100 mcg v OPN-375 200 mcg v OPN-375 400 mcg v EDS-Placebo |
| Number of subjects included in analysis | 321                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority                                                       |
| P-value                                 | < 0.001                                                           |
| Method                                  | Generalized Linear Model                                          |
| Parameter estimate                      | Mean difference (final values)                                    |
| Confidence interval                     |                                                                   |
| level                                   | 95 %                                                              |
| sides                                   | 2-sided                                                           |
| lower limit                             | -0.56                                                             |
| upper limit                             | -0.23                                                             |
| Variability estimate                    | Standard error of the mean                                        |

## Primary: Change in Total Polyp Grade

|                 |                             |
|-----------------|-----------------------------|
| End point title | Change in Total Polyp Grade |
|-----------------|-----------------------------|

**End point description:**

Assessment was done on Full Analysis Set, that included all subjects who received at least one dose of study drug, and who had baseline assessments of polyp size (nasoendoscopy) and recorded morning nasal congestion/obstruction symptoms.

Determined by a nasal polyp grading scale score (sum of scores from both nasal cavities) measured by nasoendoscopy.

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

End point timeframe:

Baseline, Week 16 of the double-blind treatment phase

| End point values                    | EDS-Placebo     | OPN-375 100 mcg | OPN-375 200 mcg | OPN-375 400 mcg |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                  | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed         | 79              | 80              | 80              | 82              |
| Units: Units on a Scale             |                 |                 |                 |                 |
| least squares mean (standard error) | -0.61 (± 0.11)  | -1.31 (± 0.11)  | -1.22 (± 0.11)  | -1.41 (± 0.10)  |

**Statistical analyses**

|                                         |                                                                   |
|-----------------------------------------|-------------------------------------------------------------------|
| Statistical analysis title              | Change in total polyp grade                                       |
| Comparison groups                       | EDS-Placebo v OPN-375 100 mcg v OPN-375 200 mcg v OPN-375 400 mcg |
| Number of subjects included in analysis | 321                                                               |
| Analysis specification                  | Pre-specified                                                     |
| Analysis type                           | superiority <sup>[1]</sup>                                        |
| P-value                                 | < 0.001                                                           |
| Method                                  | Mixed models analysis                                             |
| Parameter estimate                      | Mean difference (final values)                                    |
| Variability estimate                    | Standard error of the mean                                        |

Notes:

[1] - Inferential statistics were derived from a mixed effect repeated measures model with visit, treatment, country, and treatment by visit interaction factors and baseline total polyp grade as covariate.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From time of Screening until completion of the end-of open-label extension visit or an early termination visit (either during double-blind or open-label phase). SAEs were reported through 30 days after last dose of study drug administration.

Adverse event reporting additional description:

Safety was assessed via typical assessment of spontaneous AE reporting on the part of the subject as well as through vital signs, protocol-defined nasal examination via nasal endoscopy by a specialist and protocol-defined ocular examination, including slit lamp exam, tonometry, and visual acuity, by an ophthalmologist.

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 17.0   |

### Reporting groups

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | SAS EDC-Placebo |
|-----------------------|-----------------|

Reporting group description:

All safety analyses were performed on the SAS, ie, those subjects in the set of subjects randomly assigned to a treatment group who received 1 or more doses of placebo or active treatment (100 µg, 200 µg, and 400 µg groups) in the double-blind treatment phase of the study. The treatment group classification in the safety analysis set is according to the treatment actually received by the subject.

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | SAS OPN-375 100 mcg |
|-----------------------|---------------------|

Reporting group description:

All safety analyses were performed on the SAS, ie, those subjects in the set of subjects randomly assigned to a treatment group who received 1 or more doses of placebo or active treatment (100 µg, 200 µg, and 400 µg groups) in the double-blind treatment phase of the study. The treatment group classification in the safety analysis set is according to the treatment actually received by the subject.

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | SAS OPN-375 200 mcg |
|-----------------------|---------------------|

Reporting group description:

All safety analyses were performed on the SAS, ie, those subjects in the set of subjects randomly assigned to a treatment group who received 1 or more doses of placebo or active treatment (100 µg, 200 µg, and 400 µg groups) in the double-blind treatment phase of the study. The treatment group classification in the safety analysis set is according to the treatment actually received by the subject.

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | SAS OPN-375 400 mcg |
|-----------------------|---------------------|

Reporting group description:

All safety analyses were performed on the SAS, ie, those subjects in the set of subjects randomly assigned to a treatment group who received 1 or more doses of placebo or active treatment (100 µg, 200 µg, and 400 µg groups) in the double-blind treatment phase of the study. The treatment group classification in the safety analysis set is according to the treatment actually received by the subject.

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | OPN-375 400 mcg (Open-label phase) |
|-----------------------|------------------------------------|

Reporting group description:

A total of 299 subjects continued in the open-label extension phase of the study during which all subjects received OPN-375 400 µg bid.

| Serious adverse events                            | SAS EDC-Placebo | SAS OPN-375 100 mcg | SAS OPN-375 200 mcg |
|---------------------------------------------------|-----------------|---------------------|---------------------|
| Total subjects affected by serious adverse events |                 |                     |                     |
| subjects affected / exposed                       | 2 / 79 (2.53%)  | 0 / 80 (0.00%)      | 0 / 80 (0.00%)      |
| number of deaths (all causes)                     | 0               | 0                   | 0                   |
| number of deaths resulting from adverse events    | 0               | 0                   | 0                   |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| Nervous system disorders                        |                |                |                |
| Vertigo positional                              |                |                |                |
| subjects affected / exposed                     | 0 / 79 (0.00%) | 0 / 80 (0.00%) | 0 / 80 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Meningitis                                      |                |                |                |
| subjects affected / exposed                     | 1 / 79 (1.27%) | 0 / 80 (0.00%) | 0 / 80 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Sinusitis                                       |                |                |                |
| subjects affected / exposed                     | 1 / 79 (1.27%) | 0 / 80 (0.00%) | 0 / 80 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

| <b>Serious adverse events</b>                     | SAS OPN-375 400 mcg | OPN-375 400 mcg (Open-label phase) |  |
|---------------------------------------------------|---------------------|------------------------------------|--|
| Total subjects affected by serious adverse events |                     |                                    |  |
| subjects affected / exposed                       | 1 / 82 (1.22%)      | 0 / 299 (0.00%)                    |  |
| number of deaths (all causes)                     | 0                   | 0                                  |  |
| number of deaths resulting from adverse events    | 0                   | 0                                  |  |
| Nervous system disorders                          |                     |                                    |  |
| Vertigo positional                                |                     |                                    |  |
| subjects affected / exposed                       | 1 / 82 (1.22%)      | 0 / 299 (0.00%)                    |  |
| occurrences causally related to treatment / all   | 0 / 1               | 0 / 0                              |  |
| deaths causally related to treatment / all        | 0 / 0               | 0 / 0                              |  |
| Infections and infestations                       |                     |                                    |  |
| Meningitis                                        |                     |                                    |  |
| subjects affected / exposed                       | 0 / 82 (0.00%)      | 0 / 299 (0.00%)                    |  |
| occurrences causally related to treatment / all   | 0 / 0               | 0 / 0                              |  |
| deaths causally related to treatment / all        | 0 / 0               | 0 / 0                              |  |
| Sinusitis                                         |                     |                                    |  |
| subjects affected / exposed                       | 0 / 82 (0.00%)      | 0 / 299 (0.00%)                    |  |
| occurrences causally related to treatment / all   | 0 / 0               | 0 / 0                              |  |
| deaths causally related to treatment / all        | 0 / 0               | 0 / 0                              |  |



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

| <b>Non-serious adverse events</b>                     | SAS EDC-Placebo  | SAS OPN-375 100 mcg | SAS OPN-375 200 mcg |
|-------------------------------------------------------|------------------|---------------------|---------------------|
| Total subjects affected by non-serious adverse events |                  |                     |                     |
| subjects affected / exposed                           | 38 / 79 (48.10%) | 39 / 80 (48.75%)    | 39 / 80 (48.75%)    |
| Investigations                                        |                  |                     |                     |
| Intraocular pressure increased                        |                  |                     |                     |
| subjects affected / exposed                           | 0 / 79 (0.00%)   | 1 / 80 (1.25%)      | 3 / 80 (3.75%)      |
| occurrences (all)                                     | 0                | 1                   | 3                   |
| Injury, poisoning and procedural complications        |                  |                     |                     |
| Arthropod bite                                        |                  |                     |                     |
| subjects affected / exposed                           | 0 / 79 (0.00%)   | 2 / 80 (2.50%)      | 1 / 80 (1.25%)      |
| occurrences (all)                                     | 0                | 2                   | 1                   |
| Nervous system disorders                              |                  |                     |                     |
| Headache                                              |                  |                     |                     |
| subjects affected / exposed                           | 3 / 79 (3.80%)   | 5 / 80 (6.25%)      | 6 / 80 (7.50%)      |
| occurrences (all)                                     | 3                | 5                   | 6                   |
| Gastrointestinal disorders                            |                  |                     |                     |
| Toothache                                             |                  |                     |                     |
| subjects affected / exposed                           | 1 / 79 (1.27%)   | 0 / 80 (0.00%)      | 0 / 80 (0.00%)      |
| occurrences (all)                                     | 1                | 0                   | 0                   |
| Respiratory, thoracic and mediastinal disorders       |                  |                     |                     |
| Asthma                                                |                  |                     |                     |
| subjects affected / exposed                           | 3 / 79 (3.80%)   | 1 / 80 (1.25%)      | 1 / 80 (1.25%)      |
| occurrences (all)                                     | 3                | 1                   | 1                   |
| Nasal congestion                                      |                  |                     |                     |
| subjects affected / exposed                           | 2 / 79 (2.53%)   | 2 / 80 (2.50%)      | 5 / 80 (6.25%)      |
| occurrences (all)                                     | 2                | 2                   | 5                   |
| Nasal dryness                                         |                  |                     |                     |
| subjects affected / exposed                           | 0 / 79 (0.00%)   | 0 / 80 (0.00%)      | 1 / 80 (1.25%)      |
| occurrences (all)                                     | 0                | 0                   | 1                   |
| Nasal mucosal disorder                                |                  |                     |                     |
| subjects affected / exposed                           | 2 / 79 (2.53%)   | 6 / 80 (7.50%)      | 8 / 80 (10.00%)     |
| occurrences (all)                                     | 2                | 6                   | 8                   |
| Nasal septum disorder                                 |                  |                     |                     |

|                                                                                                    |                                                                                                                     |                        |                        |
|----------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                                                   | 2 / 79 (2.53%)<br>2                                                                                                 | 5 / 80 (6.25%)<br>5    | 4 / 80 (5.00%)<br>4    |
| Nasal septum ulceration<br>subjects affected / exposed<br>occurrences (all)                        | 3 / 79 (3.80%)<br>3                                                                                                 | 3 / 80 (3.75%)<br>3    | 6 / 80 (7.50%)<br>6    |
| Epistaxis                                                                                          | Additional description: Identified by investigator on routine nasal endoscopy or spontaneously reported by subject. |                        |                        |
| subjects affected / exposed<br>occurrences (all)                                                   | 4 / 79 (5.06%)<br>4                                                                                                 | 14 / 80 (17.50%)<br>14 | 19 / 80 (23.75%)<br>19 |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all) | 0 / 79 (0.00%)<br>0                                                                                                 | 2 / 80 (2.50%)<br>2    | 0 / 80 (0.00%)<br>0    |
| Infections and infestations<br>Acute sinusitis<br>subjects affected / exposed<br>occurrences (all) | 2 / 79 (2.53%)<br>2                                                                                                 | 0 / 80 (0.00%)<br>0    | 1 / 80 (1.25%)<br>1    |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                                     | 2 / 79 (2.53%)<br>2                                                                                                 | 2 / 80 (2.50%)<br>2    | 2 / 80 (2.50%)<br>2    |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                                      | 2 / 79 (2.53%)<br>2                                                                                                 | 1 / 80 (1.25%)<br>1    | 2 / 80 (2.50%)<br>2    |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                                | 4 / 79 (5.06%)<br>4                                                                                                 | 2 / 80 (2.50%)<br>2    | 1 / 80 (1.25%)<br>1    |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 79 (0.00%)<br>0                                                                                                 | 2 / 80 (2.50%)<br>2    | 1 / 80 (1.25%)<br>1    |
| URTI<br>subjects affected / exposed<br>occurrences (all)                                           | 10 / 79 (12.66%)<br>10                                                                                              | 4 / 80 (5.00%)<br>4    | 6 / 80 (7.50%)<br>6    |

|                                                                                      |                     |                                    |  |
|--------------------------------------------------------------------------------------|---------------------|------------------------------------|--|
| <b>Non-serious adverse events</b>                                                    | SAS OPN-375 400 mcg | OPN-375 400 mcg (Open-label phase) |  |
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed | 46 / 82 (56.10%)    | 60 / 299 (20.07%)                  |  |
| Investigations                                                                       |                     |                                    |  |

|                                                                                                                      |                                                                                                                     |                      |  |
|----------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|----------------------|--|
| Intraocular pressure increased<br>subjects affected / exposed<br>occurrences (all)                                   | 1 / 82 (1.22%)<br>1                                                                                                 | 4 / 299 (1.34%)<br>4 |  |
| Injury, poisoning and procedural complications<br>Arthropod bite<br>subjects affected / exposed<br>occurrences (all) | 0 / 82 (0.00%)<br>0                                                                                                 | 0 / 299 (0.00%)<br>0 |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)                             | 6 / 82 (7.32%)<br>6                                                                                                 | 1 / 299 (0.33%)<br>1 |  |
| Gastrointestinal disorders<br>Toothache<br>subjects affected / exposed<br>occurrences (all)                          | 2 / 82 (2.44%)<br>2                                                                                                 | 0 / 299 (0.00%)<br>0 |  |
| Respiratory, thoracic and mediastinal disorders<br>Asthma<br>subjects affected / exposed<br>occurrences (all)        | 1 / 82 (1.22%)<br>1                                                                                                 | 0 / 299 (0.00%)<br>0 |  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)                                                 | 3 / 82 (3.66%)<br>3                                                                                                 | 2 / 299 (0.67%)<br>2 |  |
| Nasal dryness<br>subjects affected / exposed<br>occurrences (all)                                                    | 3 / 82 (3.66%)<br>3                                                                                                 | 1 / 299 (0.33%)<br>1 |  |
| Nasal mucosal disorder<br>subjects affected / exposed<br>occurrences (all)                                           | 5 / 82 (6.10%)<br>5                                                                                                 | 6 / 299 (2.01%)<br>6 |  |
| Nasal septum disorder<br>subjects affected / exposed<br>occurrences (all)                                            | 4 / 82 (4.88%)<br>4                                                                                                 | 4 / 299 (1.34%)<br>4 |  |
| Nasal septum ulceration<br>subjects affected / exposed<br>occurrences (all)                                          | 8 / 82 (9.76%)<br>8                                                                                                 | 9 / 299 (3.01%)<br>9 |  |
| Epistaxis                                                                                                            | Additional description: Identified by investigator on routine nasal endoscopy or spontaneously reported by subject. |                      |  |

|                                                                                                    |                        |                        |  |
|----------------------------------------------------------------------------------------------------|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                   | 18 / 82 (21.95%)<br>18 | 26 / 299 (8.70%)<br>26 |  |
| Skin and subcutaneous tissue disorders<br>Rash<br>subjects affected / exposed<br>occurrences (all) | 0 / 82 (0.00%)<br>0    | 0 / 299 (0.00%)<br>0   |  |
| Infections and infestations<br>Acute sinusitis<br>subjects affected / exposed<br>occurrences (all) | 0 / 82 (0.00%)<br>0    | 3 / 299 (1.00%)<br>3   |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 82 (1.22%)<br>1    | 3 / 299 (1.00%)<br>3   |  |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                                      | 2 / 82 (2.44%)<br>2    | 0 / 299 (0.00%)<br>0   |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                                | 8 / 82 (9.76%)<br>8    | 3 / 299 (1.00%)<br>3   |  |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)                                    | 2 / 82 (2.44%)<br>2    | 0 / 299 (0.00%)<br>0   |  |
| URTI<br>subjects affected / exposed<br>occurrences (all)                                           | 4 / 82 (4.88%)<br>4    | 3 / 299 (1.00%)<br>3   |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                    |
|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 07 January 2013  | The amendment included clarification for the scheduled study procedures and evaluations, in addition to clarification for the efficacy assessments for polyp grading.                                        |
| 07 March 2013    | The amendment included changes to the nasoendoscopy procedures to reduce burden for the subject. Additional guidance was also added to scheduled study procedures and evaluations, and efficacy assessments. |
| 18 December 2013 | The amendment included additional clarification to the scheduled study procedures including the addition of the ophthalmology worksheet and change to the stratification.                                    |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported