# 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 | 2011-004886-34 |
| Trial protocol | CZ GB |
| Global end of trial date | 01 October 2015 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 10 March 2022 |
| First version publication date | 10 March 2022 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | OPN-FLU-NP-3101 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01622569 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | OptiNose US, Inc |
| Sponsor organisation address | 1010 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 | 29 April 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 October 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 October 2015 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to compare the efficacy of intranasal administration of 100, 200, and 400 µg of OPN-375 twice a day (bid) delivered by the OptiNose device 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.

Explanatory note about age range: age ranges for data collection in this study were 18-65 years and >/= 65 years. There were no patients in the age range of >/= 65 years.

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:

- Acetaminophen and NSAIDs were permitted for analgesia; aspirin was permitted for cardiovascular prophylaxis. Aspirin and NSAIDs were not allowed for subjects with a documented sensitivity to these medications.
- Antibiotic medications were permitted (except for those prohibited below) 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.

In subjects with comorbid asthma or COPD at study entry (ie, Visit 1 [screening]), 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 (screening) 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, nonsedating 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

| | |
|---|---|
| Evidence for comparator: - | |
| Actual start date of recruitment | 19 November 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 | Canada: 18 |
| Country: Number of subjects enrolled | Ukraine: 65 |
| Country: Number of subjects enrolled | United States: 143 |
| Country: Number of subjects enrolled | South Africa: 30 |
| Country: Number of subjects enrolled | United Kingdom: 11 |
| Country: Number of subjects enrolled | Czech Republic: 56 |
| Worldwide total number of subjects | 323 |
| EEA total number of subjects | 67 |

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) | 323 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

A total of 539 subjects were screened, 456 subjects entered the single-blind run-in phase, and a total of 323 subjects were subsequently enrolled and randomized (ITT Population) at 54 study centers in the double-blind phase.

### Pre-assignment

Screening details:

Assessments included nasoendoscopy-related procedures (nasal examination, nasoendoscopy, and surgical intervention assessment), 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 | 456[1] |
| Number of subjects completed | 323 |

### Pre-assignment subject non-completion reasons

| | |
|---|---|
| Reason: Number of subjects | Physician decision: 133 |

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: The 456 subjects who entered the pretreatment phase administered morning and evening doses of placebo and completed a daily e-diary immediately prior to morning and evening doses. 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 were recorded. At the end of the pretreatment phase only eligible subjects entered into the double-blind treatment phase.

### Period 1

| | |
|---|---|
| Period 1 title | Double-blind Treatment Phase (Wks 1-16) |
| 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, study 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. The randomization codes were maintained within the IVRS/IWRS, which allowed the investigator to break the blind for an individual subject, if needed.

### Arms

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

Arm description:

Matching placebo BID x 16 weeks

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

Dosage and administration details:

At Visit 2, Day 1 (baseline), subjects received 2 study drug kits. At subsequent visits every 4 weeks through Week 12, subjects received a single study drug kit. Each study drug kit consisted of 2 OPN-375 drug delivery units, 1 marked "1" and another marked "2." Both contained placebo.
For the morning and evening doses, subjects administered a single spray from the device marked 1 to both the right and left nostrils followed by a single spray from the device marked 2 to both the right and left nostrils. Subjects in the placebo group received 2 sprays containing placebo.

| **Arm title** | OPN-375 100 µg |
|---|---|

Arm description:

OPN-375 100 µg BID x 16 weeks,

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

Dosage and administration details:

At Visit 2, Day 1 (baseline), subjects received 2 study drug kits. At subsequent visits every 4 weeks through Week 12, subjects received a single study drug kit. Each study drug kit consisted of 2 OPN-375 drug delivery units, 1 marked "1" and another marked "2." Subjects in the 100 µg group received 2 units that dispensed 25 µg fluticasone propionate per actuation.
For the morning and evening doses, subjects administered a single spray from the device marked 1 to both the right and left nostrils followed by a single spray from the device marked 2 to both the right and left nostrils. In this way, subjects in all groups received an equal number of sprays: subjects in the 100 µg group received 4 sprays of 25 µg each

| **Arm title** | OPN-375 200 µg |
|---|---|

Arm description:

OPN-375 200 µg BID x 16 weeks

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

Dosage and administration details:

At Visit 2, Day 1 (baseline), subjects received 2 study drug kits. At subsequent visits every 4 weeks through Week 12, subjects received a single study drug kit. Each study drug kit consisted of 2 OPN-375 drug delivery units, 1 marked "1" and another marked "2."Subjects in the 200 µg group received 1 unit that dispensed placebo and 1 unit that dispensed 100 µg fluticasone propionate per actuation.
For the morning and evening doses, subjects administered a single spray from the device marked 1 to both the right and left nostrils followed by a single spray from the device marked 2 to both the right and left nostrils. In this way, subjects in all groups received an equal number of sprays: subjects in the 200 µg group received 2 sprays containing placebo and 2 sprays containing 100 µg each.

| **Arm title** | OPN-375 400 µg |
|---|---|

Arm description:

OPN-375 400 µg BID x 16 weeks

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

Dosage and administration details:

At Visit 2, Day 1 (baseline), subjects received 2 study drug kits. At subsequent visits every 4 weeks through Week 12, subjects received a single study drug kit. Each study drug kit consisted of 2 OPN-375

drug delivery units, 1 marked "1" and another marked "2." Subjects in the 400 µg group received 2 units, each dispensing 100 µg fluticasone propionate per actuation.
For the morning and evening doses, subjects administered a single spray from the device marked 1 to both the right and left nostrils followed by a single spray from the device marked 2 to both the right and left nostrils. In this way, subjects in all groups received an equal number of sprays: subjects in the 400 µg group received 4 sprays of 100µg each

| **Number of subjects in period 1** | Placebo | OPN-375 100 µg | OPN-375 200 µg |
|---|---|---|---|
| Started | 82 | 81 | 80 |
| Completed | 70 | 75 | 71 |
| Not completed | 12 | 6 | 9 |
| Consent withdrawn by subject | 2 | 2 | 2 |
| Adverse event, non-fatal | 4 | 2 | 3 |
| Lost to follow-up | - | - | 1 |
| Lack of efficacy | 6 | - | 3 |
| Protocol deviation | - | 2 | - |

| **Number of subjects in period 1** | OPN-375 400 µg |
|---|---|
| Started | 80 |
| Completed | 76 |
| Not completed | 4 |
| Consent withdrawn by subject | - |
| Adverse event, non-fatal | 1 |
| Lost to follow-up | - |
| Lack of efficacy | 2 |
| Protocol deviation | 1 |

## Period 2

| | |
|---|---|
| Period 2 title | Open-Label Extension Phase (Wks 17-24) |
| 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 with 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 µg - open label |
|---|---|

Arm description:

OPN-375 400 µg (open-label) BID x 8 weeks

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

Dosage and administration details:

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.

| **Number of subjects in period 2[2]** | OPN-375 400 µg - open label |
|---|---|
| Started | 282 |
| Completed | 274 |
| Not completed | 8 |
| Consent withdrawn by subject | 1 |
| Adverse event, non-fatal | 3 |
| Lack of efficacy | 4 |

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: 31 patients did not complete the previous double-blind treatment period for the following reasons:
lack of efficacy (11), subject withdrawal (6), adverse events (10), protocol deviations (3), lost to follow-up (1)

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: | |
| Matching placebo BID x 16 weeks | |
| Reporting group title | OPN-375 100 µg |
| Reporting group description: | |
| OPN-375 100 µg BID x 16 weeks, | |
| Reporting group title | OPN-375 200 µg |
| Reporting group description: | |
| OPN-375 200 µg BID x 16 weeks | |
| Reporting group title | OPN-375 400 µg |
| Reporting group description: | |
| OPN-375 400 µg BID x 16 weeks | |

| Reporting group values | Placebo | OPN-375 100 µg | OPN-375 200 µg |
|---|---|---|---|
| Number of subjects | 82 | 81 | 80 |
| Age categorical | | | |
| Age ranges for data collection in this study were 18-65 years and >/= 65 years. There were no patients in the age range of >/= 65 years. | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Adults (18 - 65 years) | 82 | 81 | 80 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 45.3 | 44.9 | 46.4 |
| standard deviation | ± 13.0 | ± 12.7 | ± 12.7 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 46 | 41 | 32 |
| Male | 36 | 40 | 48 |
| Race / Ethnicity | | | |
| Units: Subjects | | | |
| White | 68 | 74 | 72 |
| Black/African American | 8 | 3 | 6 |
| Asian | 5 | 2 | 2 |
| Other | 1 | 2 | 0 |
| Use of intranasal corticosteroid (ICS) treatment for polyps in past 10 years | | | |

| | | | |
|---|---|---|---|
| Units: Subjects | | | |
| Yes | 77 | 77 | 76 |
| No | 5 | 4 | 4 |
| Previous sinus surgery for polyp removal or sinus surgery | | | |
| Patients may have had both sinus surgery and polypectomy. | | | |
| Units: Subjects | | | |
| Yes | 33 | 34 | 27 |
| No | 49 | 47 | 53 |
| Previous polyp removal surgery via polypectomy only | | | |
| Patients may have had both sinus surgery and polypectomy. | | | |
| Units: Subjects | | | |
| Yes | 33 | 27 | 33 |
| No | 49 | 54 | 47 |

| **Reporting group values** | OPN-375 400 µg | Total | |
|---|---|---|---|
| Number of subjects | 80 | 323 | |
| Age categorical | | | |
| Age ranges for data collection in this study were 18-65 years and >/= 65 years. There were no patients in the age range of >/= 65 years. | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Adults (18 - 65 years) | 80 | 323 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 43.9 | | |
| standard deviation | ± 12.6 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 42 | 161 | |
| Male | 38 | 162 | |
| Race / Ethnicity | | | |
| Units: Subjects | | | |
| White | 69 | 283 | |
| Black/African American | 9 | 26 | |
| Asian | 0 | 9 | |
| Other | 2 | 5 | |
| Use of intranasal corticosteroid (ICS) treatment for polyps in past 10 years | | | |
| Units: Subjects | | | |
| Yes | 75 | 305 | |
| No | 5 | 18 | |

| | | | |
|---|---|---|---|
| Previous sinus surgery for polyp removal or sinus surgery | | | |
| Patients may have had both sinus surgery and polypectomy. | | | |
| Units: Subjects | | | |
| Yes | 30 | 124 | |
| No | 50 | 199 | |
| Previous polyp removal surgery via polypectomy only | | | |
| Patients may have had both sinus surgery and polypectomy. | | | |
| Units: Subjects | | | |
| Yes | 27 | 120 | |
| No | 53 | 203 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: Matching placebo BID x 16 weeks | |
| Reporting group title | OPN-375 100 µg |
| Reporting group description: OPN-375 100 µg BID x 16 weeks, | |
| Reporting group title | OPN-375 200 µg |
| Reporting group description: OPN-375 200 µg BID x 16 weeks | |
| Reporting group title | OPN-375 400 µg |
| Reporting group description: OPN-375 400 µg BID x 16 weeks | |
| Reporting group title | OPN-375 400 µg - open label |
| Reporting group description: OPN-375 400 µg (open-label) BID x 8 weeks | |

### 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:

The Full Analysis Set was used for all efficacy analyses unless otherwise specified.
Subjects reported nasal symptoms using the e-diary 2x/day 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
The change from baseline in instantaneous morning diary symptom scores averaged over 7 days prior to the Week 4 Visit of t

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

End point timeframe:

Baseline, Week 4 of the double-blind treatment phase

| End point values | Placebo | OPN-375 100 µg | OPN-375 200 µg | OPN-375 400 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 82 | 81 | 80 | 79 |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| Units on a scale | -0.24 (± 0.074) | -0.49 (± 0.076) | -0.54 (± 0.075) | -0.62 (± 0.075) |

## Statistical analyses

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

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Placebo v OPN-375 100 µg v OPN-375 200 µg v OPN-375 400 µg |
| Number of subjects included in analysis | 322 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [1] |
| Method | ANCOVA |
| Parameter estimate | Generalized linear model |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.46 |
| upper limit | -0.16 |
| Variability estimate | Standard error of the mean |

Notes:

[1] - P value all 3 experimental arms versus placebo

## Primary: Change in Total Polyp Grade

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

End point description:

The Full Analysis Set was used for all efficacy analyses unless otherwise specified.
Polyp grading of each nasal cavity was determined by a nasal polyp grading scale score measured by nasoendoscopy. A summary of the changes from baseline to Week 16 in total polyp grade.
0: No polyps
1: Mild polyposis: polyps not reaching below the inferior border of the middle turbinate
2: Moderate polyposis: polyps reaching below the inferior border of the middle concha, but not the inferior border of the inferior turbinate
3: Severe polyposis large polyps reaching below the lower inferior border of the inferior turbinate
Reduction in total polyp grade (sum of scores from both nasal cavities) at Week 16 of double-blind treatment phase; Included patients with nasal polyps at baseline

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

End point timeframe:

Baseline, Week 16 of the double-blind treatment phase

| End point values | Placebo | OPN-375 100 µg | OPN-375 200 µg | OPN-375 400 µg |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 82 | 81 | 80 | 79 |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | | | | |
| Units on a scale | -0.45 (± 0.135) | -0.96 (± 0.139) | -1.03 (± 0.138) | -1.06 (± 0.137) |

## Statistical analyses

| **Statistical analysis title** | Change in total polyp grade |
|---|---|

Statistical analysis description:

The change from baseline to the Week 16 assessment was analyzed using a mixed effect model for repeated measures (MMRM). The data included for each subject, the changes in bilateral polyp score from baseline to each subsequent assessment with nasoendoscopy. The MMRM model included a covariate (baseline bilateral polyp score) and the following fixed effects: treatment (400 µg, 200 µg, 100 µg, and placebo), country (6 levels), visit (4 level) and the interaction of treatment-by-visit.

| | |
|---|---|
| Comparison groups | Placebo v OPN-375 100 µg v OPN-375 200 µg v OPN-375 400 µg |
| Number of subjects included in analysis | 322 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [2] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |

Notes:

[2] - P value of 3 experimental arms versus placebo

## 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 | Placebo |
| Reporting group description: | |
| Matching placebo BID x 16 weeks | |
| Reporting group title | 100 µg OPN-375 |
| Reporting group description: | |
| OPN-375 100 µg BID x 16 weeks, | |
| Reporting group title | 200 µg OPN-375 |
| Reporting group description: | |
| OPN-375 200 µg BID x 16 weeks | |
| Reporting group title | 400 µg OPN-375 |
| Reporting group description: | |
| OPN-375 400 µg BID x 16 weeks | |
| Reporting group title | OPN-375 400 µg (Open-label) |
| Reporting group description: - | |

| Serious adverse events | Placebo | 100 µg OPN-375 | 200 µg OPN-375 |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 81 (1.23%) | 0 / 80 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Menorrhagia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 81 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Nasal Polyps | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 1 / 81 (1.23%) | 0 / 80 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 81 (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 |

| **Serious adverse events** | 400 µg OPN-375 | OPN-375 400 µg (Open-label) | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 2 / 282 (0.71%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Reproductive system and breast disorders | | | |
| Menorrhagia | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 282 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasal Polyps | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 282 (0.35%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Placebo | 100 µg OPN-375 | 200 µg OPN-375 |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 42 / 82 (51.22%) | 40 / 81 (49.38%) | 45 / 80 (56.25%) |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 81 (0.00%) | 2 / 80 (2.50%) |
| occurrences (all) | 0 | 0 | 2 |
| Intraocular pressure increased | | | |
| subjects affected / exposed | 2 / 82 (2.44%) | 1 / 81 (1.23%) | 0 / 80 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 82 (2.44%) | 2 / 81 (2.47%) | 2 / 80 (2.50%) |
| occurrences (all) | 2 | 2 | 2 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 2 / 81 (2.47%) | 0 / 80 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Eye disorders | | | |
| Cataract nuclear | | | |
| subjects affected / exposed | 2 / 82 (2.44%) | 1 / 81 (1.23%) | 0 / 80 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 82 (0.00%) | 0 / 81 (0.00%) | 0 / 80 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 82 (2.44%) | 0 / 81 (0.00%) | 0 / 80 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | Additional description: Spontaneously reported by Subject or found on Nasoendoscopy | | |
| subjects affected / exposed | 6 / 82 (7.32%) | 11 / 81 (13.58%) | 16 / 80 (20.00%) |
| occurrences (all) | 6 | 11 | 16 |
| Nasal mucosal disorder | | | |
| subjects affected / exposed | 5 / 82 (6.10%) | 11 / 81 (13.58%) | 6 / 80 (7.50%) |
| occurrences (all) | 5 | 11 | 6 |
| Nasal septal ulceration | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 82 (1.22%) | 5 / 81 (6.17%) | 5 / 80 (6.25%) |
| occurrences (all) | 1 | 5 | 5 |
| Nasal congestion | | | |
| subjects affected / exposed | 4 / 82 (4.88%) | 3 / 81 (3.70%) | 2 / 80 (2.50%) |
| occurrences (all) | 4 | 3 | 2 |
| Nasal septum disorder | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 3 / 81 (3.70%) | 2 / 80 (2.50%) |
| occurrences (all) | 1 | 3 | 2 |
| Asthma | | | |
| subjects affected / exposed | 5 / 82 (6.10%) | 0 / 81 (0.00%) | 1 / 80 (1.25%) |
| occurrences (all) | 5 | 0 | 1 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 2 / 82 (2.44%) | 0 / 81 (0.00%) | 2 / 80 (2.50%) |
| occurrences (all) | 2 | 0 | 2 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 3 / 82 (3.66%) | 0 / 81 (0.00%) | 0 / 80 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Infections and infestations | | | |
| Acute sinusitis | | | |
| subjects affected / exposed | 4 / 82 (4.88%) | 5 / 81 (6.17%) | 6 / 80 (7.50%) |
| occurrences (all) | 4 | 5 | 6 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 7 / 82 (8.54%) | 1 / 81 (1.23%) | 4 / 80 (5.00%) |
| occurrences (all) | 7 | 1 | 4 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 4 / 82 (4.88%) | 3 / 81 (3.70%) | 2 / 80 (2.50%) |
| occurrences (all) | 4 | 3 | 2 |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 82 (2.44%) | 2 / 81 (2.47%) | 2 / 80 (2.50%) |
| occurrences (all) | 2 | 2 | 2 |
| Influenza | | | |
| subjects affected / exposed | 3 / 82 (3.66%) | 2 / 81 (2.47%) | 2 / 80 (2.50%) |
| occurrences (all) | 3 | 2 | 2 |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 82 (2.44%) | 0 / 81 (0.00%) | 1 / 80 (1.25%) |
| occurrences (all) | 2 | 0 | 1 |

| | | | |
|---|---|---|---|
| Otitis media | | | |
| subjects affected / exposed | 1 / 82 (1.22%) | 2 / 81 (2.47%) | 0 / 80 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 82 (2.44%) | 0 / 81 (0.00%) | 0 / 80 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |

| **Non-serious adverse events** | 400 µg OPN-375 | OPN-375 400 µg (Open-label) | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 50 / 79 (63.29%) | 38 / 282 (13.48%) | |
| Investigations | | | |
| Weight increased | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 282 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Intraocular pressure increased | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 282 (0.35%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 2 / 282 (0.71%) | |
| occurrences (all) | 0 | 2 | |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 282 (0.35%) | |
| occurrences (all) | 0 | 1 | |
| Eye disorders | | | |
| Cataract nuclear | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 282 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 282 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 282 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Epistaxis | Additional description: Spontaneously reported by Subject or found on Nasoendoscopy | | |
| subjects affected / exposed | 19 / 79 (24.05%) | 16 / 282 (5.67%) | |
| occurrences (all) | 19 | 16 | |
| Nasal mucosal disorder | | | |
| subjects affected / exposed | 6 / 79 (7.59%) | 1 / 282 (0.35%) | |
| occurrences (all) | 6 | 1 | |
| Nasal septal ulceration | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 5 / 282 (1.77%) | |
| occurrences (all) | 4 | 5 | |
| Nasal congestion | | | |
| subjects affected / exposed | 6 / 79 (7.59%) | 1 / 282 (0.35%) | |
| occurrences (all) | 6 | 1 | |
| Nasal septum disorder | | | |
| subjects affected / exposed | 3 / 79 (3.80%) | 1 / 282 (0.35%) | |
| occurrences (all) | 3 | 1 | |
| Asthma | | | |
| subjects affected / exposed | 3 / 79 (3.80%) | 1 / 282 (0.35%) | |
| occurrences (all) | 3 | 1 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 282 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 282 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Infections and infestations | | | |
| Acute sinusitis | | | |
| subjects affected / exposed | 8 / 79 (10.13%) | 3 / 282 (1.06%) | |
| occurrences (all) | 8 | 3 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 2 / 282 (0.71%) | |
| occurrences (all) | 5 | 2 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 3 / 282 (1.06%) | |
| occurrences (all) | 4 | 3 | |
| Bronchitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 79 (3.80%) | 0 / 282 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Influenza | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 282 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 3 / 79 (3.80%) | 0 / 282 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Otitis media | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 1 / 282 (0.35%) | |
| occurrences (all) | 1 | 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 0 / 282 (0.00%) | |
| occurrences (all) | 0 | 0 | |

## 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:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported