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, Vice President Global Clinical Operations & Outsourcing, OptiNose US, Inc, +1 267 364-3500, 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