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, Vice President Global Clinical Operations & Outsourcing, OptiNose US, Inc, +1 267 364-3500, jennifer.carothers@optinose.com
Scientific contact	Jennifer Carothers, Vice President Global Clinical Operations & Outsourcing, OptiNose US, Inc, +1 267 364-3500, jennifer.carothers@optinose.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	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, 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 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[1]
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

Arm title	OPN-375 100 mcg
Arm description:	
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:	
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	
Arm title	OPN-375 200 mcg
Arm description:	
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:	
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	
Arm title	OPN-375 400 mcg
Arm description:	
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:	
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	

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

Number of subjects in period 2[2]	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

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:	
Matched placebo BID x 16 weeks	

Reporting group title	OPN-375 100 mcg
Reporting group description:	
OPN-375 100 mcg BID x 16 weeks	
Reporting group title	OPN-375 200 mcg
Reporting group description:	
OPN-375 200 mcg BID x 16 weeks.	
Reporting group title	OPN-375 400 mcg
Reporting group description:	
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 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)	73	74	74
From 65-84 years	7	7	6
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	46.7	46.7	44.8
standard deviation	± 11.95	± 13.72	± 12.87
Gender categorical Units: Subjects			
Female	38	39	34
Male	42	42	46
Race/Ethnicity 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 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)			
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). Nasal Symptom Score 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			
Units: Units on scale arithmetic mean full range (min-max)			
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). Nasal Symptom Score 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			
Units: Units on a scale arithmetic mean full range (min-max)			
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). Nasal Symptom Score 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			
Units: Units on a scale arithmetic mean full range (min-max)			
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). Nasal Symptom Score 0: Normal 1: Slightly impaired 2: Moderately impaired 3: Absent			
Units: Units ona scale arithmetic mean full range (min-max)			
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. 0: No problem 1. Very mild problem			

2. Mild or slight problem 3. Moderate problem 4. Severe problem 5. Problem as bad as it can be			
Units: Units on a scale arithmetic mean 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 arithmetic mean 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 arithmetic mean 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 arithmetic mean 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 arithmetic mean 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 arithmetic mean full range (min-max)			

Reporting group values	OPN-375 400 mcg	Total	

Number of subjects	82	323	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	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 10 years Units: Subjects			
Participants with ICS treatment for polyps	70	280	
Participants with no ICS treatment for polyps	12	43	
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). Nasal Symptom Score 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			
Units: Units on scale			
arithmetic mean			
full range (min-max)		-	
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). Nasal Symptom Score 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			
Units: Units on a scale			

arithmetic mean full range (min-max)		- 	
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). Nasal Symptom Score 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			
Units: Units on a scale arithmetic mean full range (min-max)		- 	
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). Nasal Symptom Score 0: Normal 1: Slightly impaired 2: Moderately impaired 3: Absent			
Units: Units ona scale arithmetic mean full range (min-max)		- 	
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. 0: No problem 1. Very mild problem 2. Mild or slight problem 3. Moderate problem 4. Severe problem 5. Problem as bad as it can be			
Units: Units on a scale arithmetic mean 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 arithmetic mean 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 arithmetic mean 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 arithmetic mean 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 arithmetic mean 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 arithmetic mean full range (min-max)		-	

Subject analysis sets

Subject analysis set title	EDS-Placebo 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 (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:

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:

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:

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.

Reporting group values	EDS-Placebo FAS	OPN-375 100 mcg FAS	OPN-375 200 mcg FAS
Number of subjects	79	80	80
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 Units: years arithmetic mean standard deviation	±	±	±
Gender categorical Units: Subjects			
Female Male			
Race/Ethnicity Units: Subjects			
White Black / African American Asian Other			
Use of ICS treatment for polyps in past 10 years Units: Subjects			
Participants with ICS treatment for polyps 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). Nasal Symptom Score 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			
Units: Units on scale arithmetic mean full range (min-max)	2.29 1.6 to 3.0	2.23 1.6 to 3.0	2.20 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). Nasal Symptom Score 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			
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). Nasal Symptom Score 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			
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). Nasal Symptom Score 0: Normal 1: Slightly impaired 2: Moderately impaired 3: Absent			
Units: Units ona 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. 0: No problem 1. Very mild problem 2. Mild or slight problem 3. Moderate problem 4. Severe problem 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) 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

Reporting group values	OPN-375 400 mcg 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 Units: years arithmetic mean standard deviation	 ±		
Gender categorical Units: Subjects			
Female Male			
Race/Ethnicity Units: Subjects			
White Black / African American Asian Other			
Use of ICS treatment for polyps in past 10 years Units: Subjects			
Participants with ICS treatment for polyps 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). Nasal Symptom Score 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			
Units: Units on scale arithmetic mean full range (min-max)	 2.25 1.6 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). Nasal Symptom Score 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			
Units: Units on a scale arithmetic mean full range (min-max)	 1.77 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). Nasal Symptom Score 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			
Units: Units on a scale arithmetic mean full range (min-max)	 1.35 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). Nasal Symptom Score 0: Normal 1: Slightly impaired 2: Moderately impaired 3: Absent			
Units: Units ona scale arithmetic mean full range (min-max)	 2.33 0.0 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. 0: No problem 1. Very mild problem 2. Mild or slight problem 3. Moderate problem 4. Severe problem 5. Problem as bad as it can be			
Units: Units on a scale arithmetic mean full range (min-max)	 47.1 7 to 103		
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 full range (min-max)	 39.1 0.0 to 77.8		
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 arithmetic mean full range (min-max)	 41.5 0 to 85		
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 full range (min-max)	 47.0 20.6 to 61.63		
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	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:

Matched placebo BID x 16 weeks

Reporting group title	OPN-375 100 mcg

Reporting group description:

OPN-375 100 mcg BID x 16 weeks

Reporting group title	OPN-375 200 mcg

Reporting group description:

OPN-375 200 mcg BID x 16 weeks.

Reporting group title	OPN-375 400 mcg

Reporting group description:

OPN-375 400 mcg BID x 16 weeks

Reporting group title	OPN-375 400 mcg

Reporting group 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.

Subject analysis set title	EDS-Placebo 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 (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:

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:

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:

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:

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[1]
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

Serious adverse events	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 %

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

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

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

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported