Study Title	A Double-blind, Placebo-controlled, Randomised Study to Evaluate the Safety and Reduction of Ear Pain in Adults with Acute Otitis Media
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Protocol Number:	OP0201-C-004
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Sponsor:	Novus Therapeutics 19900 MacArthur Blvd, Suite 550 Irvine, CA 92612 (949) 238-8090

-CONFIDENTIAL-

SIGNATURE PAGE

Protocol Title: A Double-blind, Placebo-controlled, Randomised Study to Evaluate the Safety and Reduction of Ear Pain in Adults with Acute Otitis Media

The undersigned have reviewed the format and content of this protocol and have approved the clinical study protocol.

Any modifications of the clinical study protocol must be agreed upon by the sponsor and the investigator and must be documented in writing.

Sponsor Approval:

Signature: [redacted] Date: [redacted]

Name (print): [redacted]

Title: [redacted]

Investigator Agreement:

I have read the clinical study protocol and agree to conduct the study as outlined herein.

Signature: _____ Date:

Name (print): _____

SYNOPSIS

Protocol Title:	A Double-blind, Placebo-controlled, Randomised Study to Evaluate the Safety and Reduction of Ear Pain in Adults with Acute Otitis Media
Protocol Number:	OP0201-C-004
Investigators/Study Centres:	This is a multicentre study. Worldwide Clinical Trials, a contract research organisation, will oversee operational aspects of this study on behalf of Novus Therapeutics, the sponsor of the study.
Phase of Development:	Phase 1
Rationale	Acute otitis media (AOM) is usually a short-term inflammation of the middle ear (ME), characterised by the rapid onset of 1 or more signs or symptoms of acute ear infection such as earache, tugging at the ear, fever, or irritability in the presence of a middle ear effusion (MEE) (as evidenced by bulging tympanic membrane [TM]). AOM results from a dysfunctional eustachian tube (ET). Recurrent or persistent AOM may lead to rupture of the TM and/or significant damage to the auditory ossicles resulting in permanent hearing loss. OP0201 is formulated with 2 active ingredients (dipalmitoylphosphatidylcholine [DPPC] + cholesteryl palmitate [CP]) that are known endogenous surfactant components in human nasal passages and ET. OP0201 acts locally to reduce the surface tension at the ET, which in turn allows the ET to open in a normal way and drain the ME. OP0201 is intended to treat and prevent AOM. This study will evaluate the safety and immediate (within 60 minutes [min]) reduction of ear pain caused by AOM in adults following a single intranasal dose of OP0201 20 mg.
Objectives:	The objectives of this study are as follows: Primary Objective: • To assess the safety of intranasal OP0201 20 mg compared to placebo

	Exploratory Objectives: • To assess the effect of intranasal OP0201 20 mg compared to placebo on ear pain scores using the Visual Analog Scale (VAS) • To assess the effect of intranasal OP0201 20 mg compared to placebo on ear pain scores using the Numeric Rating Scale (NRS-11) • To assess impression of global change in symptoms as measured by Patient Global Impression of Change (PGIC) • To assess impression of global change in symptoms as measured by Clinical Global Impressions Scale: Global Improvement (CGI-I) • To assess the effect of intranasal OP0201 20 mg compared to placebo on AOM symptoms • To assess the blinding efforts as measured by the Blinding Index (BI) • To evaluate subject experience with the device as measured by the Device Experience Questionnaire-Subject • To evaluate study staff experience with the device as measured by the Device Experience Questionnaire-Study Staff Administering the Treatment
Study Design:	This will be a single-dose, double-blind, placebo-controlled, randomised, parallel-group, proof-of-concept study to evaluate the safety and immediate (within 60 min) reduction of ear pain caused by AOM in adults following a single dose of intranasal OP0201 20 mg or placebo. All study-related procedures, including screening, will be performed on Day 1. Following Screening, but before any treatment-related procedures, eligible subjects will be randomly assigned to 1 of the following groups: • Single intranasal dose of OP0201 20 mg (4 sprays per nostril for a total of 8 sprays) • Single intranasal dose of placebo (4 sprays per nostril for a total of 8 sprays) Ear pain will be assessed in the left and the right ear separately at predose and at 10, 20, 30, and 60 min post dose using the VAS and the NRS-11. Global impression of change in symptoms will be rated by the subject at 10, 20, 30, and 60 min post dose using the PGIC. The physician investigator will rate global impression of

	change at 60 min post dose using the CGI-I. AOM symptoms (tinnitus, dizziness, vertigo, and feeling of fullness or muffled hearing in the ear) will also be evaluated at predose and at 60 min post dose. Safety evaluations include vital signs measurements, otoscopy examination of the ear, nose, and throat (ENT), appearance of the TM, and adverse events (AEs). Vital signs (oral temperature, respiratory rate, pulse, and blood pressure) will be measured (after 3 min of rest in the supine position) predose and at 60 min post dose. An ENT examination (otoscopy of the ear, nose, and oropharynx) will be performed by the physician investigator (physician qualified to perform an otoscopic exam of the ears, nose, and oropharynx) at predose and at 60 min post dose. All spontaneously reported AEs will be recorded. The appearance of the TM (contour, color, fluid, and translucency) will also be evaluated using otoscopy by the physician investigator at predose and at 60 min post dose. The appearance of the TM will be evaluated in both ears separately, regardless of whether AOM is bilateral or unilateral. After the subject has completed all assessments, except the Device Experience Questionnaire, on Day 1, the BI will be administered separately to the subject and physician investigator prior to the subject leaving the study centre. The Device Experience Questionnaire will be administered to the subject following the BI before the subject leaves the centre. Any study staff who administers treatment to subjects will also complete the Device Experience Questionnaire. Study staff only need to complete the questionnaire one time for the study, not for each subject treated, after all subjects to be treated by study staff have completed all Day 1 assessments. Subjects will receive a follow-up safety call 1 week (wk) after treatment, and reported AEs and concomitant medications will be recorded.
Planned Sample Size:	Approximately 24 adult subjects with AOM will be randomly assigned to OP0201 20 mg or placebo in a 1:1 ratio (12 subjects per arm).
Key Patient Selection Criteria:	<u>Inclusion Criteria:</u> Subjects must satisfy all of the following criteria to be included in the study: 1. Male and female subjects must be ≥ 18 years of age.

	2. Subjects must have confirmed AOM diagnosis with moderate to severe bulging of the TM and recent (< 48 hours [h]) onset of ear pain. 3. Have moderate to severe ear pain in affected ear(s), defined as a score of ≥ 5 (on a scale of 0-10) on the NRS-11 as evaluated by the subject at Screening. 4. Generally good health (other than AOM) as determined by evaluation of medical history and physical examination at Screening. 5. Negative urine pregnancy test at Screening for all female subjects of childbearing potential. Results must be available prior to randomisation. 6. Able to read and sign written informed consent prior to study participation. <u>Exclusion Criteria:</u> Subjects who meet any of the following criteria will be disqualified from entering the study: 1. Presence of a perforated TM at Screening (must be able to rule out perforated TM by speculum examination, impedance testing tympanometry, otoscopy, or Valsalva maneuver), or had a perforated TM within 6 months prior to Screening as determined by medical history 2. Subjects with tympanostomy tubes 3. Acute or chronic otitis externa 4. Chronic otitis media (OM) defined as confirmed presence of MEE for 12 wk or longer 5. Disorders with decreased mucociliary clearance or higher viscosity of the mucous (eg, cystic fibrosis, primary ciliary dyskinesia, Kartagener's syndrome) 6. Clinically relevant blockage of 1 or both nasal passages, as determined by the investigator's medical judgment 7. Permanent hearing loss irrespective of OM 8. Subjects with medical conditions that may affect interpretation of the safety or efficacy of the study drug as determined by the investigator's medical judgment 9. Subjects with craniofacial abnormalities (eg, cleft palate or Down's Syndrome)

	10. Subjects with erythema of the TM without other evidence of OM 11. Seborrheic dermatitis involving the affected external ear canal or pinna 12. Use of medications with known vasoconstrictive properties (eg, decongestants [Afrin®, Sudafed®]) currently or within 2 h prior to Screening 13. Use of oral analgesics < 2 h prior to Screening or Baseline (oral analgesics > 2 h are permitted as long as ear pain criteria are met per Inclusion Criteria) 14. Known hypersensitivity to DPPC, CP, or hydrofluoroalkane 134a (HFA-134a) 15. Female subjects who are pregnant or lactating 16. Clinically significant mental illness that may interfere with the conduct of the study (as determined by the investigator at Screening) 17. Exposure to any study drug within 30 days (d) prior to Screening 18. Investigator and study centre personnel directly affiliated with this study and/or their immediate families (defined as spouse, significant other, parent, child, or sibling, whether adopted or biologic) 19. Subject has a condition or is in a situation that, in the investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study
Study Drugs:	OP0201 is a drug-device combination product for intranasal metered dose inhaler delivery. The dry powder active ingredients (DPPC + CP) are suspended in propellant (HFA-134a). Each metered spray delivers 2.5 mg of OP0201 (20:1 ratio DPPC and CP, respectively) in 0.1 mL of HFA-134a. Subjects will receive a single intranasal dose of OP0201 20 mg or placebo (4 sprays per nostril for a total of 8 sprays).
Duration of Treatment:	Duration of treatment, including Screening, will be 1 d. Subjects will receive a follow-up safety call 1 wk after study drug administration and exit the study.
Safety Endpoints:	**Primary endpoints**

	• AEs recorded over 60 min post dose and at Day 7 for intranasal OP0201 20 mg or placebo • Change from Baseline in vital signs (oral temperature, respiratory rate, pulse, and blood pressure) at 60 min post dose for intranasal OP0201 20 mg or placebo • Change from Baseline in ENT examination (otoscopy of the ear, nose, and oropharynx) findings at 60 min post dose for intranasal OP0201 20 mg or placebo • Change from Baseline in the appearance of the TM (contour, color, fluid, and translucency) at 60 min post dose for intranasal OP0201 20 mg or placebo as measured by otoscopy
Efficacy Endpoints	**Exploratory endpoints** • Responder analysis of ear pain scores at 10, 20, 30, and 60 min post dose for intranasal OP0201 20 mg or placebo using the VAS and the NRS-11 • Change from Baseline in the VAS and the NRS-11 at 10, 20, 30, and 60 min post dose for intranasal OP0201 20 mg or placebo • Pain Intensity Difference (PID) and Sum Pain Intensity Difference (SPID) analysis of the VAS and the NRS-11 over 60 min post dose for intranasal OP0201 20 mg or placebo • Time to ear pain relief in affected ear(s), recorded as change from moderate/severe pain to mild or no pain, following intranasal OP0201 20 mg or placebo using the VAS and the NRS-11 • PGIC measured at 10, 20, 30, and 60 min post dose for intranasal OP0201 20 mg or placebo • CGI-I measured at 60 min post dose for intranasal OP0201 20 mg or placebo • Response on the BI at 60 min post dose for intranasal OP0201 20 mg or placebo
Statistical Analyses:	Data collected from all randomised subjects will be presented in data listings. Both observed values and mean change from baseline values for each subject will be given where applicable. Continuous variables will be summarised using number of non missing observations, mean, standard deviation, median, minimum,

	and maximum observed values, and observed value ranges (where applicable). Categorical variables will be summarised using the frequency count and the percentage of subjects in each category. Subject disposition data will be summarised. Demographics (sex, age, race, and ethnicity), baseline characteristics (weight, height, and BMI), and baseline VAS, NRS-11, and otoscopy assessments will be summarised using descriptive statistics. **Safety Analysis** Safety assessments will include AEs, ENT examination, appearance of the TM (otoscopy), and vital signs. AEs will be coded in accordance with the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Incidence for all reported AEs will be summarised overall, by intensity (moderate and severe AEs), and for AEs and SAEs leading to early termination. The incidence of treatment-emergent adverse events (TEAEs) will be summarised as the number and percentage of subjects and events reported by treatment and overall for each System Organ Class and Preferred Term using the Safety Analysis Population, which will include all randomised subjects who received any study drug (OP0201 or placebo). TEAEs will also be summarised by maximum severity and relationship to study drug. Prior and concomitant medications will be summarised using frequencies and percentages of subjects by treatment using the Safety Analysis Population. For appearance of the TM, 80% CIs will be calculated for the incidence of shifts from Baseline (0-60 min), from normal to abnormal for the right ear and, separately, for the left ear. A table presenting all changes from Baseline (from/to normal from/to abnormal) will be summarised by treatment for all observed timepoints. Vital signs measurements, ENT examination findings, and appearance of the TM will be summarised by treatment using descriptive statistics. The following will be summarised and listed as other variables related to safety: physical examination data, medical history, and urine pregnancy test results. **Exploratory Efficacy Analysis** PID (change from Baseline) will be computed for each post-dose assessment timepoint (10, 20, 30, and 60 min) for both the NRS-11 and the VAS. Data will be analysed using a longitudinal mixed

	model for repeated measures with fixed effects for treatment, time, treatment-by-time interaction, study site, and baseline pain score. Subject will be the random effect. Treatment differences from control (placebo) will be estimated from the Least Squares Means (LSM) from the analysis model along with 80% confidence intervals (CIs) and associated 2-sided p-values. SPID will be analysed using a linear model analysis of variance (ANOVA) with fixed effects for treatment, site, and baseline pain score for the NRS-11 and the VAS. Treatment differences from control (Placebo) are estimated using the LSM from the analysis model along with 80% CIs and associated 2-sided p-values. The ear pain data will be listed. The analysis of ear pain will focus on change of pain from Baseline to assessment at 10 min (0-10 min), 20 min (0-20 min), 30 min (0-30 min), and 60 min (0-60 min). The change of ear pain from Baseline to assessment will be described as the change of the sum of pain of right and left ear, and in addition as the change in worst reported pain across both ears. Changes from Baseline in the VAS and NRS-11 scores will be summarised by treatment using descriptive statistics for the following post-dose timepoints: 10, 20, 30, and 60 min. Statistical comparisons of ear pain, as measured by the VAS and the NRS-11, between the treatments at 60 min post dose will be performed using an ANOVA model. Time to ear pain relief in the affected ears, recorded as change from moderate/severe pain to mild or no pain using the VAS and the NRS-11, will be summarised by treatment. The 75% and 50% responder status will be assessed via a $\geq$ 75% reduction and a $\geq$ 50% reduction, respectively, in VAS and NRS-11 scores at each post-dose timepoint. The number and percentage of subjects achieving each response level ($\geq$ 75% and $\geq$ 50% decrease) in VAS and NRS-11 scoring will be presented by treatment group with corresponding 80% CIs. The percent decrease in VAS and NRS-11 scores from Baseline to each post-dose timepoint will be calculated for each subject. Responses on the PGIC at 10, 20, 30, and 60 min post dose will be summarised. Responses on the CGI-I at 60 min post dose will be summarised. Additionally, PGIC and CGI-I will be analyzed using a mixed-effects model for repeated measures with treatment group, visit, and site as factors and baseline score (PGIC and CGI-I) as a covariate.

	For all exploratory analyses, a statistically significant difference is defined as $p < 0.20$ and is presented with associated 80% confidence intervals. **Analysis of Other Assessments** Responses on the BI at the end of Day 1 (ie, after all other Day 1 assessments have been completed except the Device Experience Questionnaire) will be summarised. The Device Experience Questionnaires will be analysed at a later date. Additional details will be provided in the Statistical Analysis Plan.

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TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
ANOVA	analysis of variance
AOM	acute otitis media
BI	Blinding Index
BMI	body mass index
BP	blood pressure
bpm	beats per minute
C	Celsius
CGI-I	Clinical Global Impressions Scale: Global Improvement
CI	confidence interval
CP	cholesteryl palmitate
d	day(s)
DPPC	dipalmitoylphosphatidylcholine
eCRF	electronic case report form
ENT	ear, nose, and throat
ET	eustachian tube
GCP	Good Clinical Practice
h	hour(s)
HFA-134a	hydrofluoroalkane 134a
IB	Investigator's Brochure

Abbreviation	Definition
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
LSM	Least Squares Mean
MDI	metered-dose inhaler
ME	middle ear
MedDRA	Medical Dictionary for Regulatory Activities
MEE	middle ear effusion
min	minute(s)
mmHg	millimeters of mercury
mo	month(s)
NRS	Numeric Rating Scale
OM	otitis media
OME	otitis media with effusion
OTC	over-the-counter
PGIC	Patient Global Impression of Change
PI	Principal Investigator
PID	Pain Intensity Difference
PK	pharmacokinetic
ppm	parts per million
RDS	respiratory distress syndrome
SAE	serious adverse event

Abbreviation	Definition
SAP	Statistical Analysis Plan
SOP	standard operating procedure
SPID	Sum Pain Intensity Difference
TEAE	treatment-emergent adverse event
TM	tympanic membrane
URI	upper respiratory infection
VAS	Visual Analog Scale
WCT	Worldwide Clinical Trials
wk	week(s)
y	year(s)

ADMINISTRATIVE STRUCTURE

1 INTRODUCTION

1.1 Background

Acute otitis media (AOM) is usually a short-term inflammation of the middle ear (ME), characterised by the rapid onset of one or more signs or symptoms of acute ear infection such as earache, tugging at the ear, fever, or irritability in the presence of a middle ear effusion (MEE) (as evidenced by bulging tympanic membrane). Otitis media (OM) is frequently preceded by upper respiratory infection (URI), including cough and rhinorrhea.[1,2,3,4] Bacterial and/or viral infection of the ME may occur as a consequence of AOM. OME is fluid in the ME without prominent signs or symptoms of acute ear infection.[5] The clinical concern with OME is primarily conductive hearing loss, but also vestibular problems, ear discomfort, and reduced quality of life.[5] Morbidity associated with OM is driven by recurrence and persistence of OM. Recurrent or persistent AOM and/or OME may lead to rupture of the tympanic membrane (TM) and/or significant damage to the auditory ossicles resulting in permanent hearing loss. Data from systematic reviews of randomised controlled studies showed only a small benefit of oral antibiotic therapy for complete resolution of OME, but no significant impact on hearing levels or the rate of subsequent tympanostomy tube insertion.[6,7,8] Globally, there is a growing public health concern about the emergence of antibiotic resistant bacterial pathogens causing OM.[9,10]

Novus is developing OP0201, a non-antibiotic and non-analgesic combination product intended to treat and prevent OM. OP0201 comprises a novel formulation of 2 active ingredients (dipalmitoylphosphatidylcholine [DPPC] and cholesteryl palmitate [CP]) suspended in propellant (hydrofluoroalkane 134a [HFA-134a]). DPPC and CP are known endogenous surfactant components in human nasal passages and eustachian tube (ET). Novus predicts proactive use of OP0201, at the onset of URI, may prevent ET dysfunction in susceptible patients, significantly reducing the incidence of recurrent AOM. Additionally, concomitant treatment of OP0201 with antibiotics in patients with AOM may facilitate faster resolution of the AOM, prevent recurrence of AOM, and/or prevent the need for a second or third course of antibiotics when AOM does not adequately respond to first course antibiotic therapy. Additionally, OP0201 may reduce the duration and severity of OME, and/or prevent OME developing after occurrence of AOM.

1.1.1 Nonclinical Experience

DPPC:CP 200:1 w/w has been evaluated in proof-of-concept studies in 3 animal species (ie, chinchillas, gerbils, and mice).[11,12,13,14] Across these studies, the beneficial effects of DPPC:CP 200:1 w/w were consistently better than those of no treatment, treatment with propellant alone (considered control). No adverse reactions to the intranasal surfactant DPPC:CP 200:1 w/w were observed in any of the experimental animal group evaluations. Further details about the nonclinical evaluation of DPPC, CP, and HFA-134a are provided in the Investigator's Brochure (IB).[15]

1.1.2 Clinical Experience:

OP0201 has not yet been evaluated in clinical studies in humans.

In addition to the animal studies of DPPC:CP administered in a formulation that was a 200:1 w/w ratio, the clinical safety and tolerability of OP0201 (formulation that is 20:1 w/w

ratio) for human use is further guided by a limited amount of data from 9 human cases exposed to 1 or more doses of other formulations.[15] Eight subjects were exposed to DPPC:CP administered in a 16:1 w/w ratio in HFA-134a (each 0.1 mL spray delivered 2.5 mg of active ingredient), and 1 subject was exposed to DPPC:CP in a 200:1 w/w ratio in HFA-134a (each 0.1 mL spray delivered 5 mg of active ingredient). None of the subjects reported a serious adverse event (SAE), and no deaths due to the study drug were reported.

1.2 Study Rationale

OP0201 is formulated with 2 active ingredients (DPPC + CP) that are known endogenous surfactant components in human nasal passages and ET. Among phospholipid compounds, DPPC is the most hydrophobic and surface active.[16,17] The hydrophobic nature of DPPC causes it to spread very slowly over an aqueous surface. However, in the presence of a spreading agent (ie, CP), phospholipids easily "spread" along a surface pressure gradient of mucosal lined lumens.[17,18] OP0201 acts locally to reduce the surface tension at the ET, which in turn reduces passive opening pressure and allows the ET to open and drain the ME.

OP0201 is intended to treat and prevent AOM. This study will evaluate the safety and immediate (within 60 minutes [min]) reduction of ear pain caused by AOM in adults following a single intranasal dose of OP0201 20 mg.

1.3 Dose Rationale

The composition of OP0201 is designed to maximise the lowering of the mucosal surface tension. Safety and proof-of-concept results from animal pharmacology studies of a formulation of DPPC:CP 200:1 w/w are considered supportive of the OP0201 formulation (DPPC:CP 20:1 w/w) intended for humans. Across several nonclinical pharmacology studies, the beneficial effects of DPPC:CP 200:1 w/w were consistently better than those of no treatment and treatment with propellant alone (ie, placebo).[15] A multiple day repeat dose of 20 mg twice daily for 10 days (d) was given to chinchillas. The total exposure was 400 mg over 10 d: approximately 800 to 1100 mg/kg for chinchilla weighing 0.35 to 0.5 kg.[12] No AEs were observed in any of the animal studies.

The clinical safety and tolerability of OP0201 (DPPC:CP 20:1 w/w) for human use is further guided by a limited amount of data from 9 human cases exposed to1 or more doses of other formulations (see Section 1.1.2).

In this study, subjects will receive a single intranasal dose of OP0201 20 mg or placebo (4 sprays per nostril for a total of 8 sprays). Treatment duration will be 1 d.

The surfactant active ingredients of OP0201 are endogenous to human nasal and respiratory mucosal surfaces. Additionally, surfactants have been approved for topical administration via the trachea to infants with RDS with a long history of safety and tolerability at much higher exposure levels on a mg/kg basis than proposed herein.[15] Thus, in this study the maximum, total exposure will be 20 mg for 1 d; approximately 0.28 mg/kg for humans weighing 70 kg.

The propellant, HFA-134a, will be utilised in concentrations similar to that in other relevant products (eg, Nasacort HFA®, Aventis Pharmaceuticals, Inc., Bridgewater, NJ), with its safety and tolerability supported in publications,[19,20,21] as well as in prior approved and marketed nasal administration products.

1.4 Study Endpoint Rationale

The primary endpoint in this study is to evaluate the safety of a single intranasal dose of OP0201 20 mg in adults with AOM. Spontaneously reported AEs, vital signs measurements, and ear, nose, and throat (ENT) examination findings will be used to assess the safety of OP0201. The ENT examination findings will be used to evaluate any AEs of the ear, nose, and oropharynx that occurred during treatment. Vital signs measurements will be used to evaluate whether any clinically significant changes in blood pressure, pulse, respiratory rate, and oral temperature occurred post dose.

All efficacy assessments will be exploratory endpoints and were selected to evaluate reduction of ear pain and symptoms associated with AOM.

1.5 Risks and Benefits for Subjects

To date, no clinical studies of OP0201 have been conducted in humans. Thus, information regarding expected risks and benefits is unknown.

The clinical safety and tolerability of OP0201 (DPPC:CP 20:1 w/w) for human use is guided by the limited data from human exposure to other formulations (see Section 1.1.2) and animal studies. Of the 9 subjects exposed to study drug containing DPPC and CP, no SAEs or deaths were reported. Safety and proof-of-concept results from animal pharmacology studies are considered supportive of the formulation intended for humans. Across several nonclinical pharmacology studies, the beneficial effects of a formulation of DPPC:CP 200:1 w/w were consistently better than those of no treatment and treatment with propellant alone (ie, placebo).[15] No AEs were observed in any of the animal studies.

DPPC and CP are listed as ingredients in other marketed products indicated for the prevention of RDS in premature neonates. The safety and tolerability of these products is summarised in the IB.

Propellant HFA-134a is used in marketed nasal products and is also present in OP0201. HFA-134a has a good safety and tolerability profile in patients suffering from perennial allergic rhinitis.[22]

The most frequent AEs for 578 placebo-treated (HFA-134a) adults and adolescents with seasonal or perennial allergic rhinitis from short term (2-6 wk) controlled trials were: nasal discomfort (4.8%), epistaxis (1.2%), and headache (1.6%).[23] Nasal ulcerations occurred in 2 subjects treated with placebo in these studies. The most frequent AEs for 111 placebo-treated (HFA-134a) adults and adolescents with perennial allergic rhinitis from a long-term (52 wk) controlled trial were: epistaxis (2%; 2/111; 1 mild, 1 moderate intensity). A total of 3 subjects treated with placebo withdrew from the study due to an adverse reaction. No erosions or ulcerations were noted in subjects who received placebo in this study. No subject experienced a nasal septum perforation during the trial.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To assess the safety of intranasal OP0201 20 mg compared to placebo

2.2 Exploratory Objectives

The exploratory objectives of this study are:

- To assess the effect of intranasal OP0201 20 mg compared to placebo on ear pain scores using the Visual Analog Scale (VAS)
- To assess the effect of intranasal OP0201 20 mg compared to placebo on ear pain scores using the Numeric Rating Scale (NRS-11)
- To assess impression of global change in symptoms as measured by Patient Global Impression of Change (PGIC)
- To assess impression of global change in symptoms as measured by the Clinical Global Impressions Scale: Global Improvement (CGI-I)
- To assess the effect of intranasal OP0201 20 mg compared to placebo on AOM symptoms
- To assess the blinding efforts as measured by the Blinding Index (BI)
- To evaluate subject experience with the device as measured by the Device Experience Questionnaire-Subject
- To evaluate study staff experience with the device as measured by the Device Experience Questionnaire-Study Staff Administering the Treatment

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This will be a single-dose, double-blind, placebo-controlled, randomised, parallel-group, proof-of-concept study to evaluate the safety and immediate (within 60 min) reduction of ear pain caused by AOM in adults following a single dose of intranasal OP0201 20 mg or placebo.

All study-related procedures, including screening, will be performed on Day 1. Following Screening, but before any treatment-related procedures, eligible subjects will be randomly assigned to 1 of the following groups:

- Single intranasal dose of OP0201 20 mg (4 sprays per nostril for a total of 8 sprays)
- Single intranasal dose of placebo (4 sprays per nostril for a total of 8 sprays)

Ear pain will be assessed in the left and the right ear separately, at predose and at 10, 20, 30, and 60 min post dose using the VAS and the NRS-11. Global impression of change in symptoms will be rated by the subject at 10, 20, 30, and 60 min post dose using the PGIC. The physician investigator will rate global impression of change at 60 min post dose using the CGI-I. AOM symptoms (tinnitus, dizziness, vertigo, and feeling of fullness or muffled hearing in the ear) will also be evaluated at predose and at 60 min post dose.

Safety evaluations include vital signs measurements, ENT examination using otoscopy, appearance of the TM, and AEs. Vital signs (oral temperature, respiratory rate, pulse, and blood

pressure) will be measured (after 3 min of rest in the supine position) predose and at 60 min post dose. An ENT examination (otoscopy of the ear, nose, and oropharynx) will be performed by the physician investigator (physician qualified to perform an otoscopic exam of the ears, nose, and oropharynx) at predose and at 60 min post dose. All spontaneously reported AEs will be recorded. The appearance of the TM (contour, color, fluid, and translucency) will also be evaluated using otoscopy by the physician investigator at predose and at 60 min post dose. The appearance of the TM will be evaluated in both ears separately, regardless if AOM is bilateral or unilateral.

After the subject has completed all assessments on Day 1, the BI will be administered separately to the subject and physician investigator prior to the subject leaving the study centre. The Device Experience Questionnaire will be administered to the subject following the BI before the subject leaves the centre.

Any study staff who administer treatment to subjects will also complete the Device Experience Questionnaire. Any study staff who administered treatment only needs to complete the questionnaire one time for the study, not for each subject treated.

Subjects will receive a follow-up safety call 1 wk after treatment, and reported AEs and concomitant medications will be recorded.

3.2 Study Duration

Duration of treatment, including Screening, will be 1 d. Subjects will receive a follow-up safety call 1 wk after study drug administration and exit the study.

3.3 Selection of Study Population

The study population consists of adult subjects with a confirmed diagnosis of AOM. Specific entry criteria are detailed in Section 3.3.1 and Section 3.3.2.

3.3.1 Inclusion Criteria

Subjects must satisfy all of the following criteria to be included in the study:

1. Male and female subjects must be ≥ 18 y of age.
2. Subjects must have confirmed AOM diagnosis with moderate to severe bulging of the TM and recent (< 48 hours [h]) onset of ear pain.
3. Have moderate to severe ear pain in the affected ear(s), defined as a score of ≥ 5 (on a scale of 0-10) on the NRS-11 as evaluated by the subject at Screening.
4. Generally good health (other than AOM) as determined by evaluation of medical history and physical examination at Screening.
5. Negative urine pregnancy test at Screening for all female subjects of childbearing potential. Results must be available prior to randomisation.
6. Able to read and sign written informed consent prior to study participation.

3.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be disqualified from entering the study:

1. Presence of a perforated TM at Screening (must be able to rule out perforated TM by speculum examination, impedance testing tympanometry, otoscopy, or Valsalva maneuver), or had a perforated TM within 6 months (mo) prior to Screening as determined by medical history
2. Subjects with tympanostomy tubes
3. Acute or chronic otitis externa
4. Chronic OM defined as confirmed presence of MEE for 12 wk or longer
5. Disorders with decreased mucociliary clearance or higher viscosity of the mucous (eg, cystic fibrosis, primary ciliary dyskinesia, Kartagener's syndrome)
6. Clinically relevant blockage of 1 or both nasal passages, as determined by the investigator's medical judgment
7. Permanent hearing loss irrespective of OM
8. Subjects with medical conditions that may affect interpretation of the safety or efficacy of study drug as determined by the investigator's medical judgment
9. Subjects with craniofacial abnormalities (eg, cleft palate, Down's Syndrome)
10. Subjects with erythema of the TM without other evidence of OM
11. Seborrheic dermatitis involving the affected external ear canal or pinna
12. Use of medications with known vasoconstrictive properties (eg, decongestants [Afrin®, Sudafed®]) currently or within 2 h prior to Screening
13. Use of oral analgesics < 2 h prior to Screening or Baseline (oral analgesics > 2 h are permitted as long as ear pain criteria are met per Inclusion Criteria)
14. Known hypersensitivity to DPPC, CP, or HFA-134a
15. Female subjects who are pregnant or lactating
16. Clinically significant mental illness that may interfere with the conduct of the study (as determined by the investigator at Screening)
17. Exposure to any study drug within 30 d prior to Screening.
18. Investigator and study centre personnel directly affiliated with this study and/or their immediate families (defined as spouse, significant other, parent, child, or sibling, whether adopted or biologic)
19. Subject has a condition or is in a situation that, in the investigator's opinion, may put the subject at risk, may confound the study results, or may interfere significantly with the subject's participation in the study

3.3.3 Removal of Subjects from Therapy or Assessment

A subject will be considered to have completed the study when he or she completes the follow-up safety call on Day 7. If a subject is discontinued at any time after randomisation into the study, but before 60 min post dose, the investigator will make every effort to follow the

subject and complete the assessments at 60 min post dose/early termination assessments as shown in Section 3.5.1. Subjects who discontinue the study prematurely will be replaced.

A termination electronic case report form (eCRF) page should be completed for every subject who receives study drug, whether or not the subject completes the study. The reason for any early discontinuation should be indicated on this form. The primary reason for a subject discontinuing early should be selected from the following standard categories of early termination:

- *Adverse Event (Adverse Reaction)*: Clinical events occurred that, in the medical judgment of the investigator for the best interest of the subject, are grounds for discontinuation. This includes serious and nonserious AEs regardless of relation to the study drug.
- *Death:* The subject died.
- *Withdrawal of Consent*: The subject desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the subject gave a reason for withdrawing, it should be recorded in the eCRF.
- *Protocol Violation*: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (eg, drug noncompliance, failure to complete all assessments). The violation necessitated early discontinuation from the study.
- *Lost to Follow-Up*: The subject did not complete the follow-up safety call and study personnel were unable to contact the subject.
- *Other*: The subject was discontinued for a reason other than those listed above, such as theft or termination of study by sponsor.

3.4 Treatments

3.4.1 Details of Study Treatments

OP0201 is a drug-device combination product that comprises a novel formulation of 2 active ingredients (DPPC and CP) suspended in propellant (HFA-134a), an inactive ingredient. There are no other ingredients (ie, no excipients, no fillers) in the formulation. The drug product is formulated as a dry powder suspended in propellant and delivered via a metered-dose inhaler (MDI). The active ingredients are synthetically derived and none of the ingredients contain animal or human derivatives.

The OP0201 MDI container should be stored at room temperature between 68°F and 77°F (20°C and 25°C, respectively); excursions are permitted from 59°F and 86°F (15°C and 30°C, respectively). Store the MDI container with the actuator down.

The sponsor will provide all study drug materials.

Information about the study drugs is provided in Table 3.1.

Table 3.1: Details of Study Drugs

	Active	Placebo
Name	OP0201	Not applicable
[redacted]	[redacted]	[redacted]
Dose	20 mg (4 sprays per nostril; each 0.1 mL spray is 2.5 mg OP0201). Total of 8 sprays = 1 dose.	0 mg (4 sprays per nostril; each 0.1 mL spray is 0 mg OP0201). Total of 8 sprays = 1 dose.
Route	Intranasal	Intranasal
Formulation	Metered dose inhaler	Metered dose inhaler
Strength	20 mg	0 mg

Abbreviations: USA = United States of America

3.4.2 Dosage Schedule

Subjects will receive a single intranasal dose (4 sprays per nostril for a total of 8 sprays) of OP0201 20 mg or placebo.

3.4.3 Treatment Assignment

Following Screening, but before any treatment-related procedures, eligible subjects will be randomly assigned in a 1:1 ratio to 1 of the following groups:

- Single intranasal dose of OP0201 20 mg (4 sprays per nostril for a total of 8 sprays)
- Single intranasal dose of placebo (4 sprays per nostril for a total of 8 sprays)

3.4.4 Drug Packaging and Blinding

OP0201 and placebo will be packaged and labeled by Catalent in accordance with applicable national laws.

Kits containing OP0201 or placebo will be identical in appearance and will be provided to the study sites. Kit numbers for OP0201 and placebo will be randomly assigned through the Interactive Response Technology system using a randomisation list.

All subjects and clinical staff will be blinded to the assigned treatment. The PI will be ultimately responsible for ensuring that the integrity of the blind is maintained throughout the study, and will be required to notify the sponsor in the event of any breaking of the blind for any reason.

If an SAE occurs during the study that meets the criteria for expedited reporting (ie, is a Suspected Unexpected Serious Adverse Reaction), the subject will be unblinded by WCT pharmacovigilance. In an emergency situation, the investigator may unblind the study subject's treatment assignment. When possible, the Medical Monitor should be notified prior to

unblinding. The investigator should inform the Medical Monitor of the unblinding if there is no notification prior to the unblinding.

3.4.5 Drug Inventory and Accountability

The investigator must keep an accurate accounting of the number of study drug units delivered to the site, dispensed to subjects, and returned to the sponsor at the completion of the study. The study drug must be dispensed for subjects by an appropriately qualified study staff member who will be administering the treatment to the subject. The study drug is to be used in accordance with the protocol by subjects who are under the direct supervision of the investigator. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all study drugs received at the site before final disposition. At the end of the study, or as directed, all study drugs, including unused, partially used, and empty containers, as well as devices, will be returned to the sponsor sorted as per subject.

3.4.6 Treatment Compliance

Administration of study drug will be performed by study personnel to ensure accuracy of study drug delivery and compliance.

3.4.7 Prior and Concomitant Illnesses and Treatments

3.4.7.1 Prior and Concomitant Illnesses

Investigators should document all significant illnesses that the subject has experienced within 6 mo of Screening. Additional illnesses present at the time informed consent is given are to be regarded as concomitant illnesses. Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF.

3.4.7.2 Prior and Concomitant Treatments

Prior treatments, defined as those taken within 2 wk before Screening, should be recorded in the eCRF as prior medications. Concomitant treatments, defined as treatments taken after the first dose of study drug, should be recorded in the eCRF as concomitant medications. Concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary.

Use of medications with known vasoconstrictive properties (eg, decongestants [Afrin®, Sudafed®]) currently or within 2 h prior to Screening are not permitted.

Any medication or therapy that is taken by or administered to the subject during the course of the study must be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use. The following medications are prohibited until the end of the treatment period on Day 1 (ie, 60 min post dose):

- Medications with known vasoconstrictive properties (eg, decongestants [Afrin®, Sudafed®])
- Oral analgesics

3.5 Assessments

Unless otherwise indicated, all assessments will be performed by the investigator or designated study personnel.

3.5.1 Schedule of Assessments

The procedures to be performed throughout the study are outlined in the Schedule of Assessments (Table 3.2). A detailed description of each assessment may be found in Section 3.5.2.

Table 3.2: Schedule of Assessments

Study Period	**Screening/ Baseline**	**Treatment**					**Safety Follow-up Telephone Call/ Study Exit**
Study Day	**1**	**1**					**7**
Study Minute	**N/A**	**0**	**10**	**20**	**30**	**60/Early Termination**	**N/A**
Informed Consent	X						
Demographics	X						
Inclusion/Exclusion Criteria	X						
Medical History	X						
Physical Examination[a]	X						
ENT Examination[b,c]	X					X	
Urine Pregnancy Test[d]	X						
Randomisation[e]	X						
Vital Signs and Body Weight[f]	X					X	
NRS-11[g]	X[h]		X	X	X	X	
VAS[g]	X[i]		X	X	X	X	
Otoscopy[c,j]	X					X	
PGIC			X	X	X	X	
CGI-I[k]						X	
AOM Symptoms[l]	X					X	
BI[m]						X	
Device Experience Questionnaire-Subject						X	
Device Experience Questionnaire-Study Staff Administering the Treatment[n]						X	
Study Drug Administration[o]		X					
Prior and Concomitant Medications	X[p]	----------X----------					X
AEs		----------X----------					X

[a] Examination will include general appearance, skin, neck (including thyroid), eyes, heart, lungs, abdomen, lymph nodes, extremities, and nervous system.
[b] Otoscopy of the ear, nose, and oropharynx.
[c] To be performed by a physician investigator.
[d] For all female subjects of childbearing potential. Results must be available prior to randomisation.

[e] Subjects will be randomly assigned to OP0201 20 mg or placebo in a 1:1 ratio (OP0201:placebo) following screening procedures, but prior to baseline and treatment procedures.
[f] Oral temperature, respiratory rate, pulse, and BP measured after at least 3 min of rest in the supine position will be performed at Baseline and at 60 min post dose. Body weight will be measured at Baseline only.
[g] Both ears will be evaluated regardless if AOM is bilateral or unilateral.
[h] Administered to assess pain in both ears during the screening procedures. This score will also serve as the baseline measure for affected ear(s).
[i] To be administered after randomisation.
[j] Appearance of the TM will be rated for contour (normal, retracted, full, bulging, perforated), color (normal, partly red, completely red), fluid behind the TM (no/yes; if yes-yellow, translucent, red, blue, or black), and translucency (translucent, semi-opaque, and opaque). Both ears will be evaluated regardless if AOM is bilateral or unilateral.
[k] To be completed by the physician investigator who evaluated the subject at baseline and post dose.
[l] AOM symptoms to be evaluated include tinnitus, dizziness, vertigo, and feeling of fullness or muffled hearing in the ear.
[m] To be administered to the subject and physician investigator separately after completion of all other assessments.
[n] To be obtained only once by each qualified staff member who administers the study treatment to subjects in this study.
[o] 4 sprays of intranasal OP0201 20 mg or placebo will be delivered to each nostril for a total of 8 sprays.
[p] Prior medications will only be recorded at Screening.

Abbreviations: AE = adverse event; AOM = acute otitis media; BI = Blinding Index; BP = blood pressure; CGI-I = Clinical Global Impressions Scale: Global Improvement; ENT = ear, nose, and throat; min = minute(s); N/A = not applicable; NRS-11 = Numeric Rating Scale; PGIC = Patient Global Impression of Change; TM = tympanic membrane; VAS = Visual Analog Scale

3.5.2 Study Procedures

3.5.2.1 Screening/Baseline Procedures (Day 1)

The assessments during the screening/baseline phase will determine the subjects' eligibility for the study and also their ability to comply with protocol requirements by completing all screening/baseline assessments.

The following procedures will be performed and recorded during the screening/baseline period:

- Written informed consent
- Demographics
- Inclusion and Exclusion Criteria
- Medical history
- Physical examination
- ENT examination (physician investigator to perform otoscopy of the ear, nose, and oropharynx)
- Urine pregnancy test (for all female subjects of childbearing potential; results must be available prior to randomisation)
- Vital signs (oral temperature, respiratory rate, pulse, and blood pressure measured after at least 3 min of rest in the supine position) and body weight
- Randomisation
- NRS-11 (score will be used to assess pain in both ears during Screening and as the baseline measure for affected ear(s); both ears will be evaluated regardless if AOM is bilateral or unilateral)
- VAS (to be administered after randomisation; both ears will be evaluated regardless if AOM is bilateral or unilateral)
- Otoscopy (physician investigator to evaluate contour, color, fluid, and translucency)
- AOM symptoms (tinnitus, dizziness, vertigo, and feeling of fullness or muffled hearing in the ear)
- Prior and concomitant medications

3.5.2.2 Treatment Procedures (Day 1)

After completion of all screening/baseline procedures, subjects will receive a single intranasal dose (4 sprays per nostril for a total of 8 sprays) of OP0201 20 mg or placebo. Reported AEs will be recorded.

At 10, 20, and 30 min post dose, the following procedures will be performed:

- NRS-11 (both ears will be evaluated regardless if AOM is bilateral or unilateral)
- VAS (both ears will be evaluated regardless if AOM is bilateral or unilateral)

- PGIC
- AEs and concomitant medications

At 60 min post dose, the following procedures will be performed:

- ENT examination (physician investigator to perform otoscopy of the ear, nose, and oropharynx)
- Vital signs (oral temperature, respiratory rate, pulse, and blood pressure measured after at least 3 min of rest in the supine position)
- NRS-11 (both ears will be evaluated regardless if AOM is bilateral or unilateral)
- VAS (both ears will be evaluated regardless if AOM is bilateral or unilateral)
- Otoscopy (physician investigator to evaluate contour, color, fluid, and translucency)
- PGIC
- CGI-I (obtained from the physician investigator who evaluated the subject at baseline and post dose)
- AOM symptoms (tinnitus, dizziness, vertigo, and feeling of fullness or muffled hearing in the ear)
- AEs and concomitant medications
- BI (to be administered separately to the subject and physician investigator after completion of all other assessments)
- Device Experience Questionnaire-Subject
- Device Experience Questionnaire-Study Staff Administering Treatment

3.5.2.3 Safety Follow-up Telephone Call/Study Exit

- AEs and concomitant medications

3.5.3 Early Termination Procedures

The following assessments will be administered to subjects who terminate prematurely from the study:

- ENT examination (physician investigator to perform otoscopy of the ear, nose, and oropharynx)
- Vital signs (oral temperature, respiratory rate, pulse, and blood pressure measured after at least 3 min of rest in the supine position)
- NRS-11 (both ears will be evaluated regardless if AOM is bilateral or unilateral)
- VAS (both ears will be evaluated regardless if AOM is bilateral or unilateral)
- Otoscopy (physician investigator to evaluate contour, color, fluid, and translucency)
- PGIC

- CGI-I (obtained from the physician investigator who evaluated the subject at baseline and post dose)
- AOM symptoms (tinnitus, dizziness, vertigo, and feeling of fullness or muffled hearing in the ear)
- AEs and concomitant medications
- BI (to be administered separately to the subject and physician investigator after completion of all other assessments)
- Device Experience Questionnaire-Subject

3.5.4 Efficacy Assessments

Numeric Rating Scale (NRS-11): The NRS is commonly used in the clinical assessment of pain.[24] The NRS requires that subjects select a whole number that best represents the intensity of their pain. On the NRS-11, pain scores range from 0 to 11, with 0 representing no pain and 11 representing the worst pain possible.[25,26] Use of the NRS in the emergency department for the measurement of acute pain has been validated.[24]

The NRS-11 will be administered at Screening to evaluate pain in both ears as part of the eligibility requirements. The score obtained at Screening will also serve as a baseline measurement for the affected ear(s). The NRS-11 will also be administered at 10, 20, 30, and 60 min post dose. Ear pain will be scored by the subjects separately for the left and right ear.

Visual Analog Scale (VAS): The VAS has been widely used for the assessment of pain in clinical research.[24,26]The VAS has also been used to assess acute pain and for the assessment of pain in emergency departments.[26] The VAS -100 mm version (also labeled as the VAS-10 cm version) consists of a 100 mm line anchored by 2 extremes of pain (eg, no pain versus worse pain).[25,26] Subjects mark the line where their pain is best represented between the 2 anchors. Pain intensity scores are determined by the distance from the 'no pain' anchor to the subject's mark.

Ear pain will be scored by the subjects separately for the left and right ear using the VAS, which will be administered at Baseline and at 10, 20, 30, and 60 min post dose.

Patient Global Impression of Change (PGIC): The PGIC is a questionnaire that asks the subject to assess the global change in health status since receiving the study drug. The PGIC has been used frequently in clinical and observational studies across the spectrum of therapeutic areas and products. The PGIC is useful in assessing whether the impact of the study drug is meaningful enough to have value to the subject. PGIC instructions are as follows: "How have your symptoms been since you received the study treatment?" Scores on the PGIC range from 1 to 7 with 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. The PGIC will be evaluated at 10, 20, 30, and 60 min post dose.

Clinical Global Impressions Scale: Global Improvement (CGI-I): The CGI-I assesses the physician investigator's global impression of global change from Baseline in symptoms since the administration of study drug. The CGI-I instructions are as follows: "How has the subject's symptoms been since they received the study treatment?" Scores range from 1 to 7, with 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally

worse, 6 = much worse, and 7 = very much worse. The CGI-I will be evaluated at 60 min post dose.

AOM Symptoms: The following AOM symptoms will be evaluated predose and at 60 min post dose: (1) tinnitus, (2) dizziness, (3) vertigo, and (4) feeling of fullness or muffled hearing in the ear. The investigator will record for each subject whether the symptom is present or absent.

3.5.5 Safety Assessments

Ear, Nose, and Throat Examination: Examination of the ear, nose, and oropharynx will be performed using otoscopy at Screening and at 60 min post dose.

Otoscopy: Otoscopy assessments will be performed by the physician investigator to assess the appearance of the TM in the left and right ear. Measurements will be taken at Baseline and at 60 min post dose. The TM will be rated for the following variables:

- Contour: normal, retracted, full, bulging, or perforated
- Color: normal, partly red, or completely red
- Fluid behind the TM: no/yes; if yes-yellow, translucent, red, blue, or black
- Translucency: translucent, semi-opaque, or opaque

Details of how each variable is to be assessed and categorised are provided in Appendix 8.2.

Vital Signs: Vital signs will be measured at Baseline and at 60 min post dose or Early Termination. Vital signs will include oral temperature (C), respiratory rate (breaths per minute), pulse (beats per minute [bpm]), and systolic and diastolic blood pressure (BP) recorded after at least 3 min of rest in the supine position. Body weight (kg) will also be collected with the vital signs measurements at Baseline only. Repeat measurements may be obtained in the event the initial measurements taken at Baseline are out of range.

Adverse Events: All AEs occurring after the administration of study treatment until the follow-up safety call or early termination will be recorded.

See Section 4, for additional information.

3.5.6 Other Assessments

Blinding Index: The BI will evaluate the success of blinding efforts incorporated in the study design.[27] When the subject completes all study assessments on Day 1, but prior to administering the Device Experience Questionnaire, the subject and the physician investigator will be asked to indicate which treatment allocation they believe the subject received. If the respondent selects “I don’t know”, then the second question asks the respondent to provide a best guess, with a binary outcome: real medication or placebo. The final question asks the respondent to indicate the reason(s) why they chose their response to question 1 and question 2 (if applicable). The reason(s) will be captured as open-ended commentary by the respondent. A sample BI questionnaire is provided in Appendix 8.1.

Device Experience Questionnaire-Subject: The Device Experience Questionnaire-Subject will evaluate the subject’s experience with the device during the study. Each subject will be asked to rate their agreement (Strongly Disagree, Disagree, Neutral, Agree, or Strongly Agree) to

4 questions about using the device. Additional comments related to each question will be documented in the questionnaire. Question 5 allows the subjects to provide other comments about the device that were not captured by the previous 4 questions. The questionnaire will be administered when the subject completes all study assessments on Day 1, including the BI, prior to leaving the study centre.

Device Experience Questionnaire-Study Staff Administering Treatment: The Device Experience Questionnaire-Study Staff Administering Treatment will evaluate the study staff's experience with the device during the study. Each study staff administering treatment will be asked to rate their agreement (Strongly Disagree, Disagree, Neutral, Agree, or Strongly Agree) to 6 questions about using the device. Additional comments related to each question will be documented in the questionnaire. Question 7 allows the study staff to provide other comments about the device that were not captured by the previous 6 questions. Each study staff who administered treatment to subjects will complete one questionnaire for the study, which will be administered after all subjects to be treated by study staff have completed all Day 1 assessments.

3.5.7 Appropriateness of Measurements

The most recent version of the CONSORT statement on guidelines for parallel group randomised trials indicates that information on "how the success of blinding (masking) was assessed" is no longer recommended because of a lack of empirical evidence supporting the practice as well as theoretical concerns about the validity of any such assessment.[28] Conceptually, investigators are able to assess the success of blinding by asking participants and others (eg, outcome assessors) which treatment they believe was allocated. In theory, if blinding was successful, these people should not be able to guess the treatment more frequently than that expected by chance. Tests of the success of blinding hinge on that theoretical model. In reality, however, blinding could be successful, but people involved in the trial might deduce the treatment through supplementary information. Differential levels of side-effects or harms could yield strong clues, as can therapeutic benefits, or other pharmacologic/pharmacodynamics properties of the treatment. Nevertheless, a blinding assessment (ie, BI) to explore the integrity of the study design and masking of treatment will be performed when the subject completes all assessments on Day 1. The BI will be performed separately by the physician investigator and subject. Analysis methods proposed by Bang and collegues,[27] which have been mostly described through simulations rather than application in clinical trials, will be used.

All other assessments to be used in this study are commonly used, standard measurements in AOM studies. Assessment of device experience is common in studies of drug-device combination products.

4 ADVERSE EVENT REPORTING

Throughout the course of the study, all AEs will be monitored and recorded on an AE eCRF, including the AE's description, start and end date, seriousness, severity, action taken, and relationship to the study drug. If AEs occur, the first concern will be the safety of the subjects. All AEs will be followed until resolved or stable and the outcome documented on the eCRF.

4.1 Definitions and Criteria

4.1.1 Adverse Events

Per ICH E2A[29]: An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Medical interventions such as surgeries, diagnostic procedures, and therapeutic procedures are not AEs but the action taken to treat the medical condition. They should be recorded as treatment of the AEs.

Any AE that has an onset on or after the dose of study drug, or any pre-existing condition that has worsened on or after the first dose of study drug will be considered a treatment-emergent adverse event (TEAE).

4.1.2 Serious Adverse Events

An SAE or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; development of drug dependency or drug abuse; or malignancy tumors [histologically different from primary tumor])

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. An SAE is not necessarily severe; eg, an overnight hospitalisation for a diagnostic procedure must

be reported as an SAE even though the occurrence is not medically serious. By the same token, a severe AE is not necessarily serious: nausea lasting several hours may be rated as severe but may not be considered serious.

4.1.3 Unexpected Adverse Drug Reactions

An unexpected adverse drug reaction (ADR) is a reaction for which the nature or severity is not consistent with the applicable product information (IB). Until product information is amended, expedited reporting is required for additional occurrences of the reaction. Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an event more specific or more severe than described in the IB would be considered "unexpected." Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

Guidance on reporting AEs and SAEs is described in Section 4.2.

4.1.4 Assessing Intensity and Relationship

All AEs will be assessed on 2 descriptive parameters: intensity and relationship to the study drug:

- Intensity refers to the severity of an event and references impact on a subject's functioning.
- Relationship refers to the likelihood that the event being assessed was caused by the study drug.

Intensity

Each AE will be classified according to the following criteria:

Mild:	The AE does not interfere in a significant manner with the subject's normal level of functioning.
Moderate:	The AE produces some impairment of functioning, but is not hazardous to the subject's health.
Severe:	The AE produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be noted. If the intensity category changes over a number of days, those changes should be recorded separately (with distinct onset dates).

Relationship

The investigator must assess the causality of an AE (including SAEs) to the use of a study drug using a 2-category scale (not related or related) based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors
- The temporal association between study drug exposure and onset of the AE
- Whether the manifestations of the AE are consistent with known actions or toxicity of the study drug
- Whether the AE resolved or improved with stopping use of the study drug; judgment should be used if multiple products are discontinued at the same time
- Positive rechallenge
- Positive dechallenge (resolution upon stopping suspect study drug, in absence of other intervention or treatment)

The causal relationship between the study drug and the AE will be assessed using one of the following categories shown in Table 4.1:

Table 4.1: Adverse Event Causality

Category	Definition
Not Related	An AE is not associated with study medication if no causal relationship exists between the study drug and the AE, but an obvious alternative cause exists, eg, the subject's underlying medical condition or concomitant therapy.
Related	An AE is attributed to the study medication if there is reasonable/plausible possibility that the AE may have been caused by the study drug:

4.2 Reporting Procedures and Requirements

4.2.1 Adverse Events

AE recording will begin at administration of study drug. Any AEs occurring before the start of treatment (ie, before administration of study drug) will be recorded in the medical history. Also, the sign, symptom, or disease present before starting the treatment period are only considered AEs if they worsen after starting the treatment period.

If the investigator detects an AE in a study subject after the follow-up safety call and considers the event possibly related or related to prior study treatment, the investigator should report it to the WCT.

The investigator should report all AEs on the AE page(s) of the eCRF and source documents, regardless of seriousness, severity, and causality. Whenever possible, an AE will be reported using a diagnostic term, (eg, "common cold" or "upper respiratory infection" rather than "runny nose, cough, mild fever") and should be described with the attributes described in Section 4.1.4.

4.2.2 Serious Adverse Events

All AEs and SAEs will be reported in the eCRF. Each AE will be assessed to determine whether it meets seriousness criteria (Section 4.1.2). If the AE is considered serious, the investigator should report this event to WCT as outlined below and also to the independent ethics committee (IEC) according to its standard operating procedures (SOPs).

If the investigator detects an SAE in a study subject after the follow-up safety call, and considers the SAE related or possibly related to prior study treatment, the investigator should report it to WCT.

All information about SAEs will be collected and reported via the SAE form and sent by e-mail message to [redacted] or facsimile (contact information will be contained in the investigator site file). The investigator should send the initial report within 24 h of becoming aware of the SAE. At minimum, the initial report should include the following information:

- Event
- Study code
- Subject number, initials, and date of birth
- Study drug
- Reporter name and contact information

In the case of a "minimum report" (one that solely comprises the information bulleted above), a more detailed follow-up report should be sent as soon as more information becomes available but no later than 7 calendar days after the date of the initial report. Each SAE should be followed up until resolution or stabilisation and for reported deaths, the investigator should supply WCT and the IEC with any additional requested information (eg, autopsy reports and terminal medical reports).

The original SAE form should be kept at the study site. The sponsor or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

SAEs that are ongoing should be followed until resolved.

4.3 Procedures for Documenting Pregnancy During Study

If a female subject becomes pregnant during the study, the investigator will notify WCT immediately following pregnancy confirmation. The investigator will also: (1) notify the subject's physician that the subject may have been treated with OP0201 and (2) follow the progress of the pregnancy to term and document the outcome of the pregnancy. Subjects who become pregnant during the study will not be eligible for any further study treatments. Pregnancy outcome information should be forwarded to WCT when available.

5 DATA MANAGEMENT AND STATISTICAL ANALYSIS

5.1 Data Management Considerations

In this study, eCRFs will be used. Completed eCRFs for this study will be forwarded to the sponsor or its representative where editing and construction of a quality-assured database will occur. Data will be quality checked, double-entered, and electronically verified before entry into the database. Queries will be issued for any inconsistencies, omissions, and discrepancies and will be resolved by the appropriate parties. The statistical analysis of these data will be performed by the sponsor or its representative. All AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Data management details will be outlined in a separate data management plan.

5.2 Statistical Considerations

The information in this section is a summary of the planned statistical analyses. Further details are provided in the Statistical Analysis Plan (SAP). The SAP will be developed based on the latest version of the clinical protocol and eCRFs, and will be finalised prior to database lock. No database may be locked, or analyses completed, until the SAP has been approved.

The SAP will provide a detailed description for the handling of missing data, patient eligibility criteria for the analysis, and statistical methodology for the data summary and analysis of safety and efficacy variables. This protocol describes key analyses undertaken by WCT in collaboration with Novus Therapeutics. If differences occur between analyses described in the SAP and the current protocol, those found in the SAP will supercede analyses outlined in the protocol.

All statistical reporting will be performed using the validated software SAS® for Windows version 9.3 or higher (SAS Institute, Inc., Cary, NC, USA), unless otherwise specified. Data collected from all randomised subjects will be presented in data listings. Both observed values and mean change from baseline values for each subject will be given where applicable. Data listings will be sorted by treatment, subject number, and time point unless otherwise noted.

Data for individual subjects will be listed. Continuous variables will be summarised using number of non missing observations, mean, standard deviation, median, minimum, and maximum observed values, and observed value ranges (where applicable). Categorical variables will be summarised using the frequency count and the percentage of subjects in each category.

Any deviations from the analyses described below will be included in the SAP, which will be included in the clinical study report.

5.2.1 Sample Size Justification

Approximately 24 subjects will be enrolled in this study. On Day 1, eligible subjects will be randomly assigned in a ratio of 1:1 (12 subjects per arm) to receive 1 of 2 study treatments (20 mg, OP0201 or placebo).

5.2.2 Analysis Populations

The Screening Population will include all subjects who signed an Informed Consent Form (ICF) and have completed any screening procedures.

The Randomised Population will include all screened subjects who are assigned a randomisation number prior to dosing.

The Safety Analysis Population will include all randomised subjects who received any study drug (OP0201 or placebo).

5.2.3 Protocol Deviations

A protocol deviation plan will be prepared as a separate document. All protocol deviations will be documented in the clinical trials management system. A protocol deviation occurs when there is any non-adherence to a study procedure or schedule that is specified within the protocol.

Protocol deviations will be assessed and summarised. Protocol deviations may include but are not limited to the following: departure from eligibility criteria, failure to perform the required assessments at the specified timepoints, the wrong treatment or dose was administered, or subject safety.

5.2.4 Subject Disposition

The overall number of subjects screened and the number of subjects in each analysis population will be summarised and listed. Any differences between the number of subjects in the analysis populations will be explained. Additionally, completer and early termination status will be summarised for the Randomised Population. For subjects who discontinue from the study prior to completion, the primary reason for early termination will be summarised using frequencies and percentages for each category.

All subject disposition and outcome data will be listed.

5.2.5 Demographic and Baseline Characteristics

Demographics (sex, age, race, and ethnicity) and baseline characteristics (weight, height, and BMI) will be summarised using the appropriate descriptive statistics as described above for the Safety Population. No formal statistical analyses will be conducted. Data analyses will be provided by treatment and for all subjects combined (overall), where appropriate.

Baseline VAS, NRS-11, and otoscopy assessments will be summarised by treatment and overall (where applicable) using the appropriate descriptive statistics for all subjects in the Safety Analysis Population.

5.2.6 Efficacy Analyses

5.2.6.1 Exploratory Analysis

Pain Intensity Difference (PID) & Sum Pain Intensity Difference (SPID) will be calculated as follows:

- PID will be calculated as:

$$PID_t = PI_t - PI_{Baseline}$$

  Where t is the post-dose assessment timepoint

  Where baseline is the predose assessment timepoint

- SPID will be calculated as:

$$SPID_{ti-ti+n} = \sum_{ti}^{ti+n} (PID_i) * (t_{i+1} - t_i)$$

Where PID_i is the pain intensity difference score calculated at each post-dose timepoint

Where t_i is the scheduled assessment time

Analyses for Continuous Data

PID (change from Baseline) will be computed for each post-dose assessment timepoint (10, 20, 30, and 60 min). Data will be analysed using a longitudinal mixed model for repeated measures with fixed effects for treatment, time, treatment-by-time interaction, study site, and baseline pain score. Subject will be the random effect. Treatment differences from control (placebo) will be estimated from the Least Squares Means (LSM) from the analysis model along with 80% confidence intervals (CIs) and associated 2-sided p-values. If significance is found using 80% CIs, 90% and 95% CIs will also be tested. Only observed cases will be included in the PID computations. Graphical displays of the LSM change from Baseline will also be provided by treatment.

Descriptive summaries for each PID timepoint will be provided by treatment along with the model output for test differences in the LSM. PID analyses will be conducted for both NRS-11 and VAS pain scales.

SPID will be analysed using a linear model analysis of variance (ANOVA) with fixed effects for treatment, site, and baseline pain score. Treatment differences from control (placebo) are estimated using the LSM from the analysis model along with 80% CIs and associated 2-sided p-values. If significance is found using 80% CIs, 90% and 95% CIs will also be tested. SPID analyses will be conducted for both NRS-11 and VAS pain scales. Missing data will be handled using the Last Observation Carried Forward imputation method.

The ear pain data will be listed. The analysis of ear pain will focus on change of pain from Baseline to assessment at 10 min (0-10 min), 20 min (0-20 min), 30 min (0-30 min), and 60 min (0-60 min). The change of ear pain from Baseline to assessment will be described as the change of the sum of pain of right and left ear, and in addition as the change in worst reported pain across both ears. Thereby, worst reported pain across both ears is defined as the worst pain of either the right or the left ear determined separately for baseline and the respective assessment. These measures will be summarised as described above for continuous variables and analysed for treatment effect as further delineated in the SAP. Hodges-Lehmann point estimate and 80% 2-sided CI for the median of treatment effect differences between active and placebo will be provided. If significance is found using 80% CIs, 90% and 95% CIs will also be tested. Furthermore, tables providing the incidence of pain score > 0 at each post-baseline timepoint will be displayed. Additionally, shift tables for incidence of change from Baseline at each post-baseline timepoint with three categories (1) 'no change', (2) 'worsening' (ie, higher score than baseline), and (3) 'improvement' (ie, lower score than baseline) will be produced to describe change from Baseline for right and left ear separately.

Changes from Baseline in the VAS and NRS-11 scores will be summarised by treatment using descriptive statistics for the following post-dose timepoints: 10, 20, 30, and 60 min. Statistical comparisons of ear pain, as measured by the VAS and the NRS-11, between the treatments at 60 min post dose will be performed using an ANOVA model. Time to ear pain relief in the

affected ears, recorded as change from moderate/severe pain to mild or no pain using the VAS and the NRS-11, will be summarised by treatment.

The 75% and 50% responder status will be assessed via a ≥ 75% reduction and a ≥ 50% reduction, respectively, in VAS and NRS-11 scores at each post-dose timepoint. The number and percentage of subjects achieving each response level (≥ 75% and ≥ 50% decrease) in VAS and NRS-11 scoring will be presented by treatment group with corresponding 80% CIs. CIs will be calculated using a fixed-effects model and considered statistically significant when the 80% CI does not include 1. Figures will be presented illustrating the percentage of responders in pain intensity reductions presented by treatment group and level of response.

The percent decrease in VAS and NRS-11 scores from Baseline to each post-dose timepoint will be calculated for each subject as follows:

$$\%\text{decrease VAS} = [(\text{VAS}_{\text{baseline}} - \text{VAS}_t) \div \text{VAS}_{\text{baseline}}] \times 100$$

$$\%\text{decrease NRS-11} = [(\text{NRS-11}_{\text{baseline}} - \text{NRS-11}_t) \div \text{NRS-11}_{\text{baseline}}] \times 100$$

Where t = post-dose timepoint (10, 20, 30, or 60 min)

Responses on the PGIC at 10, 20, 30, and 60 min post dose will be summarised. Responses on the CGI-I at 60 min post dose will be summarised. Frequency and percentage of subjects reporting AOM symptoms at Baseline and at 60 min post dose will be summarised by treatment group. Additionally, PGIC and CGI-I will be analyzed using a mixed-effects model for repeated measures with treatment group, visit, and site as factors and baseline score (PGIC and CGI-I) as a covariate. This model will be based on a restricted maximum likelihood approach and will utilize an unstructured covariance type shared across treatment groups to model the within-subject errors. The primary comparison for treatment differences will be the difference in LSMs.

For all exploratory analyses, a statistically significant difference is defined as $p < 0.20$ and is presented with associated 80% CIs.

5.2.7 Safety Analyses

The Safety Analysis Population will be used for all safety analyses by treatment and for all subjects combined (overall) where appropriate. Safety assessments will include AEs, ENT examination, appearance of the TM (otoscopy), and vital signs. Prior and concomitant medications will be summarised using frequencies and percentages of subjects by treatment using the Safety Analysis Population. Only safety assessments with both predose and post-dose data will be analyzed. All other baseline assessments will be listed.

5.2.7.1 Extent of Exposure

Extent of exposure will be described by whether the subject took any study drug. All dosing and dispensing information will be listed.

5.2.7.2 Adverse Events

AEs will be coded in accordance with the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). Incidence for all reported AEs will be summarised overall (regardless of severity or relationship to study drug), moderate AEs, and severe AEs. Additionally, a summary

of SAEs and AEs leading to early termination from the study will be presented along with corresponding data listings.

The incidence of TEAEs will be summarised as the number and percentage of subjects and events reported by treatment and overall for each System Organ Class and Preferred Term using the Safety Analysis Population. TEAEs will also be summarised by maximum severity and relationship to study drug.

5.2.7.3 Vital Signs

Vital signs measurements will be summarised using descriptive statistics for all observed timepoints. Additionally, all corresponding changes from Baseline to 60 min post dose will be summarised by treatment.

If appropriate, the incidence of clinically meaningful changes will be summarised at 60 min post dose. Clinically meaningful changes are defined as:

- Systolic BP: ≤ 80 mmHg or ≥ 140 mmHg
- Diastolic BP: supine ≤ 40 mmHg or ≥ 90 mmHg
- Pulse rate: ≤ 50 bpm or ≥ 100 bpm
- Respiration rate:< 8 or > 20 breaths per minute

Changes in oral temperature measurements will also be summarised.

5.2.7.4 Ear, Nose, and Throat Examination

ENT examination findings will be summarised using descriptive statistics for all observed timepoints. Additionally, all corresponding changes from Baseline to 60 min post dose will be summarised by treatment.

5.2.7.5 Otoscopy (Appearance of the Tympanic Membrane)

For appearance of the TM, 80% CIs will be calculated for the incidence of shifts from Baseline (0-60 min), from normal to abnormal for the right ear and, separately, for the left ear. If significance is found using 80% CIs, 90% and 95% CIs will also be tested. A table presenting all changes from Baseline (from/to normal from/to abnormal) will be summarised by treatment for all observed timepoints.

5.2.7.6 Other Variables Related to Safety

A complete medical history will be obtained at Screening and data will be listed. Some examples of medical history data include previous surgical history, medications, chronic conditions, past/present illness, substance/drug abuse, and history of allergies. For each subject, it will be documented whether or not the subject has prior experience using an intranasal device. Information about prior use of intranasal devices will include how often the device was used, for what indication, and type of device(s) (aqueous or propelled) will be obtained.

A complete physical examination will be conducted at Screening to evaluate each subject's general appearance, skin, neck (including thyroid), eyes, heart, lungs, abdomen, lymph nodes, extremities, and nervous system. Physical examination findings will be summarised using the appropriate descriptive statistics. Height (cm), body weight (kg), and body mass index

(BMI [kg/m^2]) will also be collected and summarised as baseline characteristics (Section 5.2.5). Evaluation of the ear, nose, and oropharynx will be performed during the ENT examination (Section 5.2.7.4).

A urine pregnancy test will be administered at Screening for all female subjects of childbearing potential and results will be listed.

5.2.8 Interim Analyses

No interim analyses are planned.

5.3 Analysis of Other Assessments

The BI will be administered following completion of all other assessments, except the Device Experience Questionnaire, on Day 1. Responses on the BI will be summarised separately for the subject and physician investigator.

The Device Experience Questionnaires will be analyzed at a later date.

6 STUDY MANAGEMENT

6.1 Ethics and Consent

6.1.1 Regulations and Guidelines

The study will be performed in accordance with this protocol, local national laws (as applicable), ICH guidelines for Good Clinical Practice (GCP),[30] and the most recent guidelines of the Declaration of Helsinki. These guidelines are on file at WCT.

6.1.2 Independent Ethics Committees

Conduct of the study must be approved by an appropriately constituted IEC. Approval is required for the study protocol, IB, protocol amendments, ICFs, subject information sheets, and advertising materials. No study drug will be shipped to a site until written IEC authorisation has been received by the sponsor or its representative.

6.1.3 Informed Consent

For each subject, a written ICF will be obtained before any protocol-related activities. As part of this procedure, the investigator or a designated representative must explain orally and in writing the nature, duration, and purpose of the study, and the action of the study drug in such a manner that the subject and (if applicable) appointed guardian are aware of the potential risks, inconveniences, or adverse effects that may occur. Subjects should be informed that they may withdraw from the study at any time. They will receive all information that is required by local regulations and ICH guidelines. The PI or a designated representative will provide the sponsor or its representative with a copy of the IEC-approved ICF before the start of the study.

6.2 Indemnification

Indemnification will be discussed in a separate document.

6.3 Discontinuation of the Study by the Sponsor

The sponsor reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. In particular, a site that does not recruit at a reasonable rate

may be discontinued. Should the study be terminated and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the sponsor or its representative.

6.4 Study Documentation

By signing a copy of country-specific regulatory forms, the PI acknowledges that he/she has received a copy of the investigator's brochure on OP0201 and assures the sponsor that he/she will comply with the protocol and the provisions stated in country-specific forms. No changes in this protocol can be made without the sponsor's written approval.

6.5 Study Monitoring and Auditing

This study will be monitored for quality assurance at all stages of its development by the clinical research personnel employed by the sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to the protocol, SOPs, Guidelines of GCP, and applicable regulatory requirements. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. On-site review of eCRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject. Note that a variety of original documents, data, and records will be considered as source documents in this trial. The eCRF itself is not to be used as a source document under any circumstances.

Medical advisors and clinical research associates or assistants may request to witness subject evaluations occurring as part of this protocol. The investigator and appropriate personnel will be periodically requested to attend meetings/workshops organised by the sponsor to assure acceptable protocol execution. The study may be subject to audit by the sponsor or by regulatory authorities. If such an audit occurs, the investigator must agree to allow access to required subject records. By signing this protocol, the investigator grants permission to personnel from the sponsor, its representatives, and appropriate regulatory authorities, for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in eCRF generation, where clinically appropriate.

6.6 Retention of Records

The investigator must arrange for retention of study records at the site. The nature of the records and the duration of the retention period must meet the requirements of the relevant regulatory authority. The investigator should take measures to prevent accidental or premature destruction of these documents.

6.7 Use of Study Findings

By signing the study protocol, the investigator agrees to the use of results of the study for the purposes of national and international registration. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. Reports covering clinical and biometric aspects of the study will be prepared by the sponsor or its representative.

6.8 Publications

As a multicentre trial, the sponsor intends to publish clinical data from all centres participating in the investigation. A publication committee selected by the sponsor will submit draft manuscripts

to all participating investigators for their comments. In conformity with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals published by the International Committee of Medical Journal Editors (see discussion in Kassirer & Angell, 1991),[31] investigators whose contribution consists solely in the collection of data will not be named individually as authors. Rather, those investigators will receive a collective authorship as the "OP0201 Study Group" and will be identified in a note.

Individual investigators and/or their associates subsequently may publish additional findings of this study in scientific journals or present them at scientific meetings, provided that the sponsor is given ample opportunity to review any proposed abstract, manuscript, or slide presentation before its submission. This review is required to ensure that the sponsor is aware of all written and oral presentations of the data and does not imply any editorial review or restriction of the contents of the presentation or use.

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8 APPENDICES

8.1 Blinding Index Questionnaire

Version: For Subject to Complete

Sponsor and Protocol Number: _____

Subject Number: _____

Instructions: Now that you have completed this study, we want to ask your opinion about which treatment (real medication or placebo) you believe was administered to you in this clinical trial. Read all of the answer choices before circling your one answer to each question. There are no right or wrong answers. Your honest answers will be helpful for current and future research.

1. Which treatment do you believe you received? (CIRCLE ONE)
    a. Strongly believe I received real medication
    b. Somewhat believe I received real medication
    c. Somewhat believe I received the placebo
    d. Strongly believe I received the placebo
    e. I don't know

2. **If you answered "Don't know" above**, please provide your best guess of the treatment you received in this clinical trial:

    (CIRCLE ONE)

    a. I received the real medication
    b. I received placebo

3. In your own words, please describe the primary reason you believe you received this treatment?

This questionnaire was developed with primary reference from Bang H, Flaherty SP, Kolahi J, Park J. Blinding assessment in clinical trials: A review of statistical methods and a proposal of blinding assessment protocol. Clin Res Regul Aff. 2010;27:42-51.

8.2 Otoscopy Assessment of the Appearance of the Tympanic Membrane

Otoscopy will be performed by the physician investigator to assess the appearance of the TM in both ears regardless if AOM is bilateral or unilateral. Appearance of the TM will be evaluated for contour, color, fluid, and translucency as follows:

- Contour will be assessed using 1 of the following categories:
    - Normal
    - Retracted
    - Full
    - Bulging
    - Perforated
    - Not assessable

  The categorisation in normal/abnormal will be as follows:
    - Normal = normal
    - Abnormal = retracted, full, bulging, or perforated
- Color will be assessed using 1 of the following categories:
    - Normal
    - Partly red
    - Completely red
    - Not assessable

  The categorisation in normal/abnormal will be as follows:
    - Normal = normal
    - Abnormal = partly red or completely red
- Fluid will be assessed using 1 of the following categories:
    - No
    - Yes; if yes, color of fluid will be rated as yellow, translucent, red, blue, black, or not assessable.

  The categorisation in normal/abnormal will be as follows:
    - Normal = no
    - Abnormal = yes
- Translucency will be assessed using 1 of the following categories
    - Translucent
    - Semi-opaque
    - Opaque

- Not assessable

The categorisation in normal/abnormal will be as follows:

- Normal = translucent
- Abnormal = semi-opaque or opaque

For appearance of the TM, 80% CIs will be calculated for the incidence of shifts from Baseline (0-60 minutes), from normal to abnormal for the right ear and, separately, for the left ear. If significance is found using 80% CIs, 90% and 95% CIs will also be tested. A table presenting all changes from Baseline (from/to normal from/to abnormal) will be summarised by treatment for all observed timepoints.

8.3 Device Experience Questionnaire-Study Staff Administering Treatment

For Clinical Staff

Thank you for completing the study activity.
Please rate your agreement to the following statements and circle your response.

1. My first reaction to the study inhaler was positive.

Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

2. The study inhaler Instructions for Use were clear and easy to follow.

Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

3. If I was not instructed, I feel confident that I could have used the product without instruction.

Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

4. The study inhaler is easy to use.

Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

5. It was easy to place the study inhaler in the nostril.

Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

6. It was easy to press down on the study inhaler.

Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

7. Other comments.

Thank you, please hand the questionnaire back to the Principal Investigator.

Staff ID		Site No.		Date	

For Trial Subjects

Thank you for completing the study activity.

Please rate your agreement to the following statements and circle your response.

1. My first reaction to the study inhaler was positive.

Strongly Disagree | Disagree | Neutral | Agree | Strongly Agree

Comments:

2. The study inhaler was comfortable in my nostril.

Strongly Disagree | Disagree | Neutral | Agree | Strongly Agree

Comments:

3. The spray had a pleasant taste or aroma.

Strongly Disagree | Disagree | Neutral | Agree | Strongly Agree

Comments:

4. There was no discomfort or irritation from the spray inside of the nose.

Strongly Disagree | Disagree | Neutral | Agree | Strongly Agree

Comments:

5. Other comments.

Thank you, please hand the questionnaire back to the Principal Investigator.

Subject No. | **Site No.** | **Date**