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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STATISTICAL ANALYSIS PLAN

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 Version: Final, 10 Jul 2018, Administrative Change Number 1.0 Version 1.0, 15Nov2018

Protocol Number: OP0201-C-004

Statistical Analysis Plan Author: [redacted]

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Study Phase: Phase 1

Product: OP0201

Indication: Acute Otitis Media

Sponsor: Novus Therapeutics, Inc.
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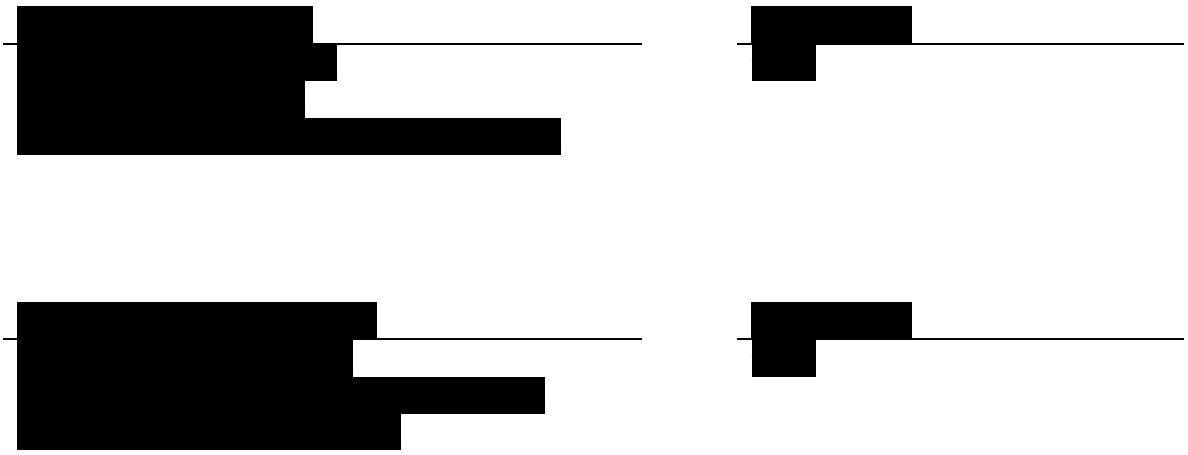
CONFIDENTIALITY STATEMENT

APPROVALS



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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	adverse event
AOM	acute otitis media
ATC	Anatomical-Therapeutic-Chemical
BMI	body mass index
CGI-I	Clinical Global Impressions Scale: Global Improvement
CI	confidence interval
CSR	Clinical Study Report
eCRF	electronic case report form
ENT	ear, nose, and throat
EOS	end of study
FCS	fully conditional specification
GEE	generalized estimating equations
GLM	general linear model
ICH	International Conference on Harmonisation
LS	least squares
MAR	missing at random
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
MNAR	missing not at random
N/A	not applicable
NRS-11	Numeric Rating Scale-11
OM	otitis media
OP0201	OP0201 nasal aerosol
PGIC	Patient Global Impression of Change
PID	Pain Intensity Difference
PT	Preferred Term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	standard error
SOC	System Organ Class
SPID	Sum Pain Intensity Difference
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TFLs	tables, figures, and listings
TM	tympanic membrane
VAS	visual analog scale
WHO-DD	World Health Organization Drug Dictionary

PREFACE

The purpose of this statistical analysis plan (SAP) is to outline the planned analyses and reporting to support the completion of the Clinical Study Report (CSR) for Novus Therapeutics Protocol OP0201-C-004. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Also, exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP will be clearly identified in the CSR.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the United States of America Food and Drug Administration and International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use : Guidance on Statistical Principles in Clinical Trials.[1] All work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association[2] for statistical practice.

The following documents were also considered in preparation for writing this SAP:

- Clinical Research Protocol OP0201-C-004, Final, 10 Jul 2018, Administrative Change Number 1.0 Version 1.0, 15Nov2018
- ICH E3 Guideline: Structure and Content of Clinical Study Reports[3]
- ICH E6 Guideline on Good Clinical Practice[4]
- ICH E8 General Considerations for Clinical Trials[5]
- ICH E9 Statistical Principles for Clinical Trials[6]
- Statistical Analysis Plans: Principles and Practice[7]

The SAP is a supplement to the study protocol, which should be referred to for additional details on study design, study conduct, and other operational aspects of the study.

1. BACKGROUND

Novus is developing OP0201 nasal aerosol ("OP0201"), a non-antibiotic and non-analgesic combination product intended to treat and prevent otitis media (OM). This study will evaluate the safety and immediate (within 60 minutes) reduction of ear pain caused by acute OM (AOM) in adults following a single intranasal dose of OP0201 20 mg.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to assess the safety of intranasal OP0201 20 mg compared to placebo.

2.2 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 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
- To evaluate Study Participant experience with the device as measured by the Device Experience, Questionnaire-Study Participant
- To evaluate study staff experience with the device as measured by the Device Experience Questionnaire-Study Staff Administering the Treatment

3. STUDY DESIGN

This is a single-dose, double-blind, placebo-controlled, randomized, parallel-group, proof-of-concept study to evaluate the safety and reduction of ear pain in adults with AOM. All study-related procedures, including screening, will be performed on Day 1. Assessment time points on Day 1 will be 10, 20, 30, and 60 minutes post dose. A safety follow-up call will occur on Day 7. The Schedule of Assessments is in Appendix A.

4. TREATMENT GROUPS AND STUDY ENDPOINTS

4.1 Treatment Group Comparisons

The treatment groups to be compared are OP0201 and placebo.

4.2 Study Endpoints

4.2.1 Primary Endpoints

Primary endpoints are related to safety:

- Incidence, seriousness, severity, and relatedness to study treatment of adverse events (AEs) recorded over 60 minutes post dose and at Day 7
- Change from Baseline in vital signs (oral temperature, respiratory rate, pulse, blood pressure) at 60 minutes post dose
- Change from Baseline in ear, nose, and throat (ENT) examination (otoscopy of the ear, nose, and oropharynx) findings at 60 minutes post dose
- Change from Baseline in the appearance of the tympanic membrane (TM) (contour, color, fluid, translucency) as measured by otoscopy at 60 minutes post dose

4.2.2 Exploratory Endpoints

Exploratory endpoints are related to efficacy and success of blinding:

- Response on ear pain scores at 10, 20, 30, and 60 minutes post dose using the VAS and the NRS-11
- Pain Intensity Difference (PID) from Baseline of the VAS and the NRS-11 at 10, 20, 30, and 60 minutes post dose
- Sum Pain Intensity Difference (SPID) of the VAS and the NRS-11 over 60 minutes post dose
- Time to ear pain relief in affected ear(s), recorded as change from moderate/severe pain to mild or no pain using the VAS and the NRS-11
- PGIC measured at 10, 20, 30, and 60 minutes post dose
- CGI-I scale measured at 60 minutes post dose
- Presence of AOM symptoms
- Response on the Blinding Index at 60 minutes post dose
- Response on Device Experience Questionnaire – Subject
- Response on Device Experience Questionnaire – Study Staff Administering Treatment

5. SAMPLE SIZE

Approximately 24 Study Participants will be randomized. Additional Study Participants will be randomized for Study Participants who discontinue the study prematurely.

6. TREATMENT ASSIGNMENT, BLINDING, AND UNBLINDING

6.1 Treatment Assignment

Following Screening, but before any treatment-related procedures, eligible Study Participants will be randomly assigned in a 1:1 ratio to either:

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

A fixed block size of 4 will be used. A sufficient number of extra randomization slots will be generated to allow for additional randomizations due to Study Participant discontinuations. The randomization scheme will be executed by an independent third-party vendor. Study treatment kit numbers will be assigned via Interactive Response Technology.

6.2 Blinding

Study treatment kits will be packaged and labeled by Catalent Pharma Solutions (Kansas City, MO, USA) in accordance with applicable national laws. Kits containing OP0201 or placebo will be identical in appearance. All clinical staff and Study Participants will be blinded to the assigned treatment.

6.3 Unblinding

If a serious AE (SAE) occurs during the study that meets the criteria for expedited reporting (i.e., is a Suspected Unexpected Serious Adverse Reaction), the Study Participant will be unblinded by Worldwide Clinical Trials pharmacovigilance. In an emergency situation, the investigator may unblind the Study Participant's treatment assignment.

7. ANALYSIS POPULATIONS

Screening Population: Study Participants who signed an Informed Consent Form and completed any screening procedures.

Randomized Population: Study Participants randomized prior to dosing. Study Participants will be summarized and analyzed per randomization assignment, regardless of treatment actually received.

Safety Population: Study Participants who received at least one spray of study treatment in either nare. Study Participants will be summarized and analyzed per treatment actually received, regardless of randomization assignment.

8. REPORTING AND ANALYSIS CONVENTIONS

8.1 Programming Environment

SAS® version 9.4 or higher (SAS Institute, Cary, North Carolina) will be used for statistical analyses and the production of tables, figures, and listings (TFLs).

8.2 Reporting Conventions

Tables of contents for TFLs to be produced are shown in Appendix B. TFLs will be appended to the final CSR. The following reporting conventions will be followed:

- Font size is to be no smaller than 9pt.

- Titles and footnotes must appear on every page of the TFL.
- Treatment group names and order in tables and figures will be Placebo, OP0201 (20 mg). Some tables and figures may also display All Study Participants as a third grouping.
- Tables and figures will present summaries/analyses by study time point or analysis visit window, as appropriate.
- Table column headers and figure legends will include subgroup sample sizes ("N = xx"). Sample sizes reported as part of descriptive statistics ("n") will be the number of non-missing observations.
- Listings will be produced for all study population, safety, and efficacy data collected, either on the electronic case report form (eCRF) or through third-party vendors, and will be ordered by unique subject identifier, parameter, date, data collection time if applicable, nominal study visit, and analysis visit window if applicable (see Section 8.7).

8.3 General Analysis Conventions

Categorical variables will be summarized using frequencies and percentages. Percentages will be reported to one decimal place. Unless otherwise noted in Section 11, categorical variables will be analyzed using chi square tests of association or, if any contingency table cell has less than 5 subjects, Fisher's exact test.

Continuous variables will be summarized using descriptive statistics (e.g., n, mean, standard deviation, least-squares mean with standard error, distribution percentiles, range). The number of decimal places for minimums and maximums will be the same as the original data. The number of decimal places for means, medians, and interquartile ranges will be the same as the original data plus one. The number of decimal places for measures of variance will be the same as the original data plus two. Unless otherwise noted in Section 11, continuous variables will be analyzed using t-tests or a non-parametric alternative.

Data with qualifiers (e.g., "<") will be listed with but summarized without the qualifier.

P-values will be presented in summary tables to two decimal places if > 0.01, to three places if < 0.01 but > 0.001, and to four places if < 0.001 but > 0.0001. However, p-values > 0.045 but < 0.055 will also be presented to three decimal places. P-values < 0.0001 will be presented as "< 0.0001."

Statistical tests will be two-sided and tested at the 0.20, 0.10, and 0.05 significance levels in a hierarchical manner.

8.4 Subgroups

There are no planned analyses by subgroups.

8.5 Missing Data

Listings will present data as reported. Missing or partially missing dates that are required for date-dependent definitions (e.g., treatment-emergent AEs, concomitant medications) will be assumed to be the most conservative date possible. For example, an AE with a completely

missing start date will be considered treatment-emergent. Missing observations will not be imputed for summaries. Handling of missing observations for statistical inference is described in Section 13.1.4.

8.6 Study Period and Time Point Definitions

Screening: Day 1 up to dosing.

Baseline Observation: for a given parameter for a given randomized Study Participant, the last observed value before the first dose of study treatment or planned first dose of study treatment if not dosed.

Study Day 1: for a given randomized Study Participant, the day of actual first dose of study treatment or planned first dose of study treatment if not dosed.

Study Day:

- Study day = date of assessment – date of dosing + 1, for assessments on or after first dose
- Study day = date of assessment – date of dosing, for assessments before first dose

Study Time: time of assessment – time of first dose

Duration:

- Duration in days = end date – start date + 1
- Duration in minutes = end time – start time

(Nominal Visit) Analysis Time Point: analysis based on data collected at the *(nominal visit)* time point, where nominal visits are as shown below in Section 8.7.

End of Study (EOS), Study Participant-Level: the date of completion of the last planned study visit or date of discontinuation for any reason.

EOS, Study-Level: the date when all randomized Study Participants have reached Study Participant-Level EOS.

8.7 Visit Windows

Visit windows are based on Study Day and Study Time. Observations will be assigned to an analysis window according to the tables below. Observations that cannot be assigned to an analysis window based on the tables below will be excluded from summaries and analyses (but will still be listed). For Study Participants not dosed, planned date and time of first dose will be used in Study Day/Time calculations, if necessary.

For NRS-11, VAS, and PGIC on Study Day 1:

Nominal Visit	Min Study Time Per Protocol	Max Study Time Per Protocol	Min Study Time for Analyses	Max Study Time for Analyses
Screening/Baseline	N/A	< 0	N/A	< 0
Day 1, Minute 10	10	10	0	14
Day 1, Minute 20	20	20	15	24
Day 1, Minute 30	30	30	25	44
Day 1, Minute 60	60	60	45	75

N/A, not applicable

For all other assessments on Study Day 1:

Nominal Time Point	Min Study Time Per Protocol	Max Study Time Per Protocol	Min Study Time for Analyses	Max Study Time for Analyses
Screening/Baseline	N/A	< 0	N/A	< 0
Day 1, Minute 60	60	60	45	75

N/A, not applicable

If multiple valid, non-missing observations exist within a given window, the observation to be used will be:

1. the observation closest to the nominal visit in question, or
2. the latest observation if the multiple observations are equidistant from the nominal visit, or
3. the average (arithmetic or geometric, as appropriate) of the observations if the multiple observations have the same actual time point.

9. STUDY POPULATION

The study population will be described by the parameters below. Listings and summaries will be based on the Randomized Population unless otherwise noted.

9.1 Study Participant Disposition

Frequencies and percentages of Study Participants who discontinued the study treatment and/or study will be summarized. Reasons for discontinuation will also be summarized. The listing of Study Participant disposition will include dates and times (if applicable) of randomization, dosing, and EOS; and reasons for study treatment and/or study discontinuation (if applicable). Reasons for screen failure will be summarized separately.

9.2 Eligibility and Informed Consent

Eligibility and informed consent parameters will include protocol version (all subjects were enrolled under Final, 10 Jul 2018, Administrative Change Number 1.0 Version 1.0, 15Nov2018), date of informed consent, and inclusion criteria met or exclusion criteria not met. Satisfaction of

inclusion/exclusion criteria will be summarized. Screen failures will be listed and summarized separately; the summary will include broad reason for screen failure.

9.3 Protocol Deviations

In addition to the listing of eligibility detailed in Section 9.2, a separate listing will show all other protocol deviations and will include protocol version and the category of the deviation (to be determined). Frequency and percentage of subjects in each deviation category will be summarized.

9.4 Analysis Populations

The analysis populations defined in Section 7 will be described in terms of the identification of Study Participants in each population and the frequency distribution of each population. Number of screened Study Participants will be the denominator for percentage of randomized Study Participants, and number of randomized Study Participants will be the denominator for percentage of Study Participants in the Safety Population.

A listing of analysis populations will be produced using the Randomized Population only and will show the analysis population(s) to which each Study Participant belonged.

9.5 Demographic and Baseline Characteristics

Demographic and other baseline characteristics will be summarized, both overall and by treatment group, for the Safety Population. Parameters will include study site, sex, age at informed consent, race, ethnicity, fertility status (women only), and measurements of weight and height, and body mass index (BMI) at screening.

9.6 Medical History

Reported medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.1 or later, to a System Organ Class (SOC) and Preferred Term (PT). Medical history, including SOCs and PTs, will be listed but not summarized. A separate listing will detail prior experience using an intranasal device.

9.7 Physical Examination

Physical examination findings for each body system will be summarized. Of note, abnormal findings are to be recorded in the eCRF as medical history.

9.8 Urine Pregnancy Test

Results from the urine pregnancy test will be listed but not summarized and will be limited to female Study Participants. If a female Study Participant is not of childbearing potential, this will be indicated in the listing in place of the test result.

10. TREATMENTS

Treatments include study treatment, prior medications, and concomitant medications.

10.1.1 Study Treatment Exposure

Total exposure will be expressed as number of sprays and will be summarized both per nostril and overall. Listings and summaries will be based on the Safety Population.

10.1.2 Prior and Concomitant Medications

Medication use from 2 weeks prior to screening to EOS will be coded to generic terms, including 2nd-level Anatomical-Therapeutic-Chemical (ATC) drug class, using the World Health Organization Drug Dictionary (WHO-DD), version September 2018 or later. Aside from parameters collected on the eCRF, listings will include date and time of study treatment dosing, WHO-DD drug class and preferred drug name, and Study Day. Frequencies and percentages of subjects reporting or receiving each medication will be summarized by WHO-DD drug class and preferred name within drug class.

Medications that were stopped prior to study treatment dosing will be considered "prior" medications," medications that were stopped earlier than 2 weeks before screening will be ignored, and all other medications will be considered "concomitant." Medications recorded with insufficient exposure dates to determine whether or not they were concomitant will be considered concomitant.

Prior medications will be listed and summarized separately from concomitant medications. Listings and summaries for prior medications will be based on the Randomized Population. Listings and summaries for concomitant medications will be based on the Safety Population.

11. SAFETY PARAMETERS

Safety parameters will be listed for the Randomized Population and summarized for the Safety Population unless otherwise noted.

11.1 AEs

AEs reported from time of first dose through EOS will be coded according to MedDRA® version 21.1 or later. Each reported AE will be mapped to a PT and SOC. Aside from parameters collected on the eCRF, listings will include date and time of study treatment dosing, MedDRA PT and SOC, Study Day, whether or not the AE is ongoing, AE duration, and whether or not the AE resulted in study discontinuation. For AEs that are ongoing, AE end date will be imputed with subject-level EOS date for the duration calculation.

A treatment-emergent AE (TEAE) will be defined as an AE that began or worsened during or after study treatment dosing on Day 1 and no later than on Day 2. AEs with insufficient date or time information to determine whether or not they were treatment-emergent will be considered treatment-emergent. AEs that began or worsened in severity from Day 3 through EOS will be defined as non-treatment-emergent. AEs that began or worsened in severity before first dose will be recorded as medical history.

All TEAEs will be listed. In addition, separate listings will be done for:

- Treatment-emergent SAEs (TESAEs), to include seriousness criteria
- TEAEs that resulted in study treatment interruption or dose reduction

- TEAEs that results in discontinuation from the study or study treatment (excluding deaths)
- TEAEs that resulted in death
- Non-treatment-emergent AEs

Listings will be done for the Safety Population.

Incidence of all TEAEs will be summarized by SOC and PTs within SOCs, sorted alphabetically by SOC and PT within SOC unless otherwise noted. In addition, separate summaries will be done for:

- TEAEs assessed as related to study treatment
- TEAEs by maximum severity, with both SOCs and PTs within SOCs sorted by descending incidence among all Study Participants combined
- TESAEs
- TESAEs assessed as related to study treatment

In summaries by relationship to study treatment and maximum severity, missing relationship will be considered related and missing severity will be considered severe. Only the most related TEAE per subject for a given PT will be counted in summaries by relationship; similarly, only the most severe TEAE will be counted in summaries by severity.

An overall summary of TEAEs (collapsed over all SOCs and PTs) will show incidence of all TEAEs as well as:

- TEAEs assessed as related to study treatment
- TESAEs
- TESAEs assessed as related to study treatment
- Severe TEAEs
- Moderate TEAEs
- TEAEs that resulted in death
- TEAEs that resulted in study treatment interruption or dose reduction
- TEAEs that results in discontinuation from the study or study treatment (excluding deaths)

Summaries of TEAEs and TESEAs (separately) in descending order of incidence among all Study Participants combined will show incidence of PTs only.

11.2 ENT Examination

ENT examination will be done at Baseline and 60 minutes post dose (or early termination). Findings are expressed as normal, abnormal not clinically significant, and abnormal clinically significant and will be summarized separately for ear, nose, and oropharynx at each time point. A shift table will summarize changes from baseline to 60 minutes post dose.

11.3 Otoscopy

Otoscopy assessment of TM appearance will be done at Baseline and 60 minutes post dose (or early termination). Findings for contour, color, fluid behind the TM, and translucency will be summarized separately for right and left ear at each time point.

Shift tables will summarize changes from baseline to 60 minutes post dose in normal/abnormal status, with "abnormal" defined as follows:

- Contour: retracted, full, bulging, or perforated
- Color: partly or completely red
- Fluid behind the TM: yes
- Translucency: semi-opaque or opaque

11.4 Vital Signs

Vital signs will be collected at Baseline and at 60 minutes post dose (or early termination). Observed values for oral temperature, respiratory rate, pulse, and systolic and diastolic blood pressure will be summarized at each time point. Changes from baseline will also be summarized for each post baseline time point. Listings will include changes from baseline.

Incidence of clinically meaningful changes from baseline to 60 minutes post dose will be summarized, with clinically meaningful changes defined as follows:

- 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

12. EXPLORATORY PARAMETERS

Exploratory parameters will be listed for the Randomized Population and summarized for the Safety Population.

12.1 Efficacy Parameters

12.1.1 VAS and NRS-11

Ear pain will be measured by VAS and NRS-11. Scores will be collected for each ear at Baseline and 10, 20, 30, and 60 minutes post dose.

The VAS consists of a 100 mm line anchored by 2 extremes of pain, with the left anchor representing "no pain" and the right anchor representing "worse pain." Study Participants mark the line where their pain is best represented between the 2 anchors. The VAS score is the distance from the left anchor to the Study Participant's mark.

NRS-11 pain scores range from 0 to 10, with 0 representing "no pain" and 10 representing the "worst pain possible." NRS-11 ≥ 5 reflects moderate to severe pain and is an inclusion criterion.

Listings will show observed values and absolute changes from baseline for each ear separately, for the sum over both ears, and for the maximum score across both ears. For both VAS and NRS-11, decreasing change scores from baseline indicate improvement and this will be footnoted in TFLs.

Endpoints

The following endpoints will be calculated for both VAS and NRS-11, unless otherwise indicated, using (a) the sum of scores over both ears, and (b) the maximum score across both ears:

- PID_{t_i} where i = 1 to 4 and t_1, t_2, t_3, t_4 = 10, 20, 30, and 60 minutes post dose, respectively, and PID_{t_i} = score at time t_i – score at baseline (ie, change from baseline).
- $SPID_{t\_I}$ defined as

$$SPID_{t\_I} = \sum_{i=1}^{I} PID_{t\_i}\,(t_i - t_{i-1})$$

  where I = 1 to 4, t_0 is baseline, and t_1, t_2, t_3, t_4 are time points 10, 20, 30, 60 minutes post dose, respectively. For example, $SPID_2$ is the sum of changes from baseline at 10 and 20 minutes post baseline weighted by time (in minutes) since the previous measurement.
- Percent change from baseline (per inclusion criteria, baseline VAS and NRS-11 are unlikely to be 0).
- Presence of any pain, defined as score > 0 at 10, 20, 30, and 60 minutes post dose.
- Improvement categorized as "worsening" (positive change score), "no change" (0 change score), "improvement" (negative change score) at 10, 20, 30, and 60 minutes post dose.
- Time to pain relief defined as time point (10, 20, 30, 60 minutes post dose or no pain relief) at which relief was achieved, where "relief" is defined as score < 5 for NRS-11 and at least a 30 mm decrease from baseline for VAS. In the unlikely event that a Study Participant has a baseline VAS less than 30 mm, they will be excluded from the VAS analysis of time to pain relief.
- Response, defined as a 25%, 50%, and 75% reduction in score, at 10, 20, 30, and 60 minutes post dose.

Summaries and Analyses (see Section 13)

- PID_{t_i} will be analyzed using mixed model for repeated measures (MMRM). A summary table will include least-squares (LS) means and standard errors (SEs) for each treatment group and the estimate of treatment group difference with 80, 90, and 95% confidence intervals (CIs) for the difference and associated p-values. LS means and SEs will also be graphically displayed using a line chart. In addition, 80, 90, and 95% CIs and associated p-values for within-group mean changes from baseline will be included in the summary table.

- $SPID_{t\_I}$ will be analyzed using mixed model for repeated measures (MMRM). A summary table will include least-squares (LS) means and standard errors (SEs) for each treatment group and the estimate of treatment group difference with 80, 90, and 95% confidence intervals (CIs) for the difference and associated p-values. LS means and SEs will also be graphically displayed using a line chart. In addition, 80, 90, and 95% CIs and associated p-values for within-group mean changes from baseline will be included in the summary table.
- Response will be analyzed using general estimating equations (GEE). A summary table will include LS means and SEs for each treatment group and the estimate of treatment group difference with 80, 90, and 95% CIs for the difference and associated p-values. Crude response rates will be graphically displayed using a bar chart.
- Percent change from baseline, presence of pain, improvement category, and time to pain relief will be summarized in tables but will not be subjected to statistical inference.

12.1.2 PGIC and CGI-I

PGIC scores will be collected at 10, 20, 30, and 60 minutes post dose. Study Participants will be asked "How have your symptoms been since you 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.

CGI-I score will be collected at 60 minutes post dose. Physician investigators will be asked "How has the subject's symptoms been since they received the study treatment?" The score range and meaning of each score are the same as for PGIC described above.

Listings will show observed values. Lower scores indicate better symptom status and this will be footnoted in TFLs.

Endpoints

The following endpoints will be calculated for both PGIC and CGI-I at each time point collected:

- Observed value.
- Response, defined as much improved or very much improved.

Summaries and Analyses (see Section 13)

- PGIC observed value will be analyzed using MMRM with baseline NRS-11 as a covariate. A summary table will include LS means and SEs for each treatment group and the estimate of treatment group difference with 80, 90, and 95% CIs for the difference and associated p-values. LS means and SEs will also be graphically displayed using a line chart. Frequency distributions of observed responses will also be summarized.
- CGI-I observed valued will be analyzed using GLM with baseline NRS-11 as a covariate. A summary table will include LS means and SEs for each treatment group and the estimate of treatment group difference with 80, 90, and 95% CIs for the difference and associated p-values. Frequency distributions of observed responses will also be summarized.
- Response will be analyzed using GEE with baseline NRS-11 as a covariate (if convergence can be achieved). A summary table will include LS means and SEs for each treatment group

and the estimate of treatment group difference with 80, 90, and 95% CIs for the difference and associated p-values.

12.1.3 AOM Symptoms

AOM symptoms are tinnitus, dizziness, vertigo, and feeling of fullness or muffled hearing in the ear. Presence/absence of each AOM symptom will be collected at Baseline and 60 minutes post dose.

Endpoints

The endpoint for each symptom will be presence of the symptom.

Summaries and Analyses

- Presence of each symptom will be summarized but not subjected to statistical inference.

12.2 Blinding Index

Success of blinding will be measured by the Bang Blinding Index.[8] Success of blinding will be measured for both physician investigators and Study Participants at the completion of Day 1 assessments but prior to administering the Device Experience Questionnaire. Study Participants will be asked to guess which treatment they received and will be asked for a "best guess" if they respond "I don't know." Similarly, physician investigators will be asked to guess which treatment the Study Participant received. Reason(s) for responses given will be entered into the eCRF as free text.

The Blinding Index will be listed and summarized for Study Participants in the Safety Population, separately for Study Participants and physician investigators.

Endpoints

The endpoint will be response to the question "Which treatment do you believe you received?"or, for physician investigators, "Which treatment do you believe the subject received?" The possible responses are:

1 = strongly believes real medication was received
2 = somewhat believes real medication was received
3 = somewhat believes placebo was received
4 = strongly believes placebo was received
5 = doesn't know

If the response is "don't know," the respondent is asked to provide their best guess as to which treatment, real medication or placebo, was received.

Summaries and Analyses

The Bang Blinding Index for the ith treatment group, i = 1 for OP0201 and 2 for placebo, will be calculated as

$$P_{1|i} + w_{2|i}(P_{2|i}) + w3_{1|i}(P3_{1|i}) - P_{3|i} - w_{4|i}(P_{4|i}) - w3_{2|i}(P3_{2|i})$$

where:

$P_{j|i}$ = probability of response j, j = 1 to 4, given treatment i was assigned, estimated by $n_{ij}/n_{.j}$ where n_{ij} is the number of Study Participants in the ith treatment group who gave response j and $n_{.j}$ is the total number of Study Participants who gave response j.

$P3_{k|i}$ = probability of response k to the "best guess" question, k = 1 to 2 with 1 = real medication and 2 = placebo, given treatment i was received, estimated by $n_{ik}/n_{.k}$ where n_{ik} is the number of Study Participants in the ith treatment group who gave response k and $n_{.k}$ is the total number of Study Participants who gave response k.

$w_{j|i}$ = weights for $P_{j|i}$, suggested by Bang to be set to 0.5.

$w3_{k|i}$ = weights for $P3_{k|i}$ suggested by Bang to be set to 0.25.

The range of the blinding index is -1 to 1, with 0 equating to random guessing, 1 to complete unblinding, and -1 to complete wrong guessing. Thus, a lower bound of the blinding index 95% CI that is greater than 0 would be suggestive of at least partial unblinding.

The variance of the blinding index and resulting 95% CI will be calculated using the statistical software package STATA[9] or by using code written for R provided by Bang (personal correspondence).

12.3 Device Experience Questionnaire

Experience with the device during the study will be measured by the Device Experience Questionnaire and will be collected from both physician investigators and Study Participants at the completion of all Day 1 assessments. Data collection will be external to the eCRF. Any study staff who administered treatment to Study Participants will also complete the Device Experience Questionnaire one time only (not for each Study Participant treated). These data will be summarized but not subjected to statistical inference.

13. STATISTICAL METHODS

13.1.1 Methods of Analysis for Repeated Continuous Endpoints

Treatment group comparisons on endpoints that are continuous variables assessed repeatedly will be done using MMRM with change from baseline as the dependent variable; nominal visit (time), treatment group, and treatment-by-time interaction as fixed effects; baseline observation as a fixed-effect covariate (if applicable); and correlated errors within subject. Site will be included as a random effect if doing so appreciably affects treatment effect estimates. Covariance estimation will be done using restricted maximum likelihood. Error degrees of freedom will be calculated using the Kenward-Rogers approximation. Unstructured covariance for the residuals (R matrix) will initially be specified but other covariance structures may be explored by examining the R matrix and using goodness-of-fit measures (e.g., Akaike's Information Criterion). If a structured covariance is used, the sandwich estimator will be used for SEs and error degrees of

freedom will be calculated using the between-within method. Model-based LS means will be reported for each treatment group, along with CIs and p-values for treatment group comparisons, for each nominal visit. A p-value for treatment group comparison over all visits will only be reported if there does not appear to be a treatment-by-time interaction, either based on the interaction p-value or by a descriptive examination of the data, and the term for treatment-by-time interaction will not be included in the model.

Model assumptions will be evaluated using diagnostic tools such as Q-Q and scatter plots of residuals, and sensitivity analyses using alternative methods (e.g., rank-based, GLM at individual time points) will be considered if there appear to be substantial deviations from model assumptions. Outlier assessment will be done using visual inspection (e.g., box-and-whisker plots) and potential outliers will be investigated for data entry accuracy and biological consistency. If unexplainable outliers are present, a sensitivity analysis may be done excluding the outliers to assess their effect on the analysis conclusion.

Within-group analyses of changes from baseline on endpoints that are continuous variables assessed repeatedly will also be done using MMRM with observed value as the dependent variable, nominal visit (time) as a fixed effect, and correlated errors within subject. Model-based means will be reported for each treatment group, along with CIs and p-values, for each post-baseline nominal visit.

13.1.2 Method of Analysis for Non-Repeated Continuous Endpoints

Treatment group comparisons on endpoints that are continuous variables not assessed repeatedly will be done using GLM with change from baseline as the dependent variable, treatment group as an independent variable, and baseline observation as a covariate (if applicable). Model-based LS means will be reported for each treatment group, along with CIs and p-values for treatment group comparisons.

Model assumptions will be evaluated using diagnostic tools such as Q-Q and scatter plots of residuals, and sensitivity analyses using alternative methods (e.g., rank-based) will be considered if there appear to be substantial deviations from model assumptions. Outlier assessment will be done using visual inspection (e.g., box-and-whisker plots) and potential outliers will be investigated for data entry accuracy and biological consistency. If unexplainable outliers are present, a sensitivity analysis may be done excluding the outliers to assess their effect on the analysis conclusion.

A random effects linear model will be used to assess the impact of site, as a random effect, on treatment effect estimates. If the effect is appreciable, a random effects model will be used in place of GLM.

13.1.3 Method of Analysis for Repeated Binary Endpoints

Treatment group comparisons on binary endpoints assessed repeatedly will be done using GEE with nominal visit (time) and treatment group as main effects, treatment-by-time as an interaction term, an appropriate baseline value as a covariate (if applicable); and correlated errors within subject.

The working correlation structure will initially be specified as unstructured but other structures may be explored by examining the covariance matrix and using goodness-of-fit measures (e.g., Quasilikelihood under the Independence model Criterion). P-values for treatment group comparisons will be reported for each nominal visit. A p-value for treatment group comparison over all visits will only be reported if there does not appear to be a treatment-by-time interaction, either based on the interaction p-value or by a descriptive examination of the data, and the term for treatment-by-time interaction will not be included in the model.

Alternative approaches for the analysis of binary endpoints, such as random-effects models (including site as a random effect if doing so appreciably affects treatment effect estimates), chi squares tests of association or Fisher's exact tests, may be considered.

13.1.4 Missing Observations

One of the assumptions of MMRM is that missing observations are missing at random (MAR), i.e., missingness is unrelated to the variable for which the observation is missing but can be related to another variable on which data have been collected. This assumption is not testable. However, given the short time frame of data collection for exploratory endpoints (60 minutes), it is unlikely that data will be missing not at random (MNAR). It is also unlikely that a substantial proportion (> 10%) of Study Participants will have missing observations. Therefore, the MAR assumption will be considered adequate to address any missing observations for variables analyzed using MMRM.

GEE assumes missing observations are missing completely at random (MCAR); i.e., missingness is independent of all other information whether it was collected or not. Again, due to the short time frame of data collection, this assumption will be considered adequate.

If > 10% of Study Participants have missing observations for a given endpoint, multiple imputation may be used for sensitivity analyses. Under an MNAR model, imputations will be based only on subjects randomized to placebo. The imputation method will be fully conditional specification (FCS) regression with 25 imputations. The imputer's model will include observed values at each time point included in the analysis, including baseline if applicable.

13.1.5 Multiplicity

There will be no adjustments for type 1 error inflation due to multiplicity.

14. SEQUENCE OF PLANNED ANALYSES

14.1 Final Analysis

The only planned analysis is the final analysis, which will occur after study-level EOS, all clinical data have been entered into the data capture system, AE and concomitant medication data have been coded, quality control checks have been completed, all data queries have been resolved, protocol deviations have been identified, and the database has been locked.

15. CHANGES FROM THE PROTOCOL

Protocol	Change
Primary endpoints: AEs recorded over 60 min post dose and at Day 7	Incidence, seriousness, severity, and relatedness to study treatment of adverse events (AEs) recorded over 60 minutes post dose and at Day 7
Change from Baseline in the VAS and the NRS-11 listed as an exploratory endpoint.	Change from Baseline removed as an exploratory endpoint (same as PID).
AOM symptoms and Device Experience Questionnaire were included as "exploratory objectives" but were not stated as "exploratory endpoints."	The following endpoints were added as exploratory endpoints: • Presence of AOM symptoms • Response on Device Experience Questionnaire – Subject • Response on Device Experience Questionnaire – Study Staff Administering Treatment
Data listings will be sorted by treatment, subject number, and time point unless otherwise noted.	Listings….will be ordered by unique subject identifier, parameter, date, data collection time if applicable, nominal study visit, and analysis visit window if applicable.
Site included as a fixed effect in mixed models.	Site included as a random effect if doing so appreciably affects treatment effect estimates.
Only observed cases will be included in the PID computations.	If > 10% of Study Participants have missing observations for a given endpoint, multiple imputation may be used for sensitivity analyses.
SPID will be analysed using a linear model analysis of variance (ANOVA) with fixed effects for treatment, site, and baseline pain score. Missing data will be handled using the Last Observation Carried Forward imputation method.	SPID will be analyzed using MMRM. Site will be included as a random effect if doing so appreciably affects treatment effect estimates. If > 10% of Study Participants have missing observations for a given endpoint, multiple imputation may be used for sensitivity analyses.
For ear pain: Hodges-Lehmann point estimate and 80% 2-sided CI for the median of treatment effect differences between active and placebo will be provided. Statistical comparisons of ear pain, as measured by the VAS and the NRS-11,	There is no separate analysis for "ear pain"; covered by analyses of VAS and NRS-11.

between the treatments at 60 min post dose will be performed using an ANOVA model.	
Ear pain responder analysis: Based on ≥ 50 and 75% reduction CIs will be calculated using a fixed-effects model.	Based on ≥ 25%, 50% and 75% reduction Response will be analyzed using general estimating equations (GEE).
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.	Site included as a random effect if doing so appreciably affects treatment effect estimates. Baseline NRS-11 will be used as a covariate.
Prior and concomitant medications will be summarised using frequencies and percentages of subjects by treatment using the Safety Analysis Population.	Summaries for prior medications will be based on the Randomized Population. Summaries for concomitant medications will be based on the Safety Population.
Only safety assessments with both predose and post-dose data will be analyzed.	All safety data will be summarized.
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.	Statistical inference for appearance of TM has been removed.
Extent of exposure will be described by whether the subject took any study drug.	Total exposure will be expressed as number of sprays and will be summarized both per nostril and overall.
--	Within-subject analyses will be done for PID and SPID.

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APPENDIX A: 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

APPENDIX B: TABLES OF CONTENTS FOR TABLES, FIGURES, AND LISTINGS

TABLES

NUMBER	TITLE	POPULATION
Study Population		
14.1.1	Study Participant Disposition	Randomized
14.1.2	Eligibility	Randomized
14.1.3	Reasons for Screen Failure	Screening excluding Randomized
14.1.4	Protocol Deviations	Randomized
14.1.5	Analysis Populations	Randomized
14.1.6	Demographic and Baseline Characteristics	Safety
14.1.7	Physical Examination	Randomized
14.1.8	Prior Medications	Randomized
14.1.9	Study Treatment Exposure	Safety
Exploratory Endpoints		
14.2.1.1.1	VAS Observed Values and Changes from Baseline (PID)	Safety
14.2.1.1.2	NRS-11 Observed Values and Changes from Baseline (PID)	Safety
14.2.1.2.1	SPID, VAS	Safety
14.2.1.2.2	SPID, NRS-11	Safety
14.2.1.3.1	Presence of Any Pain, VAS	Safety
14.2.1.3.2	Presence of Any Pain, NRS-11	Safety
14.2.1.4.1	Improvement, VAS	Safety
14.2.1.4.2	Improvement, NRS-11	Safety
14.2.1.5.1	Time to Pain Relief, VAS	Safety
14.2.1.5.2	Time to Pain Relief, NRS-11	Safety
14.2.1.6.1	Response, VAS	Safety
14.2.1.6.2	Response, NRS-11	Safety
14.2.2.1.1	PGIC, Summary Statistics for Observed Values	Safety
14.2.2.1.2	PGIC, Frequency Distributions of Observed Values and Response	Safety
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14.2.2.2.2	CGI-I, Frequency Distributions of Observed Values and Response	Safety
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14.2.4	Blinding Index, Study Participants and Physician Investigators	Safety
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14.3.1.1	Summary of TEAE Incidence	Safety
14.3.1.2.1	Incidence of TEAEs by System Organ Class (SOC) and Preferred Term (PT)	Safety
14.3.1.2.2	Incidence of TEAEs Related to Study Treatment by SOC and PT	Safety
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14.3.1.3.3	TESAEs by PT in Descending Order of Incidence	Safety
14.3.1.4	Non-Treatment-Emergent Adverse Events	Safety

14.3.6	Concomitant Medications	Safety
14.3.7.1	ENT Examination, Observed Values	Safety
14.3.7.2	ENT Examination, Shifts from Baseline	Safety
14.3.8.1	Otoscopy, Observed Values	Safety
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14.3.9.1	Vital Signs, Observed Values and Changes from Baseline	Safety
14.3.9.2	Vital Signs, Incidence of Clinically Meaningful Changes from Baseline	Safety

FIGURES

LISTINGS

NUMBER	TITLE	POPULATION
Study Population		
16.2.1	Study Participant Disposition	Randomized
16.2.2.1	Eligibility and Informed Consent	Randomized
16.2.2.2	Reasons for Screen Failure	Screening excluding Randomized
16.2.2.3	Protocol Deviations	Randomized
16.2.3	Analysis Populations	Randomized
16.2.4.1	Demographic and Baseline Characteristics	Randomized
16.2.4.2.1	Medical History	Randomized
16.2.4.2.2	Prior History Using an Intranasal Device	Randomized
16.2.4.3.1	Physical Examination	Randomized
16.2.4.3.2	Urine Pregnancy Test	Randomized excluding males
16.2.4.5	Prior Medications	Randomized
16.2.5	Study Treatment Exposure	Safety
Exploratory Endpoints		
16.2.6.1	Visual Analog Scale (VAS)	Randomized
16.2.6.2	Numeric Rating Scale-11 (NRS-11)	Randomized
16.2.6.3.1	PGIC	Randomized
16.2.6.3.2	CGI-I	Randomized
16.2.6.4	Acute Otitis Media (AOM) Symptoms	Randomized
16.2.6.5.1	Blinding Index, Study Participants	Safety
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16.2.9.2	Ear, Nose, and Throat (ENT) Examination	Randomized
16.2.9.3	Otoscopy	Randomized
16.2.9.4	Vital Signs	Randomized