Study Title	A Study to Assess the Safety, Tolerability, and Efficacy of OP0201 as an Adjunct Treatment for Acute Otitis Media in Infants and Children Aged 6 to 24 Months
NCT Number	NCT03818815
Document Description	Statistical Analysis Plan, V1.0
Document Date	07 Jan 2020

STATISTICAL ANALYSIS PLAN

Protocol Title: A Study to Assess the Safety, Tolerability, and Efficacy of OP0201 as an Adjunct Treatment for Acute Otitis Media in Infants and Children Aged 6 to 24 Months

Protocol Version: Amendment 3 (21 August 2019)
Protocol Number: OP0201-C-006

Statistical Analysis Plan Author: [redacted]
Version: Version 1.0
Release Date: January 7, 2020

Study Phase: 2a
Product: OP0201
Indication: Acute Otitis Media

Sponsor: Novus Therapeutics, Inc.
[redacted]

CONFIDENTIALITY STATEMENT

This document and its contents are the property of and confidential to Novus Therapeutics. Any unauthorized copying or use of this document is prohibited.

APPROVALS

[redacted]

Date

[redacted]

Date

REVISION HISTORY

Version	Date	Author(s)	Summary of Revision(s)
1.0	07Jan2020	J. Pogoda	New document

TABLE OF CONTENTS

APPENDIX B: TABLES OF CONTENTS FOR TABLES, FIGURES, AND LISTINGS...32

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	adverse event
AOM	acute otitis media
AOM-SOS	Acute Otitis Media Severity of Symptom
ATC	Anatomical-Therapeutic-Chemical
BID	twice per day
BMI	body mass index
CSR	Clinical Study Report
eCRF	electronic case report form
EOS	end of study
GLM	general linear model
ICH	International Conference on Harmonisation
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MEE	middle ear effusion
mITT	modified intent-to-treat
N/A	not applicable
OME	otitis media with effusion
OP0201	OP0201 nasal aerosol
pMDI	pressurized metered dose inhaler
PP	per protocol
PT	Preferred Term
SAP	Statistical Analysis Plan
SD	standard deviation
SE	standard error
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TFLs	tables, figures, and listings
TM	tympanic membrane
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-006. 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-006, Amendment 3 (21 August 2019)
- 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

It has been established that most young children with acute otitis media (AOM) will have persistent middle ear effusion (MEE) or otitis media with effusion (OME) 2 to 3 weeks after AOM diagnosis, despite treatment with oral antibiotics. Bulging tympanic membrane (TM) and recent onset of acute symptoms are the main findings that clinicians use to discriminate AOM from OME. The purpose of this study is to develop a better understanding of the safety, tolerability, and efficacy of intranasal OP0201 as an adjunct treatment to oral antibiotics for AOM in infants and children, and to assist in the design of future clinical trials.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of the study are to evaluate the safety, tolerability, and efficacy of intranasal OP0201 compared with placebo in accelerating AOM resolution by reducing and/or eliminating MEE in infants and children when given as an adjunct treatment to oral antibiotics as assessed using pneumatic otoscopy.

2.2 Secondary Objectives

The secondary objectives of the study are to evaluate the efficacy of intranasal OP0201 compared with placebo in accelerating and maintaining AOM resolution, and reducing the likelihood of MEE (OME) in infants and children when given as an adjunct treatment to oral antibiotics as assessed using other measures (ie, tympanometry, Acute Otitis Media Severity of Symptom (AOM-SOS) score, and AOM recurrence and AOM relapse rates).

2.3 Other Objective

Another objective of this study is to obtain feedback from parents/caregivers on the pressurized metered dose inhaler (pMDI) device to optimize design of the device for pivotal studies.

3. STUDY DESIGN

This is a Phase 2a, single-center, double-blind, randomized, placebo-controlled, parallel-group study to assess the safety, tolerability, and efficacy of 20 mg per day intranasal OP0201 (10 mg administered twice/day (BID) over 10 days for a total of 20 doses) as an adjunct therapy to oral antibiotic treatment of AOM in infants and children aged 6 to 24 months (inclusive). Subjects will be followed for up to 20 days after study treatment is discontinued. The total duration of study participation for each subject is up to 30 days, which includes 4 clinic visits. An unscheduled interim/sick visit may occur for safety purposes or if AOM symptoms have relapsed or worsened. The Schedule of Activities 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 Safety Endpoints

- Incidence, seriousness, severity, and relationship to IP of treatment-emergent adverse events (TEAEs)
- Shifts from baseline (normal, abnormal) in vital signs (temperature, respiratory rate and pulse)
- Shifts from baseline (normal, abnormal) in physical examination, including visual examination of the nasopharynx and oropharynx
- Shifts from baseline in examination of the TM (via otoscopy and endoscopy)

4.2.2 Primary Efficacy Endpoint Family

The primary efficacy endpoint family is comprised of the following endpoints:

- No bulging of the TM assessed at the Day 4 visit by pneumatic otoscopy
- No MEE (OME) assessed at the Day 12 visit by pneumatic otoscopy

4.2.3 Secondary Efficacy Endpoints

Secondary efficacy endpoints are:

- No MEE assessed at the Day 4 and Day 28 visits by pneumatic otoscopy
- No bulging of the TM assessed at the Day 12 and Day 28 visits by pneumatic otoscopy
- Normal tympanogram (Type A) assessed at the Day 4, Day 12, and Day 28 visits by tympanometry
- Complete or near complete resolution of symptoms (AOM cure), defined as an AOM-SOS score ≤ 2, assessed at the Day 4 Visit, the Day 12 Visit and the Day 28 Visit.
- Change from baseline in the AOM-SOS score over the 10-day planned treatment period by parent/caregiver diary data
- At least a 50% reduction from baseline in the in-clinic AOM-SOS score, assessed at the Day 4, Day 12, and Day 28 visits
- AOM treatment failure (clinical failure) at the Day 12 Visit, with treatment failure defined as moderate to severe bulging of the TM, or mild bulging of TM with recent (less than 48 hours) onset of ear pain (otalgia), or mild bulging of the TM with intense erythema of the TM.
- AOM relapse defined as those with clinical success at the Day 12 visit and who return for an interim/sick visit before Day 17 and have AOM. Clinical success is defined as no moderate to severe bulging of the TM, and no mild bulging of the TM with recent (less than 48 hours) onset of ear pain (otalgia), and no mild bulging of the TM with intense erythema of the TM.
- AOM recurrence defined as clinical success at the Day 12 visit and return for an interim/sick visit from Day 17 through Day 28 and have AOM. Clinical success is defined as no moderate to severe bulging of the TM, and no mild bulging of the TM with recent (less than 48 hours) onset of ear pain (otalgia), and no mild bulging of the TM with intense erythema of the TM.

4.2.4 Other Endpoints

- Parent/caregiver's input on device experience on Day 12.

5. SAMPLE SIZE AND POWER

The power calculation is based on a 2-sided Pearson chi square test of each of the two endpoints in the primary efficacy endpoint family and control of type 1 error using the step-up Hochberg procedure.[8] The minimally important difference in proportions for both endpoints is approximately 0.25. With 70 subjects randomized per treatment group, an assumed dropout rate of 10%, and using multiple imputation as described in Section 13.3, this study will have 93% power to detect a treatment effect in at least one of the two endpoints assuming 40% of placebo-treated subjects will have no bulging TM at Day 4 and 30% of placebo-treated subjects will have no MEE at Day 12. A summary of sample size requirements is as follows:

Total N	Power
100	82%
102	82%
120	88%
132	91%
140	93%

6. TREATMENT ASSIGNMENT, BLINDING, AND UNBLINDING

6.1 Treatment Assignment

Following Screening, but before any treatment-related procedures, eligible subjects will be randomly assigned in a 1:1 ratio to either OP0201or placebo. The randomization schedule will be generated by the University of Pittsburgh Statistics Department. Randomization will be stratified by daycare attendance (yes, no) and age (≥ 6 to <12 months, ≥ 12 to ≤ 24 months). Daycare attendance will be defined as exposure to 3 or more children outside of the home for 10 or more hours per week. A fixed block size of 4 will be used.

6.2 Blinding

OP0201 and placebo will be identical in physical appearance. The specific treatment each subject will receive (OP0201 or placebo) will not be disclosed to the Investigator, study center staff, subject, Sponsor, study vendors, or the Safety Monitoring Committee (SMC). The treatment codes will be held by the University of Pittsburgh Statistics Department.

7. ANALYSIS POPULATIONS

Screened Population: Subjects whose parent/legal guardian signed the informed consent form.

Safety Population: Subjects who received at least one intranasal spray of study treatment. Subjects will be summarized and analyzed based on treatment received.

Modified Intent to treat (mITT) Population: Subjects who were randomized excluding the first 3 subjects dosed (subject numbers 1001, 1002 and 1003), as there was a known device malfunction for these subjects. Subjects will be summarized and analyzed based on randomization assignment, regardless of treatment received.

Per Protocol (PP) Population: Subset of the mITT population with no protocol violations that may have affected the primary efficacy endpoint family.

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. Mock-up TFLs to be produced are provided in separate documents from the SAP. Sponsor approval of mock-up TFLs is included with Sponsor approval of the SAP. Final 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 Subjects 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). Listings will also include site identifier.

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 12, categorical variables will be analyzed using chi square tests of association (or Fisher's exact test if any contingency table cell has less than 5 observations) or logistic regression to adjust for covariates.

Continuous variables will be summarized using descriptive statistics (e.g., n, mean, standard deviation (SD), least-squares (LS) mean with standard error (SE), 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 12, continuous variables will be analyzed using t-tests, general linear models to adjust for covariates, or non-parametric alternatives.

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

P-values will be presented in summary tables to three decimal places. P-values < 0.001 will be presented as "< 0.001."

Statistical tests will be two-sided with 0.05 significance levels unless otherwise noted.

8.4 Subgroups

Summary statistics for the primary efficacy endpoint family will be provided for the following subgroups:

- Male, female
- White, non-white
- Unilateral, bilateral disease at baseline
- History, no history of recurrent AOM, defined as 3 or more episodes in the preceding 6 months or 4 or more episodes over the course of 12 months
- Age stratum (≥ 6 to <12 months, ≥ 12 to ≤ 24 months)
- Daycare attendance stratum (exposed, not exposed to 3 or more children outside of the home for 10 or more hours per week)
- Study site

8.5 Missing Data

Listings will present data as reported. Missing or partially missing dates that are required for date-dependent definitions (e.g., TEAEs, concomitant medications) will be assumed to be the most conservative date possible. For example, an adverse event (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 13.4.

8.6 Study Period and Time Point Definitions

Screening: Day 1 up to dosing.

Baseline Observation: for a given parameter for a given randomized subject, 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 subject, 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), Subject-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 subjects have reached Subject-Level EOS.

8.7 Visit Windows

Visit windows are based on Study Day. 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 subjects not dosed, planned date of first dose will be used in Study Day calculations, if necessary.

For otoscopy and tympanogram parameters:

Nominal Visit	Target Study Day	Min Study Day Per Protocol	Max Study Day Per Protocol	Min Study Day for Analyses	Max Study Day for Analyses
Visit 1 (Day 1 Pre-Dose)	1 (pre-dose)	1	1 (pre-dose)	N/A	1 (pre-dose)
30 Minutes Post-Dose	1 (post-dose)	1 (post-dose)	1 (post-dose)	1 (post-dose)	1 (post-dose)
Visit 2 (Day 4)	4	4	6	4	6
Visit 3 (Day 12)	12	12	14	12	14
Visit 4 (Day 28)	28	26	30	26	30

N/A, not applicable

For all other parameters collected in-clinic:

Nominal Visit	Target Study Day	Min Study Day Per Protocol	Max Study Day Per Protocol	Min Study Day for Analyses	Max Study Day for Analyses
Visit 1 (Day 1)	1 (pre-dose)	1	1 (pre-dose)	N/A	1 (pre-dose)
Visit 2 (Day 4)	4	4	6	4	6
Visit 3 (Day 12)	12	12	14	12	14
Visit 4 (Day 28)	28	26	30	26	30

N/A, not applicable

For AOM-SOS score collected by diary:

Nominal Visit	Target Study Day	Min Study Day Per Protocol	Max Study Day Per Protocol	Min Study Day for Analyses	Max Study Day for Analyses
Visit 1 (Day 1)	1 (pre-dose)	1	1 (pre-dose)	N/A	1 (pre-dose)
Diary Day x, x=2-10	x	x	x	x	x

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 target study day of the nominal visit in question, or
2. the latest observation if the multiple observations are equidistant from the target study day of 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 include all randomized subjects unless otherwise noted.

9.1 Subject Disposition

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

9.2 Informed Consent and Eligibility

Informed consent (for the Screened Population) and eligibility parameters will be listed. Reasons for screen failure will be summarized.

9.3 Visit Summaries and 10-Day Diary

Listings of visit summaries and 10-day diary entries will be provided.

9.4 Protocol Deviations

A listing of protocol deviations 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.

9.5 Analysis Populations

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

A listing of analysis populations will be produced showing the analysis population(s) to which each subject belonged.

9.6 Demographic and Baseline Characteristics

Demographic and other baseline characteristics will be summarized both overall and by treatment group. Parameters will include sex; age at informed consent; age stratum for randomization; race; ethnicity; weight, height, and body mass index (BMI) at screening; baseline otitis media risk factors (private or public health insurance, mother's education level, attends daycare, at least 3 other children in household, smoker in household), study site, and tympanogram status (yes or no).

9.7 Medical History

Reported medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0, to a System Organ Class (SOC) and Preferred Term (PT). Medical history will be summarized by SOC and PT.

10. TREATMENTS

Treatments include study treatment, oral antibiotic treatment, device incidents, device experience, prior medications, and concomitant medications.

10.1 Study Treatment Exposure

Exposure to study treatment will be expressed as total exposure, mean daily exposure, and duration of exposure.

Exposure per study treatment administration E_a (mg) will be calculated as

$$E_a(mg) = (S_{L_a} + S_{R_a})\ x\ 2.5$$

where

a = 1 to A, A = total number of administrations

S_{L_a} = number of sprays to the left nostril during administration a
S_{R_a} = number of sprays to the right nostril during administration a

Total exposure E_T (mg) will be calculated as

$$E_T(mg) = \sum_{a=1}^{A} E_a\ (mg)$$

Duration of Exposure E_D (days) is defined as the total number of days that treatment was administered, ie,

$$E_D = \textit{date of last dose} - \textit{date of first dose} + 1$$

Mean daily exposure E_M (mg) will be calculated for each subject as

$$E_M\ (mg) = \frac{E_{T\ (mg)}}{E_{D\ (days)}}$$

and will be rounded to the nearest hundredth.

Listings and summaries will be based on the Safety Population. Listings will show each study treatment administration per nostril and will also display cumulative total exposure, duration of exposure, and mean daily exposure.

10.2 Study Treatment and Oral Antibiotic Compliance

10.2.1 Study Treatment Compliance

Study treatment compliance will be expressed as both overall and mean daily percent compliance. For mean daily percent compliance, only days on which exposure occurred will be counted.

Percent compliance will be calculated for each study day of exposure as

$$C_d = 100\ x\ (S_{L_{ACTUAL_d}} + S_{R_{ACTUAL_d}})/8$$

rounded to the nearest tenth, where

d = 1 to D, D = total number of study days of exposure
$S_{L\_ACTUAL\_d}$ = actual number of sprays to the left nostril on day d
$S_{R\_ACTUAL\_d}$ = actual number of sprays to the right nostril on day d

For subjects who prematurely discontinue treatment, percent compliance will be calculated only for study days prior to discontinuation.

Percent overall compliance C_T will be calculated as

$$C_T = 100\ X\ \frac{\sum_{d=1}^{D}\left(S_{L_{ACTUAL_d}} + S_{R_{ACTUAL_d}}\right)}{S_{EXPECTED}}$$

rounded to the nearest tenth, where

$$S_{EXPECTED} = E_D\ x\ 8$$

with E_D as defined in Section 10.1.

Mean daily percent compliance C_M will be calculated for each subject as

$$C_M = \frac{\sum_{d=1}^{D} C_d}{E_D}$$

and will be rounded to the nearest hundredth.

Listings and summaries will be based on the Safety Population. Listings will show compliance for each study day and will also display cumulative overall compliance and mean daily compliance.

10.2.2 Oral Antibiotic Compliance

Oral antibiotic exposure will be collected by diary as number of administrations. Daily and overall antibiotic compliance will be calculated as 100 x (number of administrations / expected number of administrations) rounded to the nearest tenth. For daily compliance, the expected number is 2. For overall compliance, the expected number is the number of days of study participation x 2; ie, for subjects who prematurely discontinue from the study, compliance will be calculated only for study days prior to discontinuation. Oral antibiotic compliance will be listed and summarized for the Safety Population.

10.3 Device Incidents

A listing of device incidents will be provided for the Safety Population.

10.4 Device Experience

The Device Experience questionnaire will be completed by parents/caregivers at the Day 12 visit. Data will be listed for the Safety Population.

10.5 Prior and Concomitant Medications

Medication use from 7 days prior to enrollment 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 01Mar2018B3 Enhanced. 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 7 days before enrollment 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 all subjects randomized. Listings and summaries for concomitant medications will be based on the Safety Population.

11. SAFETY PARAMETERS

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

11.1 AEs

AEs reported from time of informed consent through EOS will be coded according to MedDRA® version 21.0. Each reported AE will be mapped to a PT and SOC. Aside from parameters collected on the eCRF, listings will include MedDRA PT and SOC, Study Day, whether or not the AE is ongoing, and AE duration. For AEs that are ongoing, AE end date will be imputed with subject-level EOS date for the duration calculation.

TEAEs will be AEs that began or worsened in severity during or after first dose of study treatment and no later than 2 calendar days after last dose of study treatment. 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 2 calendar days after last dose through EOS will be defined as non-treatment-emergent (non-TEAEs). AEs that began or worsened in severity after informed consent but before the first dose will be counted as pre-treatment AEs.

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

- Treatment-emergent SAEs (TESAEs)
- TEAEs that resulted in study treatment interruption or dose reduction
- TEAEs that results in study treatment discontinuation (excluding deaths)
- TEAEs that resulted in death
- Pre-treatment AEs among the Screened Population
- Non-TEAEs

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. In addition, separate summaries will be done for:

- TEAEs assessed as related to study treatment

- TEAEs by severity
- TESAEs
- TESAEs assessed as related to study treatment
- Pre-treatment AEs among the Screened Population
- Non-TEAEs

In summaries by relationship to study treatment, missing relationship will be considered related. In summaries by AE severity, missing severity will be counted as severe.

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
- Mild TEAEs
- 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

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

11.2 Vital Signs

Vital signs will be collected at each study visit. Observed values for oral temperature, respiratory rate, and pulse 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.

11.3 Physical Examination

Physical examination will be done at each study visit. Findings for each body system, including extended data for throat and nose, will be summarized. Body system shifts from baseline to normal/abnormal status will also be summarized.

11.4 Ear Examination

Examination of each ear will be done at each study visit. Summaries, by ear and visit, will be done for: TM findings (intact, perforated,), color (gray, pink, pale yellow, white, amber, blue), translucency (translucent, semi-opaque, opaque), mobility (none, 1+, 2+, 3+, 4+), air fluid interface (yes, no), otalgia (yes, no), distinct erythema (yes, no), position of the TM (neutral, retracted, 1+ bulging, 2+ bulging, 3+ bulging), otorrhea (no, serous, purulent), and diagnosis (no effusion, OME, AOM).

Shift tables will summarize changes from baseline in normal/abnormal status, where "abnormal" will be limited to "definitely abnormal" defined as follows:

- TM findings: perforated
- Color: pale yellow, white, amber, blue
- Translucency: semi-opaque or opaque
- Mobility: none
- Air fluid interface: yes
- Otalgia: yes
- Distinct erythema: yes
- Position of TM: retracted, 1+ bulging, 2+ bulging, 3+ bulging
- Otorrhea: serous, purulent
- Diagnosis: AOM, OME

Parameters will be summarized within treatment group for (a) first or only affected ear and (b) second or non-affected ear. Since either one ear or both ears can have AOM at baseline, this approach will allow descriptive comparisons between OP0201 and placebo treatment groups on number of affected ears (ie, one or both ears) and shifts from baseline, by visit, for both affected and non-affected ears at baseline.

12. EFFICACY PARAMETERS

Efficacy parameters will be listed for the mITT population. For the family of primary efficacy endpoints, summaries and analyses will be done using the mITT population unless otherwise noted. For secondary efficacy endpoints, complete-cases analyses will be done using the mITT population, whereby for each endpoint only subjects with complete data are included. Results from statistical analyses of treatment group differences in secondary endpoints may be reported to aid in interpretation and to assist in the design of future clinical trials.

12.1 Bulging TM

The presence/absence of bulging TM will be evaluated as part of the ear examination (see Section 11.4) done at each study visit; each ear will be evaluated separately.

A listing of bulging TM will be produced separately from the listing of ear examination parameters noted in Section 11.4.

Endpoints

The definition of bulging TM will be presence of 1+, 2+, or 3+ bulging on ear examination.

Note: at least mild bulging is an inclusion criterion.

No bulging TM at the Day 4 visit is one of two endpoints in the primary efficacy endpoint family (see Section 13.5). The hypothesis set to be tested is:

$$H_o: P_A = P_P$$
vs.
$$H_A: P_A \neq P_P$$

where P_A and P_P are the population proportions for OP0201 and placebo, respectively, for no bulging TM 4 days after the start of a 10-day treatment regimen.

The following sensitivity analyses will be done:

- PP analysis population
- Complete case (ie, mITT subjects who completed the Day 4 visit; see Section 13.3)
- Complete case with the endpoint defined as no bulging TM at the Day 4 visit and no recurrence of bulging TM (see Section 12.7) throughout the remainder of the study, assessed at the Day 28 visit. In this instance, "complete case" is equivalent to mITT subjects who completed the Day 28 visit.

No bulging TM assessed at the Day 12 and Day 28 visits are secondary endpoints.

Summaries and Analyses (see Section 13)

No bulging TM will be summarized and analyzed separately by visit using logistic regression. Summary tables will include frequencies and percentages of no bulging TM for each treatment group by visit and p-values for the differences. Crude rates of no bulging TM by treatment group and visit will be graphically displayed using bar charts.

12.2 MEE

Otoscopy will be performed at each study visit (as well as 30 minutes post-dose on Day 1, for safety only) to evaluate the presence/absence of MEE; each ear will be evaluated separately, and a listing will show presence/absence of MEE for each ear separately.

Endpoints

No MEE at the Day 12 visit is one of two endpoints in the primary efficacy endpoint family (see Section 13.5). The following sensitivity analyses will be done:

- PP analysis population
- Complete case (ie, mITT subjects who completed the Day 12 visit; see Section 13.3)
- Complete case with the endpoint defined as no MEE at the Day 12 visit and no recurrence of MEE throughout the remainder of the study. In this instance, "complete case" is equivalent to mITT subjects who completed the Day 28 visit.

The hypothesis set to be tested is:

$$H_o: P_A = P_P$$
vs.
$$H_A: P_A \neq P_P$$

where P_A and P_P are the population proportions for OP0201 and placebo, respectively, for no MEE 12 days after the start of a 10-day treatment regimen.

No MEE at the Day 4 and Day 28 visit are secondary endpoints.

Summaries and Analyses (see Section 13)

No MEE will be summarized and analyzed separately by visit using logistic regression. Summary tables will include frequencies and percentages of no MEE for each treatment group by visit and p-values for the differences. Crude rates of no MEE by treatment group and visit will be graphically displayed using bar charts.

12.3 Tympanogram

For a subset of the mITT population, tympanograms will be performed at each study visit to assess middle ear function. Each ear will be rated separately as Type A, Type B, or Type C.

Endpoints

Secondary endpoints based on tympanogram will be:

- Normal tympanogram (Type A) in either ear, assessed at the Day 4, 12, and 28 visits

A listing of tympanogram parameters will show peak height, gradient width, peak pressure, values derived, test results, ear canal volume value, predictive value, and rating.

Summaries and Analyses

Summary tables will include frequencies and percentages of shifts from baseline for each treatment group by visit. Crude rates of normal tympanogram by treatment group and visit will be graphically displayed using bar charts. There will be no statistical analysis of normal tympanogram.

12.4 AOM-SOS Scale

The AOM-SOS scale is scored by the parent/caregiver once daily at home and recorded in a diary over the 10-day duration of the antibiotic and study treatment period and also at in-clinic visits on Day 1, 4, 12 and 28. The scale consists of 5 questions rated on a 6-point scale, with lower scores associated with better symptom status: 0 = no, 1 = almost none, 2 = a little, 3 = some, 4 = a lot, 5 = an extreme amount. A total score for each day will be calculated in the AOM-SOS analysis data set (ie, not in the eCRF) as the sum of the 5 individual scores. Missing observations for individual questions will not be possible, which is a built-in feature of the data collection instrument; either all 5 questions will have responses or none of the 5 questions will have responses.

At the screening visit the parent/caregiver will be asked to score the AOM-SOS scale as part of the screening criteria for the study; a score of at least 5 is an inclusion criterion. This is the only baseline assessment of the AOM-SOS scale.

Listings for AOM-SOS scale will show observed values at each time point collected for both diary and in-clinic, the 10-day mean from diary, and absolute and percent changes from baseline in the in-clinic AOM-SOS scores for Days 4, 12, and 28.

Endpoints

Secondary endpoints based on the AOM-SOS scale will be:

- 10-day mean AOM-SOS total score based on diary data, calculated for each subject as the mean total score over the 10-day treatment period. If the Day 4 assessment is missing from the diary, the Day 4 in-clinic assessment may be used but only if done on Study Day 4. If more than 10 days of AOM-SOS scores are available, only the first 10 days will be used to calculate the mean. If less than 10 days of AOM-SOS scores are available, 10-day mean score will not be calculated.
- Complete or near complete resolution of symptoms (AOM cure), defined as in-clinic AOM-SOS score ≤ 2, assessed at the Day 4, 12, and 28 visits.
- AOM-SOS response, defined as at least a 50% reduction from baseline in the in-clinic AOM-SOS score, assessed at the Day 4, 12, and 28 visits.

Since a Day 4 assessment should be available from both the diary and the in-clinic visit, the in-clinic assessment will be used for the resolution and response endpoints. If the in-clinic assessment is not available, the Day 4 diary assessment will be used.

In a sensitivity analysis, AOM cure will be defined as AOM-SOS score = 0.

Summaries and Analyses (see Section 13)

The 10-day mean AOM-SOS total score will be analyzed using a general linear model (GLM) with baseline AOM-SOS total score included as a covariate. A summary table will include means and SDs for each treatment group and a p-value for the difference.

AOM cure and AOM-SOS response will be summarized and analyzed separately by visit using logistic regression with baseline AOM-SOS total score included as a covariate. Summary tables will include frequencies and percentages of AOM cure and AOM-SOS response for each treatment group by visit and p-values for the differences.

12.5 AOM Treatment Failure

AOM treatment failure (clinical failure) will be defined as:

- moderate to severe bulging of the TM, or
- mild bulging of the TM with
    - recent (less than 48 hours) onset of ear pain (otalgia), or
    - intense erythema of the TM

AOM treatment failure (clinical failure) will be available in the eCRF and will not be programmatically derived. As a cross-check, a listing will be provided that shows degree of bulging TM, otalgia, and erythema in each ear and AOM treatment failure status at Day 12.

Endpoints

AOM treatment failure (clinical failure) at the Day 12 visit will be a secondary endpoint.

Summaries and Analyses (see Section 13)

AOM treatment failure (clinical failure) will be analyzed using logistic regression. A summary table will include frequencies and percentages of treatment failure and a p-value for the treatment group difference.

12.6 AOM Relapse

AOM relapse will be defined as clinical success at the Day 12 visit and return for an interim/sick visit before Day 17 with AOM at that visit. Clinical success is defined as:

- no moderate to severe bulging of the TM, and
- no mild bulging of the TM with
    - recent (less than 48 hours) onset of ear pain (otalgia), or
    - intense erythema of the TM

Clinical success will be available in the eCRF and will not be programmatically derived. AOM relapse status will be shown in a listing.

Endpoints

AOM relapse will be a secondary endpoint and will be assessed using the subset of the mITT population that achieved clinical success at the Day 12 visit. Subjects in this subset who did not have an interim/sick visit before Day 17 at which AOM was diagnosed and who discontinued the study before Day 17 will be excluded from summaries and analyses.

Summaries and Analyses (see Section 13)

AOM relapse will be analyzed using logistic regression. A summary table will include frequencies and percentages of relapse and a p-value for the treatment group difference.

12.7 AOM Recurrence

AOM recurrence will be defined as clinical success at the Day 12 visit and return for an interim/sick visit Day 17 through Day 28 (including the Day 28 visit, which can be out-of-window) with AOM at that visit. Clinical success is defined as in Section 12.6.

AOM recurrence status will be shown in a listing.

Endpoints

AOM recurrence will be a secondary endpoint and will be assessed using the subset of the mITT population that achieved clinical success at the Day 12 visit. Subjects in this subset who did not have an interim/sick visit Day 17 through Day 28 at which AOM was diagnosed and who discontinued the study before Day 28 will be excluded from summaries and analyses.

Summaries and Analyses (see Section 13)

AOM recurrence will be analyzed using logistic regression. A summary table will include frequencies and percentages of recurrence and a p-value for the treatment group difference.

13. STATISTICAL METHODS

13.1 Logistic Regression

Logistic regression models will include treatment group as a main effect and the randomization stratifiers (age group, daycare attendance) and an appropriate baseline value (if applicable) as covariates. Model-based LS means and SEs will be reported for each treatment group, along with a p-value for the treatment group comparison. For sparse data, two-sided Fisher's exact tests will be used (ie, with no covariate adjustment).

13.2 GLM

GLMs will include treatment group as a main effect and the randomization stratifiers and an appropriate baseline value (if applicable) as covariates. Model-based LS means and SEs will be reported for each treatment group, along with a p-value for the treatment group comparison.

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.

13.3 Missing Observations

For the primary efficacy analysis, multiple imputation will be used for missing observations with only treatment group included in the imputation model; ie, the observed within-treatment-group Bernoulli distribution of response will be the distribution from which random values are drawn to replace missing observations. The number of imputations will be the percentage of subjects with missing data, rounded up to an integer. Results from multiple imputations will be combined using the Rubin method.[8] A complete-case sensitivity analysis will also be done, whereby for each endpoint only subjects with complete data are included. For secondary endpoints, only complete-case analyses will be done.

13.4 Multiplicity

The familywise type 1 error rate for the primary efficacy endpoint family will be 0.05 and will be controlled using the Hochberg procedure.[9] Specifically, the p-value of the endpoint with the highest p-value will be compared against the 0.05 significance level and, if significant, both endpoints will be declared significant; if the endpoint with the highest p-value is not significant at the 0.05 level, the other endpoint will be tested at the 0.025 significance level. A positive treatment effect on efficacy will be concluded if at least one of the two endpoints is significant.

14. SAFETY MONITORING COMMITTEE

An SMC will review blinded safety data for all subjects when approximately 25% of enrolled subjects have completed Day 12 (Visit 3). Safety data will be evaluated on an ongoing basis to ensure it is safe to continue study enrollment and treatment. The composition, responsibilities, and meeting schedule of the SMC will be specified in a charter document.

15. SEQUENCE OF PLANNED ANALYSES

15.1 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.

16. CHANGES FROM THE PROTOCOL

Protocol	Change
Primary efficacy analysis to be done using the ITT population defined as all randomized subjects.	ITT population replaced by mITT population which excludes the first 3 subjects dosed.
Subjects with missing data at the Day 4 Visit will be considered as having bulging TM and those with missing data at the Day 12 Visit will be considered as having MEE.	Multiple imputation will be used for missing data for the primary efficacy analysis, with a complete-case sensitivity analysis added.
GEE will be used for analyses of repeating binary endpoints.	All binary endpoints will be analyzed separately by visit using logistic regression.
Secondary efficacy endpoints, which included “normal tympanogram,” will be statistically analyzed.	Tympanogram findings will not be analyzed and will be reported as descriptive statistics only.
Secondary efficacy endpoints will be analyzed using the Safety population.	Complete-case analyses using the mITT population will be done for secondary efficacy endpoints.

REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), September 1998.

2. American Statistical Association (ASA). (2018) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2018. http://www.amstat.org/ASA/Your-Career/Ethical-Guidelines-for-Statistical-Practice.aspx.

3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), November 1995.

4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Good Clinical Practice (E6), April 1996.

5. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, General Considerations for Clinical Trials (E8), July 1997.

6. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), September 1998.

7. Johnson JR, Fitts D. Statistical Analysis Plans: Principles and Practice. Workshop Number 8. Presented at the Society for Clinical Trials 2007 Annual Meeting Montreal, Canada Sunday May 20, 2007. http://docshare01.docshare.tips/files/9381/93818340.pdf.

8. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons, 1987.

9. Hochberg Y. A sharper Bonferroni procedure for multiple significance testing. Biometrika 1988:75;800–2.

APPENDIX A: SCHEDULE OF ACTIVITIES

Procedure	Visit	Screening/ Enrollment Visit 1	Visit 2	Visit 3	Study Exit Visit 4/Early Discontinuation[f]
	Study Day	Day 1	Day 4 (+2)	Day 12 (+2)	Day 28 (±2)
Informed consent		X			
Inclusion/exclusion criteria		X			
Demographics		X			
Medical/surgical/ear history		X			
Baseline otitis media risk factors		X			
AOM-SOS score[a]		X	X	X	X
Physical examination[b]		X	X	X	X
Height and weight		X			
Vital signs (temperature, pulse and respiratory rate)		X	X	X	X
Pneumatic otoscopy of each ear[c]		X	X	X	X
Tympanogram of each ear[c]		X	X	X	X
Endoscopic examination with image capture of each ear (when possible) using the iPhone application		X	X	X	X
Randomization to OP0201 or placebo		X			
Train parent/caregiver on study treatment administration		X			
Train parent/caregiver on daily completion of AOM-SOS score and daily electronic diary		X			
Nasal saline rinse and/or nasal suction, as needed[d]		X	X	X	X
Observe parent/caregiver administer first dose of intranasal study treatment		X			
Dispense 10-day supply of study treatment		X			
Safety observation[e]		X			
Check electronic diary, study treatment adherence, AOM-SOS assessment adherence/retrain as needed			X	X	
Concomitant medications		X	X	X	X
Adverse event		X	X	X	X
Device Experience Questionnaire				X	X[g]

AOM-SOS = Acute Otitis Media Severity of Symptom

[a] The AOM-SOS scale is scored by the parent/caregiver once daily at home for the total duration of the antibiotic and study treatment period. At the screening visit the parent/caregiver will be asked to score the AOM-SOS scale as part of the screening criteria for the study. Parents/caregivers must not be informed of the score required to meet study enrollment criteria.

[b] Physical examination including visual examination of the nasopharynx and oropharynx at each visit.

[c] Otoscopy and tympanometry (when possible) to be performed prior to the first dose of the study treatment on Day 1. When possible, otoscopy and tympanometry to be performed 30 minutes following administration of the first dose of the study treatment on Day 1. Trained otoscopists who have undergone comprehensive educational program (enhancing proficiency in otitis media) for training in the diagnosis of AOM will perform the otoscopy assessments. This training includes training on cerumen removal, which is required (as needed) prior to performing pneumatic otoscopy or tympanogram.

[d] Train parent/caregiver on nasal saline rinse and/or nasal suction on Day 1 and remind parent/caregiver of rinse and/or suction during the study treatment period, as needed.

[e] Safety observation for 30 minutes following administration of the first dose of study treatment.

[f] If a Participant exits the study prior to the Day 28 Study Exit visit, all Day 28 final measurements should be performed and recorded on the appropriate eCRF.

[g] Device Experience Questionnaire should only be completed for all Early Discontinuation Participants if they exit prior to Day 12 and did NOT complete the questionnaire.

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

TABLES

NUMBER	TITLE	POPULATION
Study Population		
14.1.1	Subject Disposition	all randomized
14.1.2	Eligibility	all randomized
14.1.3	Reasons for Screen Failure	Screened excluding randomized
14.1.4	Protocol Deviations	all randomized
14.1.5	Analysis Populations	all randomized
14.1.6	Baseline Characteristics	all randomized
14.1.7.1	Medical History	all randomized
14.1.7.2	Baseline Symptoms	all randomized
14.1.8	Pre-Treatment Adverse Events	Screened
Treatments		
14.1.9.1	Study Treatment Exposure	Safety
14.1.9.2.1	Study Treatment Compliance	Safety
14.1.9.2.2	Oral Antibiotic Compliance	Safety
14.1.10.1	Prior Medications	all randomized
14.1.10.2	Concomitant Medications	Safety
Efficacy Endpoints		
14.2.1.1	Bulging TM	mITT
14.2.1.2	Bulging TM	Per Protocol
14.2.1.3	Bulging TM	Complete Case
14.2.1.4	Bulging TM and No Recurrence	mITT
14.2.1.5	Bulging TM by age group	mITT
14.2.1.6	Bulging TM by sex	mITT
14.2.1.7	Bulging TM by race	mITT
14.2.1.8	Bulging TM by disease laterality	mITT
14.2.1.9	Bulging TM by history of recurrent AOM	mITT
14.2.1.10	Bulging TM by daycare attendance	mITT
14.2.1.11.1	Bulging TM by study site	mITT
14.2.2.1	MEE	mITT
14.2.2.2	MEE	Per Protocol
14.2.2.3	MEE	Complete Case
14.2.2.4	MEE and No Recurrence	mITT
14.2.2.5	MEE by age group	mITT
14.2.2.6	MEE by sex	mITT
14.2.2.7	MEE by race	mITT
14.2.2.8	MEE by disease laterality	mITT
14.2.2.9	MEE by history of recurrent AOM	mITT
14.2.2.10	MEE by daycare attendance	mITT
14.2.2.11.1	MEE by study site	mITT
14.2.3.1	Tympanogram Shifts from Baseline	Tympanogram Subset
14.2.4.1	AOM-SOS Scale Score – 10-Day Mean	mITT
14.2.5.1.1	AOM Cure	mITT

14.2.5.1.2	AOM Cure – Sensitivity Analysis	mITT
14.2.6.1	AOM-SOS Response	mITT
14.2.7.1	AOM Treatment Failure, AOM Relapse, AOM Recurrence	mITT
Safety Endpoints		
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
14.3.1.2.3	Incidence of TEAEs by Severity, by SOC and PT	Safety
14.3.1.2.4	TEAEs by PT in Descending Order of Incidence	Safety
14.3.1.3.1	Incidence of TESAEs by SOC and PT	Safety
14.3.1.3.2	Incidence of TESAEs Related to Study Treatment by SOC and PT	Safety
14.3.1.3.3	TESAEs by PT in Descending Order of Incidence	Safety
14.3.1.4	Non-TEAEs	Safety
14.3.9.1	Vital Signs, Observed Values and Changes from Baseline	Safety
14.3.9.2.1	Physical Exam, Observed	Safety
14.3.9.2.2	Physical Exam, Shifts from Baseline	Safety
14.3.9.3.1	Ear Exam, Observed	Safety
14.3.9.3.2	Ear Exam, Shifts from Baseline	Safety
14.3.9.4.1	Nose and Throat Exam, Observed	Safety
14.3.9.4.2	Nose and Throat Exam, Shifts from Baseline	Safety

FIGURES

LISTINGS

NUMBER	TITLE	POPULATION
Study Population		
16.2.1	Subject Disposition	all randomized
16.2.2.1	Informed Consent	Screened
16.2.2.2	Eligibility	all randomized
16.2.2.3	Reasons for Screen Failure	Screened excluding randomized
16.2.2.4	Protocol Deviations	all randomized
16.2.3	Analysis Populations	all randomized
16.2.4.1	Demographic Characteristics (incl ht/wt/bmi)	all randomized
16.2.4.2	Baseline otitis media risk factors	all randomized
16.2.4.3.1	Medical History	all randomized
16.2.4.3.2	Baseline Symptoms	all randomized
16.2.4.4	Pre-Treatment Adverse Events	Screened
Treatments		
16.2.5.1	Study Treatment Exposure	Safety
16.2.5.2.1	Study Treatment Compliance	Safety
16.2.5.2.2	Oral Antibiotic Compliance	Safety
16.2.5.3	Device Incidents	Safety
16.2.5.4	Device Experience	Safety
16.2.5.5	Prior Medications	all randomized
16.2.5.6	Concomitant Medications	Safety
Efficacy Endpoints		
16.2.6.1	Bulging Tympanic Membrane & MEE	mITT
16.2.6.2	Tympanogram	mITT
16.2.6.4.1	AOM-SOS Scale, Diary	mITT
16.2.6.4.2	AOM-SOS Scale, Clinic	mITT
16.2.6.5	AOM Treatment Failure, Relapse, and Recurrence	mITT
Safety Endpoints & Other Clinical Observations/Measurements		
16.2.7.1	Treatment-Emergent Adverse Events (TEAEs)	Safety
14.3.2.1	Treatment-Emergent Serious Adverse Events (TESAEs)	Safety
14.3.2.2	TEAEs Resulting in Study Treatment Interruption or Dose Reduction	Safety
14.3.2.3	TEAEs Resulting in Study or Study Treatment Discontinuation	Safety
14.3.2.4	TEAEs Resulting in Death	Safety
16.2.7.2	Non-TEAEs	Safety
16.2.9.1	Vital Signs	Safety
16.2.9.2	Physical Examination	Safety
16.2.9.3	Ear Examination	Safety
16.2.9.4	Nose Examination	Safety
16.2.9.5	Throat Examination	Safety
16.2.9.6	Visit Summaries	Safety
16.2.9.7	10-Day Diary Entries	Safety
16.2.9.8	Comments	all randomized